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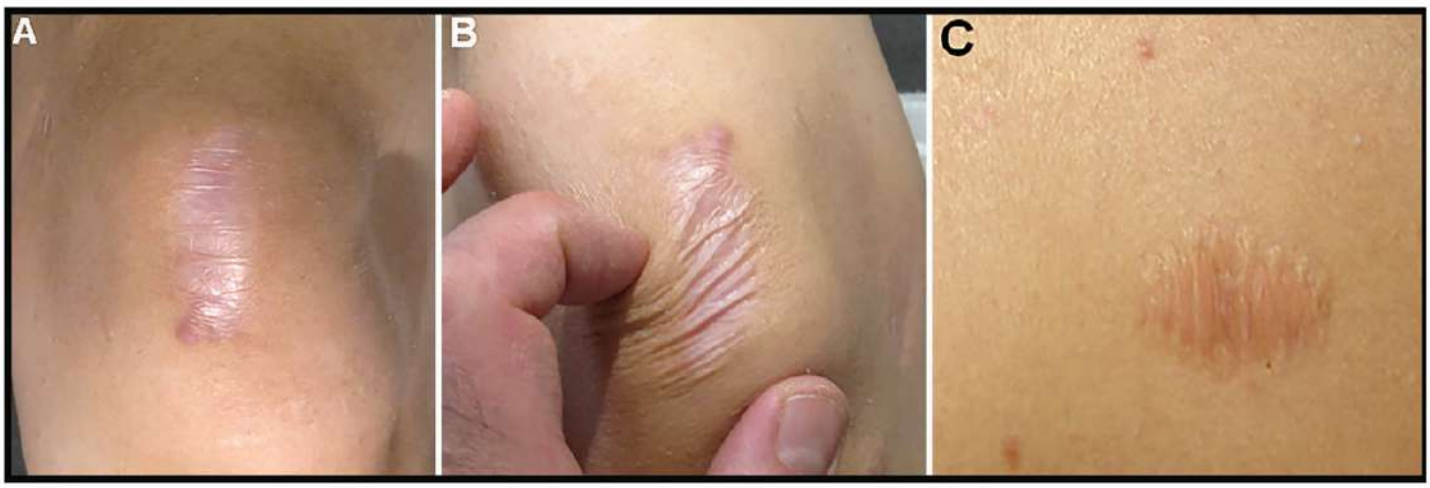
Seminars in Medical Genetics

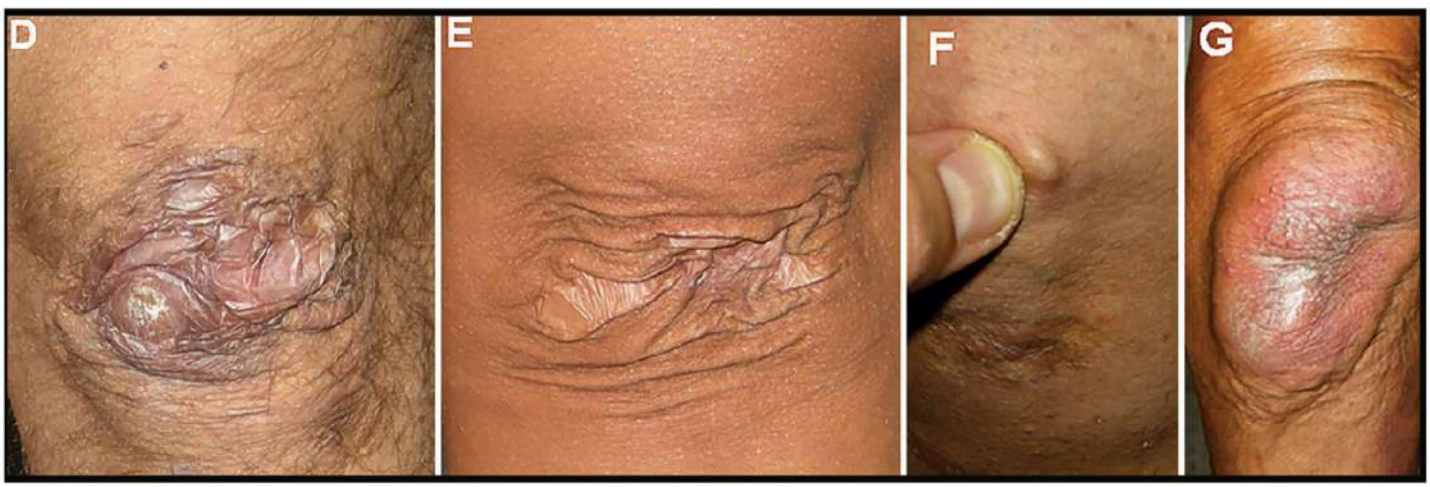
The Ehlers-Danlos Syndromes: Reports from the International Consortium on the Ehlers-Danlos Syndromes

Guest Editors: Brad T. Tinkle, Fransiska Malfait, Clair A. Francomano and Peter H. Byers

Hypermobile EDS



Classical EDS



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COVER FIGURE

The cover image, by Brad Tinkle et al., is based on the Research Article *Hypermobile Ehlers–Danlos syndrome (a.k.a. Ehlers–Danlos syndrome Type III and Ehlers–Danlos syndrome hypermobility type): Clinical description and natural history*, DOI: 10.1002/ajmg.c.31538.

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INTRODUCTION

The International Consortium on the Ehlers–Danlos Syndromes

LARA BLOOM,* PETER BYERS, CLAIR FRANCOMANO, BRAD TINKLE, AND FRANSISKA MALFAIT ON BEHALF OF THE STEERING COMMITTEE OF THE INTERNATIONAL CONSORTIUM ON THE EHLERS-DANLOS SYNDROMES

Since 1998, two developments have led to concerns that the EDS nosology needs to be substantially revised. The first development was the clinical and molecular characterization of several new EDS variants, which substantially broadened the molecular basis underlying EDS. The second was the growing concern, in the absence of genetic diagnosis, that the hypermobile type of EDS had an expanded phenotype, may be genetically heterogeneous, and that the diagnostic criteria currently in use were inadequate. Furthermore, there is a dire need for the development of guidelines for management for each type of EDS to allow both the specialist and the generalist to care for affected individuals and their families. We have been meeting together as an international consortium over the past 2 years to establish these new criteria and management and care guidelines

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INTRODUCTION

The Ehlers–Danlos syndromes (EDS) have fascinated people throughout the ages. The first report of this disorder dates back to Hippocrates (fourth century BC). For many centuries, affected individuals earned their livings as The Elastic Skin Man, The India Rubber Man and The Human Pretzel, amazing their audiences in fairgrounds and circus side shows by exhibiting contortionist tricks and a remarkable ability to stretch their skin. Job Janszoon van Meek'ren [1657] provided a first partial description, but the first classical description of the syndrome in the medical literature is attributed to Tschernogubow, a Russian dermatologist in 1891 [Tschernogubow, 1891; Denko, 1978]. In 1901 and 1908, respectively, the Danish and French dermatologists Edvard Ehlers [Ehlers, 1901] and Henri-Alexandre Danlos [Danlos, 1908] identified people with striking alterations in the mechanical properties of the skin and in the 1930s the condition received its eponymous title, and, by this, its scientific respectability [Parkes Weber, 1936]. In the mid-20th century it was suggested that a genetic defect in the collagen "wickerwork" of the connective tissues probably accounted for the phenotype and not much later the first genetic defect was identified as a deficiency of lysyl hydroxylase, a collagen modifying enzyme [Krane et al., 1972].

The Ehlers–Danlos syndromes are classically defined as a heterogeneous group of heritable disorders of connective tissue characterized by articular hypermobility, skin hyperextensibility

Lara Bloom is the Co-Executive Director of The Ehlers–Danlos Society and responsible for globally raising awareness of The Ehlers–Danlos syndromes, managing coordinated medical collaboration, raising funds for research and focusing on the progression of EDS throughout the world.

Peter H. Byers, M.D. is a medical geneticist and Professor of Pathology and Medicine at the University of Washington. He has studied collagen biosynthesis and structure in attempt to identify the underlying bases of heritable connective tissue disorders including forms of Ehlers–Danlos syndrome and osteogenesis imperfecta.

Clair Francomano, M.D. is an internist and clinical geneticist as well as Director of Adult Genetics at the Harvey Institute of Human Genetics at the Greater Baltimore Medical Center. Her research interests over the years have centered on Hereditary Disorders of Connective Tissue and Skeletal Dysplasias. She is currently the Director of The Ehlers–Danlos Society Center for Clinical Care and Research at the Greater Baltimore Medical Center.

Brad Tinkle, M.D. is a clinical geneticist with interests in connective tissue disorders and is Division Head of Clinical Genetics at the Advocate Children's Hospital.

Fransiska Malfait, M.D., Ph.D. is a rheumatologist and clinical geneticist. She is an Associate Professor at the Centre for Medical Genetics at the Ghent University Hospital, where she directs the research, clinical service and laboratory facility for diagnosis and genetic testing for the Ehlers–Danlos syndrome and other heritable disorders of connective tissue. She has (co-)authored over 80 papers in international journals, and 6 book chapters, and is the Chair of the medical and scientific board of the Ehlers–Danlos Society.

*Correspondence to: Lara Bloom, Co-Executive Director, The Ehlers–Danlos Society, 7918 Jones Branch Drive, Suite 300, McLean VA 22102. E-mail: lara@internationaleds.org

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and tissue fragility affecting skin, ligaments, joints, blood vessels, and internal organs [Steinman et al., 1990]. Classification of this clinically and genetically heterogeneous group of conditions began in the late 1960s. Barabas [1967] and then Beighton [1970] recognized sufficient diversity in the clinical presentations and natural history to delineate five apparently discrete types of EDS. In 1986, a nosology was proposed at a meeting in Berlin, which formalized the nomenclature of the various types [Beighton et al., 1988]. In the Berlin Nosology, eleven subtypes were recognized and each subtype was designated a Roman number. Developments in the elucidation of the biochemical and molecular bases of EDS, together with increasing clinical experience, permitted refinement of the nosology, leading to the Villefranche nosology [Beighton et al., 1998]. This nosology proposed a simplified classification into six major subtypes, for which major and minorclinical criteria were defined, and substituted the previous Roman numeral types by a descriptive nomenclature.

Since 1998, two developments have led to concerns that the EDS nosology needs to be substantially revised. The first development was the clinical and molecular characterization of several new EDS variants, which substantially broadened the molecular basis underlying EDS. The second was the growing concern, in the absence of genetic diagnosis, that the hypermobile type of EDS had an expanded phenotype, may be genetically heterogeneous, and that the diagnostic criteria currently in use were inadequate. Furthermore, there is a dire need for the development of guidelines for management for each type of EDS to allow both the specialist and the generalist to care for affected individuals and their families.

At the First International Meeting on EDS held in Ghent, Belgium, in September 2012, an International Consortium on EDS was formed with the objective to convene a group of clinicians, scientists and lay members of the EDS Community to come to grips with the increasingly difficult aspects of definition and management of EDS types, to define research agenda's, and to continue EDS meetings. Ehlers–Danlos Support UK (EDS UK) and the Ehlers–Danlos National Foundation (EDNF) took up the task to fund this enterprise and develop a framework in which this work could be completed. Five working committees were established, including a (i) Steering Committee (consisting of the chairs of each of the other four committees, a representative from EDS UK and EDNF and a representative from OMIM), and committees on (ii) classical EDS, (iii) hypermobile EDS, (iv) vascular EDS, and (v) rare subtypes of EDS. Since it has become clear that the clinical characteristics of many of the types of EDS extend well beyond the realms of skin and joints, specific working groups (pain, fatigue, cardiovascular, gastrointestinal, orthopedic, oromandibular, physical therapy, Beighton scoring, neurology, allergy/immunology, psychological aspects) engaging specialists from all areas of medicine, were organized to review specific manifestations and formulate recommendations. Each committee and working group were made up of several specialists representing multiple countries and disciplines as well as had representation from the patient support groups worldwide.

The type-specific committees were charged with performing a comprehensive review of the literature and defining the nosology and diagnostic criteria of each EDS type. The working groups also were charged with reviewing the literature with a further focus on management. Each group was also charged in identifying the areas of needed research. These groups met in person or through tele/videoconferencing on a regular basis over a two-year timespan.

The proposed criteria, literature review and recommendations were presented to other professionals working in the field during an International Symposium on the Ehlers–Danlos Syndrome in New York, in May 2016, and manuscripts were subsequently circulated for critical review. The work presented in this issue of the American Journal of Medical Genetics, Seminars in Medical Genetics represents the consensus of the group after critical review of the literature and considering the professional experience of each of the authors.

The Consortium is the beginning of a process that should be ongoing. It will (i) identify a set of participants that can revise the classification on an ongoing basis, (ii) implement both general and type specific registries to help better define the natural history, medical history, and epidemiology of EDS, (iii) be the basis of periodic international scientific meetings to advance recognition and treatment, and (iv) support smaller disorder specific meetings to focus on advances and to define needs for research. This effort will continue forward with the support of the newly formed international charity The Ehlers–Danlos Society, which was established with this mission at its forefront.

ACKNOWLEDGMENTS

We wish to thank all the participants within the Consortium for their tireless long work over the past few years to help bring this effort to the forefront. We also acknowledge the contributions of many professionals and lay persons alike to the recognition and understanding of these disorders. We would also like to thank our generous sponsors including but not limted to the Ehlers-Danlos National Foundation (now the Ehlers-Danlos Society) and the Ehlers-Danlos Support UK.

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ARTICLE

The 2017 International Classification of the Ehlers–Danlos Syndromes

FRANSISKA MALFAIT,* CLAIR FRANCOMANO, PETER BYERS, JOHN BELMONT, BRITTA BERGLUND, JAMES BLACK, LARA BLOOM, JESSICA M. BOWEN, ANGELA F. BRADY, NIGEL P. BURROWS, MARCO CASTORI, HELEN COHEN, MARINA COLOMBI, SERWET DEMIRDAS, JULIE DE BACKER, ANNE DE PAEPE, SYLVIE FOURNEL-GIGLEUX, MICHAEL FRANK, NEETI GHALI, CECILIA GIUNTA, RODNEY GRAHAME, ALAN HAKIM, XAVIER JEUNEMAITRE, DIANA JOHNSON, BIRGIT JUUL-KRISTENSEN, INES KAPFERER-SEEBACHER, HANADI KAZKAZ, TOMOKI KOSHO, MARK E. LAVALLEE, HOWARD LEVY, ROBERTO MENDOZA-LONDONO, MELANIE PEPIN, F. MICHAEL POPE, EYAL REINSTEIN, LEEMA ROBERT, MARIANNE ROHRBACH, LYNN SANDERS, GLENDA J. SOBEY, TIM VAN DAMME, ANTHONY VANDERSTEEN, CAROLINE VAN MOURIK, NICOL VOERMANS, NIGEL WHEELDON, JOHANNES ZSCHOCKE, AND BRAD TINKLE

The Ehlers–Danlos syndromes (EDS) are a clinically and genetically heterogeneous group of heritable connective tissue disorders (HCTDs) characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. Over the past two decades, the Villefranche Nosology, which delineated six subtypes, has been widely used as the standard for clinical diagnosis of EDS. For most of these subtypes, mutations had been identified in collagen-encoding genes, or in genes encoding collagen-modifying enzymes. Since its publication in 1998, a whole spectrum of novel EDS subtypes has been described, and mutations have been identified in an array of novel genes. The International EDS Consortium proposes a revised EDS classification, which recognizes 13 subtypes. For each of the subtypes, we propose a set of clinical criteria that are suggestive for the diagnosis. However, in view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between EDS subtypes, but also with other HCTDs, the definite diagnosis of all EDS subtypes, except for the hypermobile type, relies on molecular confirmation with identification of (a) causative genetic variant(s). We also revised the clinical criteria for hypermobile EDS in order to allow for a better distinction from other joint hypermobility disorders. To satisfy research needs, we also propose a pathogenetic scheme, that regroups EDS subtypes for which the causative proteins function within the same pathway. We hope that the revised International EDS Classification will serve as a new standard for the diagnosis of EDS and will provide a framework for future research purposes.

KEY WORDS: classification; Ehlers–Danlos syndromes; genetic basis; collagen

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INTRODUCTION

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders (HCTDs) characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. The clinical and genetic heterogeneity of this condition has long been recognized. The 1988 "Berlin Nosology" recognized 11 subtypes, defined by Roman numerals, based on

*Correspondence to: Fransiska Malfait, Center for Medical Genetics, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium. E-mail: Fransiska.Malfait@Ugent.be

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clinical findings and mode of inheritance [Beighton et al., 1988]. The subjective interpretation of several semi-quantitative clinical signs, such as joint hypermobility, skin hyperextensibility, tissue fragility and bruising, however, led to clinical uncertainty, diagnostic confusion regarding the type of EDS and the inclusion of phenotypically similar conditions under the broad diagnosis of EDS. With the elucidation of the biochemical and molecular basis of many of these EDS types, a revised classification, the "Villefranche Nosology," was published in 1998 [Beighton et al., 1998]. This classification delineated six subtypes, for which major and minor clinical criteria were defined, and which included the biochemical and molecular basis, when known. The Roman numerals were substituted by a descriptive name, which captured the characteristic manifestations of each type. One underlying assumption was that most, if not all, of these types of EDS were a consequence of alterations in fibrillar collagen genes or in genes that encoded collagen modifiers.

With the elucidation of the biochemical and molecular basis of many of these EDS types, a revised classification, the "Villefranche Nosology," was published in 1998. This classification delineated six subtypes, for which major and minor clinical criteria were defined, and which included the biochemical and molecular basis, when known.

Over the past two decades the Villefranche Nosology has served its purpose and has been widely used as the standard for the clinical diagnosis of EDS, and for clinical research on various aspects of these conditions. However, since its publication, a whole spectrum of novel EDS subtypes has been described, and with the advent of next-generation sequencing (NGS) facilities, mutations have been identified in an array of new genes, that are not always, at first sight, involved in collagen biosynthesis and/or structure. As such, the Villefranche classification is showing its age. Furthermore, in the persistent lack of a genetic defect, there is a dire need for a better clinical definition of the hypermobile type of EDS and its delineation from other hypermobility disorders. Therefore, we undertook a comprehensive review of the EDS-related literature, and, based on our findings, revised the EDS Classification.

THE 2017 INTERNATIONAL CLASSIFICATION FOR THE EHLERS–DANLOS SYNDROMES

The new classification recognizes 13 subtypes, as outlined in Table I. After careful discussions whether to maintain a clinically orientated classification versus a genetic classification, we propose to maintain a clinical classification, in which the previously established descriptive names are maintained, since they are generally accepted and widely used in the medical, scientific and patient community. For newly defined EDS phenotypes, we propose a novel descriptor that captures the characteristic manifestations of the phenotype.

We included all phenotypes that present the basic clinical hallmarks of EDS, that is joint hypermobility, skin hyperextensibility and tissue fragility. In particular, such features should distinguish the redefined hypermobile type (hypermobile EDS, hEDS) from other joint hypermobility disorders (*See also* "*A framework for the classification of Joint Hypermobility and Related Conditions*" by Castori et al., this issue*)*. Some of the phenotypes clinically overlap with other HCTDs, such as "myopathic EDS," which is caused by heterozygous or biallelic mutations in *COL12A1 (*mEDS) and which clinically overlaps with Bethlem Myopathy, and " spondylodysplastic EDS" caused by biallelic *B3GALT6* mutations (spEDS-*B3GALT6*), which clinically overlaps with spondylo-epimetaphyseal dysplasia with joint laxity type I (SEMD-JL1). Since several patients with these conditions are clinically suspected to have a form of EDS, we believe that inclusion in the EDS classification is justified. This is also the case for Brittle Cornea Syndrome. We currently did not retain the filaminA-related periventricular nodular heterotopia (PVNH) with EDS-features within the classification, as the majority of patients primarily present with a neurological phenotype. A minority of patients has varying features of a HCTD, which may include life-threatening aneurysms, however, there is insufficient published data to reliably differentiate and prognosticate PVNH from PVNH-EDS. We recommend that in- or exclusion of these conditions in the EDS classification is reviewed in future years, when more information becomes available.

In line with the 1997 Villefranche Nosology, we propose a set of major and minor clinical criteria for each EDS subtype. A major criterion has high diagnostic specificity because it is present in the vast majority of the affected individuals and/or it is characteristic for the disorder and allows differentiation from other EDS subtypes and/or other HCTDs. A minor criterion is a sign of lesser diagnostic specificity, but its presence supports the diagnosis. For each of the subtypes, we defined minimal major ± minor clinical criteria that are suggestive for the diagnosis of a specific subtype. However, in view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other HCTDs, the *definite diagnosis relies* for all subtypes, except hEDS, *on molecular confirmation* with identification of (a) causative variant(s) in the respective gene. A molecular diagnosis is extremely important for counseling

TABLE I. Clinical Classification of the Ehlers-Danlos Syndromes, Inheritance Pattern, and Genetic Basis

	Clinical EDS subtype	Abbreviation	IP	Genetic basis	Protein
1	Classical EDS	cEDS	AD	Major: *COL5A1*, *COL5A1* Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type V collagen Type I collagen
2	Classical-like EDS	clEDS	AR	*TNXB*	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
4	Vascular EDS	vEDS	AD	Major: *COL3A1* Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type III collagen Type I collagen
5	Hypermobile EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	*COL1A1, COL1A2*	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	*ADAMTS2*	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	*PLOD1* *FKBP14*	LH1 FKBP22
9	Brittle Cornea syndrome	BCS	AR	*ZNF469* *PRDM5*	ZNF469 PRDM5
10	Spondylodysplastic EDS	spEDS	AR	*B4GALT7* *B3GALT6* *SLC39A13*	β4GalT7 β3GalT6 ZIP13
11	Musculocontractural EDS	mcEDS	AR	*CHST14* *DSE*	D4ST1 DSE
12	Myopathic EDS	mEDS	AD or AR	*COL12A1*	Type XII collagen
13	Periodontal EDS	pEDS	AD	*C1R* *C1S*	C1r C1s

IP, inheritance pattern; AD, autosomal dominant; AR, autosomal recessive, NMD, nonsense-mediated mRNA decay.

purposes, as it allows confirmation of the precise diagnosis and gives information on inheritance pattern, recurrence risk and prognosis, and it may guide management. Moreover, it allows for the formation of homogeneous cohorts for research purposes, and future therapeutic interventions. Since the genetic basis of hEDS is still unknown, the diagnosis of this subtype rests on clinical findings, as delineated in the revised criteria for hEDS.

In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other HCTDs, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene.

Molecular diagnostic strategies should rely on NGS technologies, which offer the potential for parallel sequencing of multiple genes. Targeted resequencing of a panel of genes, for example, *COL5A1, COL5A2,*

COL1A1 and *COL1A2*, is a time- and cost-effective approach for the molecular diagnosis of the genetically heterogeneous EDS. When no mutation (or in case of an autosomal recessive condition only one mutation) is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications, for example Multiplex Ligation-dependent Probe Amplification (MLPA), qPCR, or targeted array analysis. Alternatively, or in a second phase, whole exome sequencing (WES) or whole genome sequencing (WGS) and RNA sequencing techniques can be used, with data-analysis initially focusing on the genes of interest for a given EDS subtype. In absence of the identification of a causal mutation, this approach allows to expand the analysis to other genes within the genome. This is particularly interesting in view of the clinical overlap between EDS subtypes and with other HCTDs, and the observation that in an important proportion of EDS-patients, no pathogenic variants are identified in any of the known EDS-associated genes.

The interpretation of variants of uncertain significance (VUS), especially missense variants, should include correlation with the complete clinical phenotype. In keeping with the ACMG guidelines, variants that are supported by some evidence of pathogenicity (e.g., high *in silico* scores, presence in a functionally active domain) can be considered "likely pathogenic." Familial segregation studies may help to interpret the pathogenicity of the variant, and for some genes, ultrastructural, biochemical and/or functional protein assays are available, as outlined below. Individuals harboring such a "likely pathogenic" variant should be followed clinically. Initial counseling for such patients should point out that the true significance of the variant will not be known until these additional tests are completed. In the longer term, assignment of pathogenicity is likely to be facilitated by data from large-scale genome-sequencing projects in patient and control cohorts [Weerakkody et al., 2016].

For patients who fulfill the set of minimal clinical requirements for a specific EDS subtype, but (i) who have no access to molecular confirmation; (ii) in whom one or more VUS is/are identified in one the EDS subtype-specific genes; or (iii) in whom no causative variants are identified in any of the EDS-subtype-specific genes, a "provisional clinical diagnosis" of an EDS subtype can be made, and patients should be followed clinically. However, alternative diagnoses and hence expanded molecular testing should be considered.

PATHOGENETIC MECHANISMS UNDERLYING THE EHLERS–DANLOS SYNDROMES

While the proposed clinically orientated classification aims to be user-friendly for the EDS non-specialist, and offers the affected patients and their family members a "descriptive" diagnosis that he or she can identify with, a genetic classification provides a better framework for research purposes and for the development of future treatment strategies. To satisfy both clinical and research needs, we propose, in addition to the clinical classification, a pathogenetic scheme, that regroups EDS subtypes for which the proteins, coded by the causative genes, function within the same pathway, and which are likely to have shared pathogenic mechanisms, based on current knowledge (Table II). A similar regrouping of osteogenesis imperfecta (OI) subtypes by gene function was proposed and is widely adapted in clinical and in research settings.

CLASSIFICATION OF EDS

Classical EDS (cEDS)

- Inheritance
  Autosomal dominant
- Major criteria
  1. Skin hyperextensibility[1] and atrophic scarring[2]
  2. Generalized joint hypermobility (GJH)[3]
- Minor criteria
  1. Easy bruising[4]
  2. Soft, doughy skin[5]
  3. Skin fragility (or traumatic splitting)
  4. Molluscoid pseudotumors[6]
  5. Subcutaneous spheroids[7]
  6. Hernia (or history thereof)
  7. Epicanthal folds[8]
  8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
  9. Family history of a first degree relative who meets clinical criteria

[1]Skin extensibility should be measured by pinching and lifting the cutaneous and subcutaneous layers of the skin on the volar surface at the middle of the non-dominant forearm as described in Remvig et al. [2009]. Skin is hyperextensible if it can be stretched over a standardized cut-off in three of the following areas: 1.5 cm for the distal part of the forearms and the dorsum of the hands; 3 cm for neck, elbow, and knees.

[2]Abnormal scarring can range in severity. Most patients have extensive atrophic scars at a number of sites (Fig. 1). These can sometimes be haemosiderotic. A minority of patients are more mildly affected.

[3]GJH is evaluated according to the Beighton score; a Beighton score of ≥ 5 is considered positive for the presence of GJH (Fig. 2). Since laxity decreases with age, patients with a Beighton score $<5/9$ may be considered positive based on their historical observations (see "five-point questionnaire (5PQ)" (Table III).

[4]Easy bruising can occur anywhere on the body, including unusual sites. The pretibial area often remains stained with hemosiderin from previous bruises.

[5]Subjective abnormality of the skin texture is appreciable by touching the skin.

[6]Molluscoid pseudotumors are fleshy lesions associated with scars, found over pressure points (e.g., elbow, fingers).

[7]Subcutaneous spheroids (Fig. 1F) are small spherical hard bodies, frequently mobile, and palpable on the forearms and shins. Spheroids may be calcified and detectable radiologically.

[8]Epicanthal folds are often seen in childhood but may also be seen in adults.

TABLE II. Regrouping of the Ehlers-Danlos Syndromes According to Underlying Genetic and Pathogenetic Mechanisms

Former nomenclature and other names	Villefranche nomenclature	New Nomenclature	OMIM condition	Locus	Gene	OMIM gene	Protein	IP
GROUP A: Disorders of collagen primary structure and collagen processing								
Gravis/EDS I	Classical type	Classical EDS (cEDS)	130000	9q34.3	*COL5A1*	120215	Type V collagen	AD
Mitis/EDS II			130010	2q32.2	*COL5A2*	120190	Type V collagen	
				17q21.33	*COL1A1*	120150	Type I collagen (p. Arg312Cys)	
Arterial-Ecchymotic EDS	Vascular type	Vascular EDS (vEDS)	130050	2q32.2	*COL3A1*	120180	Type III collagen	AD
EDS IV				17q21.33	*COL1A1*	120150	Type I collagen p.(Arg312Cys) p.(Arg574Cys) p.Arg1093Cys)	
Arthrochalasis Multiplex Congenita	Arthrochalasia type	Arthrochalasia EDS (aEDS)	130060	17q21.33	*COL1A1*	120150	Type I collagen	AD
EDS VIIA			130060	7q21.3	*COL1A2*	120160		
EDS VIIB								
Human dermatosparaxis EDS VIIC	Dermatosparaxis type	Dermatosparaxis EDS (dEDS)	225410	5q35.3	*ADAMTS2*	604539	ADAMTS-2	AR
Cardiac-valvular EDS	/	Cardiac-valvular EDS (cvEDS)	225320	7q21.3	*COL1A2*	120160	Type I collagen Total absence of pro α2(I) collagen chains	AR
GROUP B: Disorders of collagen folding and collagen cross-linking								
Ocular-Scoliotic EDS	Kyphoscoliosis type	Kyphoscoliotic EDS (kEDS-*PLOD1*)	225400	1p36.22	*PLOD1*	153454	Lysylhydroxylase 1	AR
EDS VI								
EDS VIA								
/	/	Kyphoscoliotic EDS (kEDS-*FKBP14*)	614557	7p14.3	*FKBP14*	614505	FKBP22	AR
GROUP C: Disorders of structure and function of myomatrix, the interface between muscle and ECM								
		Classical-like EDS (clEDS)	606408	6p21.33-p21.32	*TNXB*	600985	Tenascin XB	AR
/	/	Myopathic EDS (mEDS)	616471	6q13-q14	*COL12A1*	120320	Collagen XII	AD/AR
GROUP D: Disorders of glycosaminoglycan biosynthesis								
EDS Progeroid	EDS Progeroid type	Spondylodysplastic EDS (spEDS-*B4GALT7*)	130070	5q35.3	*B4GALT7*	604327	Galactosyltransferase I β4GalT7	AR
	EDS Progeroid type 1							
EDS Progeroid type 2	β3GalT6-deficient EDS	Spondylodysplastic EDS (spEDS-*B3GALT6*)	615349	1p36.33	*B3GALT6*	615291	Galactosyltransferase II β3GalT6	AR
β3GalT6-deficient EDS								
Adducted Thumb Clubfoot syndrome		Musculocontractural EDS (mcEDS-*CHST14*)	601776	15q15.1	*CHST14*	608429	Dermatan-4 sulfotransferase-1	AR
EDS Kosho type		Musculocontractural EDS (mcEDS-*DSE*)	615539	6q22.1	*DSE*	605942	Dermatan sulfate epimerase-1	AR
EDS Musculocontractural type								
D4ST1-deficient EDS								

TABLE II. (*Continued*)

Former nomenclature and other names	Villefranche nomenclature	New Nomenclature	OMIM condition	Locus	Gene	OMIM gene	Protein	IP
GROUP E: Disorders of complement pathway								
EDSVIII	EDS periodontitis	Periodontal EDS (pEDS)	130080	12p13.31	*C1R*	613785	C1r	AD
					C1S	120580	C1s	
GROUP F: Disorders of intracellular processes[a]								
Spondylocheirodysplastic EDS		Spondylodysplastic EDS (spEDS-*SLC39A13*)	612350	11p11.2	*SLC39A13*	608735	ZIP13	AR
Brittle Cornea Syndrome		Brittle Cornea Syndrome (BCS)	229200	16q24	*ZNF469*	612078	ZNF469	AR
			614170	4q27	*PRDM5*	614161	PRDM5	AR
Unresolved forms of EDS								
Hypermobile EDS III	Hypermobility type	Hypermobile EDS (hEDS)	130020	?	?		?	AD
Conditions not included in EDS spectrum anymore								
Occipital horn syndrome	/	/	304150	Xq21.1	*ATP7A*	300011	ATP7A	X-L
Fibronectin-deficient (EDS X)	/	/						AD
Familial Articular hypermobility (EDS XI)	/	/						AD
X-linked EDS with muscle hematoma (EDSV)	/	/						X-L
Filamin A related EDS with periventricular nodular heterotopia	/	/	300049	Xq28	*FLNA*	300017	Filamin A	X-L

IP, inheritance pattern; AD, autosomal dominant; AR, autosomal recessive; X-L, X-linked recessive.

[a]For EDS subtypes implemented in this category, the underlying pathophysiological mechanism is not readily understood, and classification within this subgroup is provisionary, until further functional information becomes available.

- Minimal criteria suggestive for cEDS:
  - Major criterion (1): skin hyperextensibility and atrophic scarring

  Plus
  - Either major criterion (2): GJH
  - And/or: at least three minor criteria

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis

  More than 90% of cEDS patients harbor a heterozygous mutation in one of the genes encoding type V collagen (*COL5A1* and *COL5A2*) [Symoens et al., 2012; Ritelli et al., 2013; Zoppi et al., 2015] (*see also "Ehlers–Danlos Syndrome, Classical Type," by Bowen et al., this issue*). Rarely, specific mutations in the genes encoding type I collagen can be associated with a cEDS-phenotype. These include the heterozygous *COL1A1* c.934C>T, p.(Arg312Cys) substitution [Malfait et al., 2007a]. Patients harboring this mutation are particularly at risk for vascular rupture, whereas patients harboring other *COL1A1* arginine-to-cysteine substitutions are associated with other specific phenotypes (*see also "Ehlers–Danlos Syndromes, Rare Types," by Brady et al., this issue*). Sodium Dodecyl Sulfate PolyAcrylamide Gel Electrophoresis (SDS PAGE) demonstrates the migration of an extra band in the cell fraction, and sometimes also in the medium fraction. This band, which disappears after reduction with β-mercaptoethanol, consists of disulfide-bonded α chains [Malfait et al., 2007b]. Furthermore, biallelic *COL1A2* mutations that lead to complete absence of the proα2(I) collagen chain may also present with a classical EDS-like phenotype, but these patients are at risk for developing severe cardiac-valvular problems. Moreover, inheritance of this condition is autosomal recessive (*see also "Cardiac-valvular EDS," below, and "Ehlers–Danlos Syndromes, Rare Types," by Brady et al., this issue*). SDS PAGE demonstrates complete absence of (pro-) α2 chains of type I (pro) collagen extracted from dermis [Schwarze et al., 2004; Malfait et al., 2006].
- Verification of clinical diagnosis

  Molecular screening by means of targeted resequencing of a gene panel

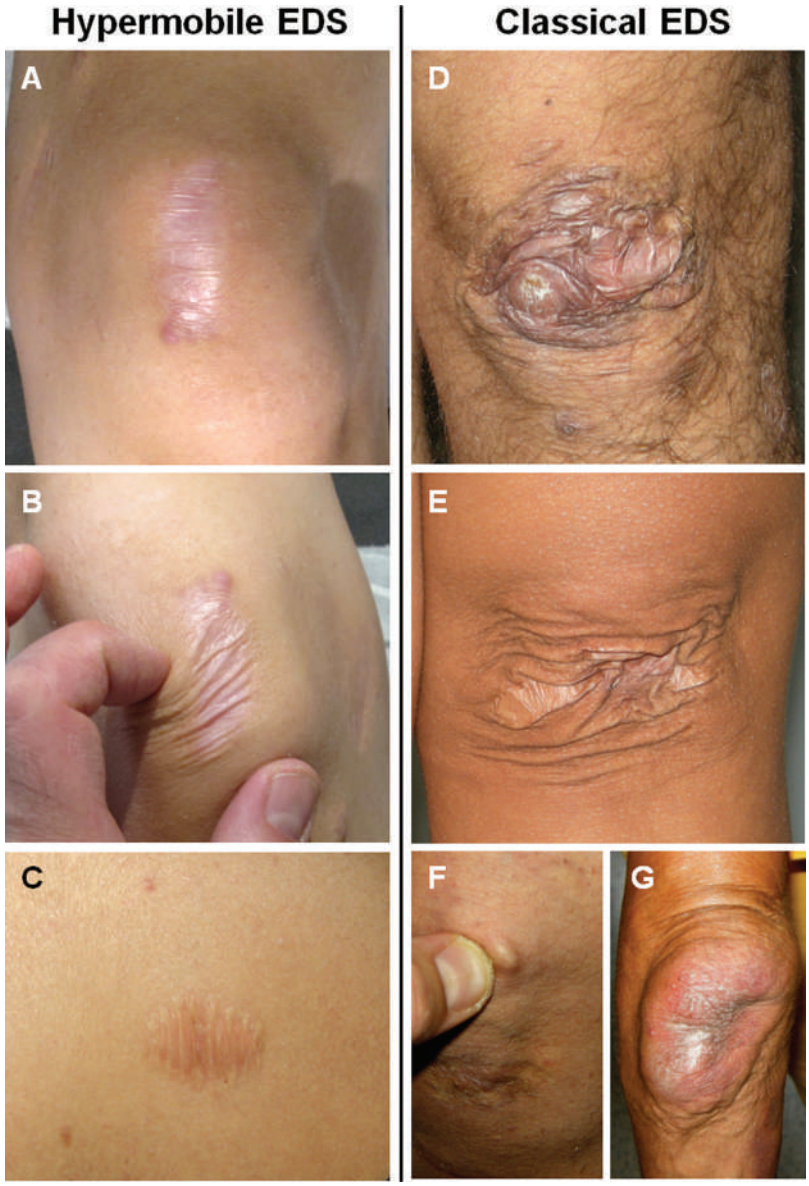

Figure 1. The atrophic skin/widened scars seen in hypermobile EDS as compared to classic EDS. Hypermobile EDS. Post-traumatic, atrophic, and widened scar in a young man (**A**). Skin stretching between the examiner's fingers discloses mild atrophy of the underlying dermis (**B**). A further atrophic and widened scar due to wound healing delay after excision of a melanocytic nevus in a young woman (**C**). Classical EDS. Typical papyraceous and hemosideric scar after repetitive wound re-opening and molluscoid pseudotumor in an adult man (**D**). Papyraceous, but not hemosideric scar and acquired cutis laxa in a young woman (**E**). Subcutaneous spheroid (**F**). Huge molluscoid pseudotumor of the elbow (**G**).

More than 90% of cEDS patients harbor a heterozygous mutation in one of the genes encoding type V collagen (COL5A1 and COL5A2).

that includes at least the *COL5A1*, *COL5A2, COL1A1,* and *COL1A2* genes, or by WES or WGS, is indicated. When no mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

In case of unavailability of genetic testing, transmission electron microscopy (TEM) findings of collagen flowers on skin biopsy can support the clinical diagnosis, but cannot confirm it.

Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques; however, alternative diagnoses should be considered in the absence of (a) *COL5A1*, *COL5A2, COL1A1,* or *COL1A2* mutation(s).

Classical-Like EDS (clEDS)

- Inheritance
  Autosomal Recessive
- Major criteria
  1. Skin hyperextensibility,[9] with velvety skin texture and absence of atrophic scarring
  2. GJH[9] with or without recurrent dislocations (most commonly shoulder and ankle)
  3. Easy bruisable skin/spontaneous ecchymoses
- Minor criteria
  1. Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules
  2. Edema in the legs in absence of cardiac failure
  3. Mild proximal and distal muscle weakness
  4. Axonal polyneuropathy
  5. Atrophy of muscles in hands and feet
  6. Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly
  7. Vaginal/uterus/rectal prolapse
- Minimal criteria suggestive for clEDS:
  – All three major criteria AND a family history compatible with autosomal recessive transmission.

  Confirmatory molecular testing is obligatory to reach a final diagnosis.

[9]For definitions of GJH and skin hyperextensibility, see criteria for "Classical EDS."

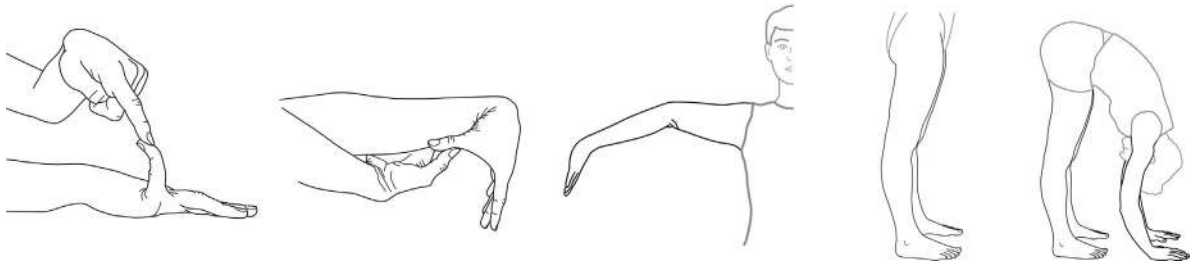

Figure 2. The Beighton scoring system. Each joint is measured using a goniometer and each side is scored independently as outlined [Juul-Kristensen et al., 2007]. (**A**) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive, scoring 1 point. (**B**) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm it is considered positive scoring 1 point. (**C**) With the arms outstretched to the side and hand supine, if the elbow extends more than 10°, it is considered positive scoring 1 point. (**D**) While standing, with knees locked in genu recurvatum, if the knee extends more than 10°, it is considered positive scoring 1 point. (**E**) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet, it is considered positive scoring 1 point. The total possible score is 9. *Figure courtesy of Dr. Juul-Kirstensen.*

- Molecular basis
  clEDS is caused by a complete lack of Tenascin XB (TNX) due to biallelic *TNXB* mutations, that lead to nonsense-mediated mRNA decay, or biallelic deletion of *TNXB*. As a result the TNX protein is completely absent. *TNXB* is the only gene associated with clEDS.
- Verification of diagnosis
  Molecular analysis of the *TNXB* gene should be used as the standard confirmatory test. Difficulties in DNA testing are related to the presence of a pseudogene (*TNXA*), which is more than 97% identical to the 3′ end of *TNXB* (exons 32–44). With the only exception of exon 35, which partially shows a *TNXB*-specific sequence, exon and intron sequences in this region are identical or almost identical in both the gene and the pseudogene. This has implications both for sequencing and deletion/duplication analysis.
  For sequence analysis of *TNXB*, two approaches are recommended.
  1. Sanger sequencing of the entire *TNXB* gene.
  2. Next-generation sequencing of *TNXB* + Sanger sequencing of the pseudogene region.

Both approaches will require sequence analysis of the pseudogene-homolog region in a few large multi-exons amplicons.

If no or only one causative mutation is identified by classic sequencing, additional methods that allow detection of large deletions/duplications should be added. So far no method is able to specifically detect *TNXB* CNVs in the highly homologous exons 32–34 and 36–44. CNV analysis of exon 35 is currently used to detect deletions in this region, including the 30 kb deletion previously described by Schalkwijk et al. [2001].

TNX, a large 450 kDa extracellular matrix glycoprotein, secreted by skin fibroblasts, can be detected with antibodies directed against its carboxyterminal end. Patients with clEDS are completely depleted of the TNX protein in serum. We refer to the paper of Schalkwijk et al. [2001] for more detailed information concerning the used method to detect TNX.

Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques; however, alternative diagnoses should be considered in the absence of a *TNXB* mutation.

Cardiac-Valvular EDS (cvEDS)

- Inheritance
  Autosomal recessive
- Major criteria
  1. Severe progressive cardiac-valvular problems (aortic valve, mitral valve)[10]
  2. Skin involvement: skin hyperextensibility,[11] atrophic scars, thin skin, easy bruising
  3. Joint hypermobility (generalized or restricted to small joints)
- Minor criteria
  1. Inguinal hernia
  2. Pectus deformity (especially excavatum)
  3. Joint dislocations
  4. Foot deformities: pes planus, pes planovalgus, hallux valgus
- Minimal criteria suggestive for cvEDS:
  – Major Criterion (1): severe progressive cardiac-valvular problems
  – AND a family history compatible with autosomal recessive inheritance
  Plus
  – Either: one other major criterion
  – And/or: at least two minor criteria
  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis
  cvEDS is caused by a complete lack of the proα2-chain of type I collagen due to biallelic *COL1A2* mutations, that

[10]The cardiac-valvular problems were reported in all affected adult individuals, but were absent in the two reported children (both <10 years of age).

[11]For definition of skin hyperextensibility, see criteria for "Classical EDS."

lead to nonsense-mediated mRNA decay. *COL1A2* is the only gene associated with cvEDS.

- Verification of diagnosis
  Molecular screening by Sanger sequencing of *COL1A2*, or targeted resequencing of a gene panel that includes *COL1A2* is indicated. When no mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

  In case of unavailability of genetic testing, SDS PAGE demonstrates total absence of (pro-) α2(I) collagen chains.

  Whereas absence of these confirmatory biochemical findings allows to exclude the diagnosis of cvEDS, absence of confirmatory genetic findings does not exclude the diagnosis, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques.

Vascular EDS (vEDS)

- Inheritance
  Autosomal dominant
- Major criteria
  1. Family history of vEDS with documented causative variant in *COL3A1*
  2. Arterial rupture at a young age
  3. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
  4. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
  5. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma
- Minor criteria
  1. Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
  2. Thin, translucent skin with increased venous visibility
  3. Characteristic facial appearance
  4. Spontaneous pneumothorax
  5. Acrogeria
  6. Talipes equinovarus
  7. Congenital hip dislocation
  8. Hypermobility of small joints
  9. Tendon and muscle rupture
  10. Keratoconus
  11. Gingival recession and gingival fragility
  12. Early onset varicose veins (under age 30 and nulliparous if female)
- Minimal criteria suggestive for vEDS:
  A family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS should all lead to diagnostic studies to determine if the individual has vEDS. Testing for vEDS should also be considered in the presence of a combination of the other "minor" clinical features listed above.

A family history of the disorder, arterial rupture, or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS should all lead to diagnostic studies to determine if the individual has vEDS.

Even for experienced clinicians the clinical diagnosis of vEDS may be difficult. Because of implications for treatment, natural history, and recurrence risk, the diagnosis of vEDS rests on the identification of a causative variant in one allele of *COL3A1*.

- Molecular basis
  Patients with vEDS typically harbor a heterozygous mutation in the *COL3A1* gene, encoding type III collagen, with the rare exception of specific heterozygous arginine-to-cysteine substitution mutations in *COL1A1* (c.934C>T, p.Arg312Cys; c.1720C>T, p.Arg574Cys and c.3277C>T, p.Arg1093Cys) that are also associated with vascular fragility, mimicking *COL3A1*-vEDS [Malfait et al., 2007b], (*see also "Ehlers–Danlos Syndrome, Rare Types," by Brady et al., this issue*).

  In very rare instances, biallelic pathogenic variants in *COL3A1* may be identified.
- Verification of clinical diagnosis
  Molecular screening by Sanger sequencing of *COL3A1*, or targeted resequencing of a gene panel that includes *COL3A1* and *COL1A1* (the latter to identify the above-listed arginine-to-cysteine substitution mutations) is indicated. When no mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

  Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques; however, alternative diagnoses should be considered in the absence of a *COL3A1* or *COL1A1* mutation.

Hypermobile EDS (hEDS)

- Inheritance
  Autosomal dominant
- Molecular basis
  Unknown
- Clinical diagnosis
  The diagnosis of hEDS remains clinical as there is yet no reliable or appreciable genetic etiology to test for in the vast majority of patients. This, in part, likely reflects genetic heterogeneity. In addition, the syndromic presentation may vary according to age and gender. There is also a clinical spectrum ranging from asymptomatic joint hypermobility, through "non-syndromic" hypermobility with secondary manifestations, to hEDS (*see "A Framework for the Classification of Joint Hypermobility and Related Conditions" by Castori et al., this issue*). A diagnosis of hEDS should be assigned only in those who meet all of the criteria described below, which should help to reduce heterogeneity and facilitate efforts to discover the

underlying genetic cause(s) of the syndrome which, in turn, may help clinical management. Since there is currently no "gold standard" laboratory test to confirm or refute the diagnosis, we anticipate that future research will lead to further revisions of these clinical criteria necessitating regular review of the relevant medical literature. It is also imperative, as this is a clinical diagnosis, to be relatively confident that the patient's presentation does not represent one of the many other disorders of connective tissue. Therefore, the clinician should be experienced at the physical examination described herein as well the historical and clinical presentation of other HCTD and their diagnoses.

The clinical diagnosis of hEDS needs the simultaneous presence of criteria 1 AND 2 AND 3. Specific annotations and further explanations (i.e., footnotes [FN]) are reported for select features.

Criterion 1: Generalized Joint Hypermobility (GJH)

To date, the Beighton score (Fig. 2) is the most recognized tool for assessing GJH (*see "Measurement Properties of Clinical Assessment Methods for Classifying Generalized Joint Hypermobility—a Systematic Review" by Juul-Kristensen et al., this issue*). According to the original definition of the Beighton score and its subsequent incorporation into the Villefranche nosology for the hEDS, the cut-off for the definition of GJH is $\geq$5 points out of 9. However, joint range of motion decreases with age [Soucie et al., 2011; McKay et al., 2016] and there is an inverse relationship between age at ascertainment and the Beighton score [Remvig et al., 2007], so the cut-off of five may prompt an over-diagnosis in children and an under-diagnosis among adults and elders. As GJH is considered a prerequisite for the diagnosis of hEDS and GJH is a constitutional trait strongly influenced by acquired and inherited conditions (e.g., sex, age, past-traumas, co-morbidities, etc.), some minor adaptations to the cut-off of five should be considered for the diagnosis of hEDS. The Committee on behalf of the International Consortium on the Ehlers–Danlos Syndromes proposes $\geq$6 for pre-pubertal children and adolescents, $\geq$5 for pubertal men and women up to the age of 50, and $\geq$4 for those >50 years of age for hEDS. This may vary from other types of EDS but such types have confirmatory testing.

According to the original definition of the Beighton score and its subsequent incorporation into the Villefranche nosology for the hEDS, the cut-off for the definition of GJH is $\geq$5 points out of 9. However, joint range of motion decreases with age and there is an inverse relationship between age at ascertainment and the Beighton score, so the cut-off of five may prompt an over-diagnosis in children and an under-diagnosis among adults and elders.

In individuals with acquired joint limitations (past surgery, wheelchair, amputations, etc.) affecting the Beighton score calculation, the assessment of GJH may include historical information using the five-point questionnaire (5PQ) (Table III) [Hakim and Grahame, 2003; Mulvey et al., 2013], although this has not been validated in children (*see "Measurement Properties of Clinical Assessment Methods for Classifying Generalized Joint Hypermobility—a Systematic Review" by Juul-Kristensen et al., this issue*). If the Beighton score is 1 point below the age- and sex-specific cut-off AND the 5PQ is 'positive' (= at least two positive items), then a diagnosis of GJH can be made.

For patients with lower Beighton scores, the assessment of other joints is often considered, including temporomandibular joint, shoulder, hip, foot, wrist, ankle, and other digits. Increased ankle and wrist dorsiflexion, increased internal and external hip rotation, and pes planus have been correlated with Beighton score [Smits-Engelsman et al., 2011] However, similar concerns about age, gender, and environmental influences as well as measurement methodology and reliable cut-off values, limit such analysis as too subjective in the determination of GJH. Therefore, the use of such measurements cannot be factored into a diagnostic algorithm at this time. Obviously, more information regarding the assessment methodology (ies) in the determination of GJH is needed (*see "Measurement Properties of Clinical Assessment Methods for Classifying Generalized Joint Hypermobility—a*

TABLE III. The Five-Point Questionnaire. Adapted From [Grahame and Hakim, 2003]

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?

A "yes" answer to two or more questions suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity

Systematic Review" by Juul-Kristensen et al., this issue).

Lastly, the use of the Beighton scoring system is meant to be a diagnostic screening method. It is understood that gender, age, ethnicity, strength training, stretching exercises, and warming up all affect JH and therefore GJH. However, muscular overcompensation, injury and surgery can cause either joint hypermobility or hypomobility. Muscular overcompensation, such as tight hamstrings, can affect the degree of knee extension and lumbar flexion negatively, while stretching exercises and warming up affects positively. Injury can destabilize a joint or alternatively reduce movement. Surgery can similarly affect a joint. For example, a person with lumbar spine fusion may not be able to have a "positive" forward spinal flexion for Beighton scoring. There is a temptation by clinicians to consider this a positive score but without current ability or historical demonstration, it should be scored negative. An argument could be made to invalidate spinal flexion scoring thus the total score would be eight and not nine. However, it is not known if the numerator (determinant of GJH) should be adjusted in this situation. In theory, this makes sense but what is the appropriate cut-off? Therefore, like any clinical tool, there is some subjectivity and this is a guideline not to replace the judgment of the experienced clinician; however, standardization of performance procedures is required. One may want to label such persons as having "probable GJH" but at the present time, "probable GJH" should not be considered an alternative of the objectively diagnosed GJH (as described above) into the diagnostic flow-chart of hEDS. Stronger scrutiny of phenocopies should be contemplated.

Criterion 2: Two or More Among the Following Features (A–C) MUST Be Present (for Example: A and B; A and C; B and C; A and B and C)

Feature A: systemic manifestations of a more generalized connective tissue disorder (a total of five must be present)[12]

1. Unusually soft or velvety skin[13]
2. Mild skin hyperextensibility[14]
3. Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or prepubertal women without a history of significant gain or loss of body fat or weight
4. Bilateral piezogenic papules of the heel[15]
5. Recurrent or multiple abdominal hernia(s) (e.g., umbilical, inguinal, crural)
6. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS[16]
7. Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
8. Dental crowding and high or narrow palate[17]
9. Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides
10. Arm span-to-height ≥ 1.05
11. Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria[18]
12. Aortic root dilatation with Z-score $> +2$

Feature B: positive family history, with one or more first degree relatives

[12]If marfanoid features are present, consider other conditions such as: Marfan syndrome, Loeys–Dietz syndrome, congenital contractural arachnodactyly, Shprintzen–Goldberg syndrome, Stickler syndrome, Homocystinuria, multiple endocrine neoplasia type 2B, and the familial thoracic aortic aneurysmal disorders [Pyeritz and Loeys, 2012]. Molecular testing for many of these conditions is clinically available.

[13]While skin softness and texture remain subjective, it is often very notable in some individuals and useful when present but not quantifiable; we therefore recommend a high threshold for positivity.

[14]Skin extensibility as measured by pinching and lifting the cutaneous and subcutaneous layers of the skin on the volar surface at the middle of the non-dominant forearm as described in Remvig et al. [2009]. Skin extensibility of >1.5 cm is considered the upper end of normal. It is likely that the hyperextensibility of the skin in hEDS overlaps significantly with that of "normal" skin. Therefore, extensibility of more than 1.5 cm is "positive." If extensibility >2.0 cm is present especially in combination with other cutaneous features, such as papyraceous scars, molluscoid pseudotumors and/or subcutaneous spheroids, consider other EDS types as possible alternative diagnoses (mainly cEDS and classical-like EDS).

[15]Piezogenic papules are herniations of subcutaneous fat often demonstrable in the heel upon standing (Fig. 3). It is considered uncommon in children but can be found in adults with history of prolonged standing (occupational), marathon runners, or weightlifters [Poppe and Hamm, 2013] However, in a sex- and age-matched study of 29 Dutch EDS patients, piezogenic papules were found in 34.5% but none in the control group [Kahana et al., 1987].

[16]Atrophic scarring is defined as scars from linear traumatic lacerations or single-surgery that are unusually shallow (i.e., thin and sunken) and/or wider than the original wound due to impaired repair and subsequent dermal hypotrophy. Atrophic scars as the result of multiple incisions, wound infections, or inflammatory conditions (such as viral infections, cystic acne, etc.) are not to be considered. Elliptical incisions (e.g., for removal of nevi) may be difficult to assess without knowing the size of the original wound. True skin fragility, such as the propensity to have an open wound due to trivial trauma, is not a typical feature of hEDS. Atrophic scarring in hEDS is mildly to moderately different from that usually considered typical of cEDS (Fig. 1).

[17]Includes history of dental crowding or orthodontic intervention(s) to correct such problems. Both conditions must be positive to meet this criterion.

[18]Some studies show no increase in the frequency of clinically significant MVP [Dolan et al., 1997; McDonnell et al., 2006; Atzinger et al., 2011] and others show an MVP frequency of 28–67% among hEDS patients [Camerota et al., 2014; Kozanoglu et al., 2016]. This feature is included in the diagnostic criteria because it can be a marker of connective tissue laxity, but is usually not clinically significant in patients with hEDS.

independently meeting the current diagnostic criteria for hEDS.

Feature C: musculoskeletal complications (must have at least one):

1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
2. Chronic, widespread pain for ≥3 months
3. Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b)[19]
   a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
   b. Medical confirmation of joint instability at two or more sites not related to trauma[20]

Criterion 3: All the Following Prerequisites MUST Be Met

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (e.g., lupus, rheumatoid arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted towards a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g., myopathic EDS, Bethlem myopathy), other HCTD (e.g., other types of EDS, Loeys–Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g., OI). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

- General comment

Many other features are described in hEDS but most are not sufficiently specific nor sensitive at the moment to be included in formal diagnostic criteria (*see "Hypermobile Ehlers–Danlos Syndrome (a.k.a. Ehlers–Danlos Syndrome Type III and Ehlers–Danlos syndrome hypermobility type): Clinical Description, and Natural History" by Tinkle et al., this issue*). These include but are not limited to: sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastrointestinal disorders, dysautonomia, anxiety, and depression. These other systemic manifestations may be more debilitating than the joint symptoms, often impair functionality and quality of life, and should always be determined during clinical encounters. While they are not part of the diagnostic criteria, the presence of such systemic manifestations may prompt consideration of hEDS in the differential diagnosis. Future research will need to focus on such symptoms to validate any association with hEDS, describe sub-groups or sub-phenotypes, and be focused on evidence-based management of the symptoms in the context of hEDS.

Arthrochalasia EDS (aEDS)

- Inheritance
  Autosomal dominant
- Major criteria
  1. Congenital bilateral hip dislocation[21]
  2. Severe GJH, with multiple dislocations/subluxations[22]
  3. Skin hyperextensibility[22]
- Minor criteria
  1. Muscle hypotonia
  2. Kyphoscoliosis
  3. Radiologically mild osteopenia
  4. Tissue fragility, including atrophic scars
  5. Easy bruisable skin
- Minimal criteria suggestive for aEDS:
  – Major criterion (1): Congenital bilateral hip dislocation

  Plus
  – Either major criterion (3): skin hyperextensibility
  – Or major criterion (2): severe GJH with multiple dislocations/subluxations and at least two other minor criteria

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis
  aEDS is caused by heterozygous mutations in either *COL1A1* or *COL1A2*, that cause entire or partial loss of exon 6 of the respective gene. No other genes are associated with aEDS.
- Verification of diagnosis
  Molecular screening by Sanger sequencing of *COL1A1* and *COL1A2*, or targeted resequencing of a gene panel that includes these genes, is indicated. When no mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

  In case of unavailability of genetic testing, SDS PAGE of the pepsin-digested collagen in the medium or cell layer of cultured dermal fibroblasts demonstrates the presence of a mutant pNα1(I) or pNα2(I) chain (precursor procollagen chains in which the carboxy (C)-but not the amino (N)-propetide is cleaved off).

  TEM of skin specimens shows loosely and randomly organized collagen fibrils with a smaller and more variable diameter, and an irregular outline. These findings may support the diagnosis, but cannot confirm it.

  Absence of a causative mutation in *COL1A1* or *COL1A2* that leads to

[19]"Dislocation" is defined as displacement of a bone out of the joint socket (or out of normal position in the case of sesamoid bones such as the patella), sufficiently severe to limit motion of the joint and requiring manual reduction.

[20]Refers to sites regardless of laterality. For example, right and left patellar instability would count as two. Instability should be evaluated and determined by a qualified practitioner using recommended guidelines.

[21]All reported aEDS patients had congenital bilateral hip dislocation. One unreported molecularly proven aEDS patient is known to have had congenital unilateral hip dislocation [Byers et al., personal communication].

[22]For definition of GJH, see criteria for "Classical EDS."

complete or partial deletion of the exon 6 of either gene excludes the diagnosis of aEDS.

Dermatosparaxis EDS (dEDS)

- Inheritance
  Autosomal recessive
- Major criteria:
  1. Extreme skin fragility with congenital or postnatal skin tears
  2. Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood[23]
  3. Redundant, almost lax skin, with excessive skin folds at the wrists and ankles
  4. Increased palmar wrinkling
  5. Severe bruisability with a risk of subcutaneous hematomas and haemorrhage
  6. Umbilical hernia
  7. Postnatal growth retardation
  8. Short limbs, hand and feet
  9. Perinatal complications due to connective tissue fragility[24]
- Minor criteria
  1. Soft and doughy skin texture
  2. Skin hyperextensibility
  3. Atrophic scars
  4. GJH[25]
  5. Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse)
  6. Delayed motor development[26]
  7. Osteopenia
  8. Hirsutism
  9. Tooth abnormalities
  10. Refractive errors (myopia, astigmatism)
  11. Strabismus
- Minimal criteria suggestive for dEDS:
  – Major criterion (1): extreme skin fragility
  – AND major criterion (2): characteristic craniofacial features

  Plus
  – Either: one other major criterion
  – And/or: three minor criteria

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis
  dEDS is caused by biallelic mutations in *ADAMTS2*, the gene encoding ADAMTS-2, the main procollagen I N-proteinase. It is the only gene associated with dEDS.
- Verification of diagnosis
  Molecular screening by Sanger sequencing of targeted resequencing of a gene panel that includes *ADAMTS2* is indicated. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

  In case of unavailability of genetic testing, SDS PAGE demonstrates presence of pNα1(I) and pNα2(I) chains of type I procollagen extracted from dermis in the presence of protease inhibitors or detected in fibroblast cultures.

  TEM shows collagen fibrils in affected skin specimens with a hieroglyphic pattern. These ultrastructural findings are usually typical but may be almost indistinguishable from those observed in aEDS. As such, they are not sufficient to confirm the diagnosis.

  Absence of these confirmatory findings does not exclude the diagnosis of dEDS, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques; however, alternative diagnoses should be considered in the absence of *ADAMTS2* mutations.

Kyphoscoliotic (kEDS)

- Inheritance
  Autosomal recessive
- Major criteria
  1. Congenital muscle hypotonia[27]
  2. Congenital or early onset kyphoscoliosis (progressive or non-progressive)[28]
  3. GJH[29] with dislocations/subluxations (shoulders, hips, and knees in particular)
- Minor criteria:
  1. Skin hyperextensibility[29]
  2. Easy bruisable skin
  3. Rupture/aneurysm of a medium-sized artery
  4. Osteopenia/osteoporosis
  5. Blue sclerae
  6. Hernia (umbilical or inguinal)
  7. Pectus deformity
  8. Marfanoid habitus
  9. Talipes equinovarus
  10. Refractive errors (myopia, hypermetropia)
- Gene-specific minor criteria
  1. *PLOD1*
     1. Skin fragility (easy bruising, friable skin, poor wound healing, widened atrophic scarring)
     2 Scleral and ocular fragility/rupture[30]
     3. Microcornea
     4. Facial dysmorphology[31]
  2. *FKBP14*
     1. Congenital hearing impairment (sensorineural, conductive, or mixed)
     2. Follicular hyperkeratosis
     3. Muscle atrophy
     4. Bladder diverticula

[23]Craniofacial features include: prominent and protuberant eyes with puffy, oedematous eyelids and excessive periorbital skin, epicanthal folds, downslanting palpebral fissures, blue sclerae, large fontanels and/or wide cranial sutures, delayed closure of fontanels and hypoplastic chin.

[24]Reported perinatal complications due to connective tissue fragility include: congenital skull fractures, intracerebral hemorrhage, friable umbilical cord, congenital skin tears, neonatal pneumothorax.

[25]For definition of GJH, see criteria for "Classical EDS."

[26]Most patients identified to date display a severe phenotype, recognizable from birth or first months of life. Milder forms of the condition have recently been described.

[27]Muscular hypotonia can be very pronounced and lead to delayed gross motor development. This condition should be considered in the initial differential diagnosis of a floppy infant. Neuromuscular work-up is however normal.

[28]Kyphoscoliosis is usually present at birth or develops in infancy. In patients with biallelic *PLOD1* mutations, it may be absent throughout adulthood.

[29]For definitions of GJH and skin hyperextensibility, see criteria for "Classical EDS."

[30]Scleral and ocular fragility were removed from the major clinical criteria of kEDS-*PLOD1*, as rupture of the eye globe following minimal trauma has only been reported in five individuals, including one patient with both eyes affected.

[31]Facial dysmorphic features include: low-set ears, epicanthal folds, down-slanting palpebral fissures, synophrys, and high palate.

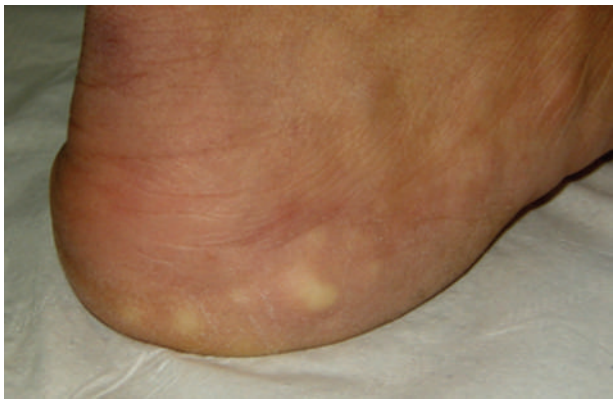

Figure 3. Piezogenic papules of the feet which are subcutaneous fat herniations through the fascia. They often appear as blanching white nodules only while bearing weight.

- Minimal criteria suggestive for kEDS:
  - Major criterion (1): congenital muscle hypotonia
  - AND major criterion (2): congenital or early-onset kyphoscoliosis

  Plus
  - Either major criterion (3): GJH
  - And/or three minor criteria (either general or gene-specific criteria)

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis

  The majority of patients with kEDS harbor biallelic mutations in *PLOD1,* the gene encoding the collagen-modifying enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1 or LH1 [lysylhydroxylase1]). LH1 plays an important role as a post-translational modifying enzyme in collagen biosynthesis through (i) hydroxylation of helical lysyl residues in—Xaa-Lys-Gly-collagen sequences to hydroxy-lysyl residues which serve as sites of attachment for carbohydrate units (either galactose or glucosyl-galactose) and (ii) in the formation of intra- and intermolecular collagen cross-links. LH1 deficiency results in underhydroxylation of lysyl residues and underglycosylation of hydroxylysyl residues in collagens and, hence, impaired cross-link formation with consequent mechanical instability of the affected tissues.

The majority of patients with kEDS harbor biallelic mutations in PLOD1, the gene encoding the collagen-modifying enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1 or LH1 [lysylhydroxylase1]).

  Recently, biallelic mutations have been identified in *FKBP14*, encoding FKBP22, a member of the F506-binding family of peptidyl-prolyl cis-trans isomerases, in patients displaying a phenotype that clinically largely overlaps with kEDS-*PLOD1* [Baumann et al., 2012].
- Verification of diagnosis

  Laboratory confirmation of kEDS should start with the quantification of deoxypyridinoline (Dpyr or LP for lysyl-pyridinoline) and pyridinoline (Pyr or HP for hydroxylysyl-pyridinoline) cross-links in urine quantitated by means of high-performance liquid chromatography (HPLC). An increased Dpyr/Pyr ratio is a highly sensitive and specific test for kEDS caused by biallelic *PLOD1* mutations (kEDS-*PLOD1*), but is normal for biallelic *FKBP14* mutations (kEDS-*FKBP14*).

  The normal ratio of Dpyr/Pyr cross-links is approximately 0.2, whereas in kEDS-*PLOD1* the ratio is significantly increased (approximately 10–40 times increase, range 2–9). This method is fast and cost-effective and it can also be used to determine the pathogenic status of a VUS in *PLOD1*.

  SDS–PAGE may detect faster migration of underhydroxylated collagen chains and their derivatives in kEDS-*PLOD1* but not in kEDS-*FKBP14*. However, abnormalities in migration can be subtle.

  Molecular analysis for kEDS-*PLOD1* may start with MLPA analysis of *PLOD1*, for the evaluation of the common intragenic duplication in *PLOD1* caused by an Alu-Alu recombination between introns 9 and 16 (the most common mutant allele) [Hautala et al., 1993].

  Molecular screening by means of targeted resequencing of a gene panel that includes *PLOD1* and *FKBP14*, is indicated when MLPA of *PLOD1* fails to identify the common duplication. Such a gene panel my also include other genes associated with phenotypes that clinically overlap with kEDS, such as *ZNF469, PRDM5, B4GALT7, B3GALT6, SLC39A13, CHST14*, and *DSE*. Alternatively, WES may be performed. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications in these genes.

  TEM on skin specimens has shown variable diameters and abnormal contours of the collagen fibrils and irregular interfibrillar space, but these abnormalities are not unique to this condition. As such, whereas TEM on a skin biopsy can support diagnosis, it cannot confirm it.

  Whereas absence of an abnormal urinary LP/HP ratio excludes the diagnosis of kEDS-*PLOD1*, absence of the confirmatory genetic findings does not exclude the diagnosis of kEDS, as specific types of mutations (e.g., deep intronic mutations) may go undetected

by standard diagnostic molecular techniques and/or other, yet to be discovered, genes, may be associated with this phenotype; however, alternative diagnoses should be considered in the absence of *PLOD1* or *FKBP14* mutations.

Brittle Cornea Syndrome (BCS)

- Inheritance
  Autosomal recessive
- Major criteria
  1. Thin cornea, with or without rupture (central corneal thickness often $<400\ \mu m$)
  2. Early onset progressive keratoconus
  3. Early onset progressive keratoglobus
  4. Blue sclerae
- Minor criteria
  1. Enucleation or corneal scarring as a result of previous rupture
  2. Progressive loss of corneal stromal depth, especially in central cornea
  3. High myopia, with normal or moderately increased axial length
  4. Retinal detachment
  5. Deafness, often with mixed conductive and sensorineural components, progressive, higher frequencies often more severely affected ("sloping" pure tone audiogram),
  6. Hypercompliant tympanic membranes
  7. Developmental dysplasia of the hip
  8. Hypotonia in infancy, usually mild if present
  9. Scoliosis
  10. Arachnodactyly
  11. Hypermobility of distal joints
  12. Pes planus, hallux valgus
  13. Mild contractures of fingers (especially 5th)
  14. Soft, velvety skin, translucent skin
- Minimal criteria suggestive for kEDS:
  – Major criterion (1): thin cornea, with or without rupture (central corneal thinckness often <100 micrometer)

  Plus
  – Either: at least one other major criterion
  – And/or three other minor criteria

  Confirmatory molecular testing is obligatory to reach a final diagnosis
- Molecular basis
  BCS is caused by biallelic mutations in either *ZNF469*, encoding ZNF469, a zinc finger protein of unknown function, or *PRDM5*, encoding a DNA-binding transcription factor of the PR/SET protein family that lacks the intrinsic histon methyltransferase activity. At least one family with a clinical BCS phenotype did not harbor mutations in these genes, suggesting that at least one other gene might be associated with BCS [Rohrbach et al., 2013].
- Verification of diagnosis
  Molecular screening by means of targeted resequencing of a gene panel that includes *ZNF469* and *PRDM5* is indicated. Such a gene panel my also include other genes associated with phenotypes that clinically overlap with BCS, such as *PLOD1, FKBP14, B4GALT7, B3GALT6, SLC39A13, CHST14* and *DSE*. Alternatively, WES may be performed. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications in these genes.

  Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques, and other, yet unknown genes, might be associated with BCS.

Spondylodysplastic EDS (spEDS)

- Inheritance
  Autosomal recessive
- Major criteria
  1. Short stature (progressive in childhood)
  2. Muscle hypotonia (ranging from severe congenital, to mild later-onset)
  3. Bowing of limbs
- Minor criteria
  1. Skin hyperextensibility,[32] soft, doughy skin, thin translucent skin
  2. Pes planus
  3. Delayed motor development
  4. Osteopenia
  5. Delayed cognitive development
- Gene-specific minor criteria
  – *B4GALT7*
    – Radioulnar synostosis
    – Bilateral elbow contractures or limited elbow movement
    – GJH[32]
    – Single transverse palmar crease
    – Characteristic craniofacial features[33]
    – Characteristic radiographic findings[34]
    – Severe hypermetropia
    – Clouded cornea
  – *B3GALT6*
    – Kyphoscoliosis (congenital or early onset, progressive)
    – Joint hypermobility, generalized or restricted to distal joints, with joint dislocations
    – Joint contractures (congenital or progressive) (especially hands)
    – Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges)
    – Talipes equinovarus
    – Characteristic craniofacial features[35]
    – Tooth discoloration, dysplastic teeth

[32]For definitions of GJH and skin hyperextensibility, see criteria for "Classical EDS."

[33]Characteristic craniofacial features associated with biallelic *B4GALT7* mutations include: triangular face, wide-spaced eyes, proptosis, narrow mouth, low-set ears, sparse scalp hair, abnormal dentition, flat face, wide forehead, blue sclerae, and cleft palate/bidif uvula.

[34]Reported radiographic findings associated with biallelic *B4GALT7* mutations include: include radioulnar synostosis, metaphyseal flaring, osteopenia, radial head subluxation or dislocation, and short clavicles with broad medial ends.

[35]Characteristic craniofacial features associated with biallelic *B3GALT6* mutations include: midfacial hypoplasia, frontal bossing, proptosis, or prominent eyes, blue sclerae, downslanting palpebral fissures, depressed nasal bridge, long upperlip, low-set ears, micrognathia, abnormal dentition, cleft palate, sparse hair.

  - Characteristic radiographic findings[36]
  - Osteoporosis with multiple spontaneous fractures
  - Ascending aortic aneurysm
  - Lung hypoplasia, restrictive lung disease
- S*LC39A13:*
  - Protuberant eyes with bluish sclerae
  - Hands with finely wrinkled palms
  - Atrophy of the thenar muscles, and tapering fingers
  - Hypermobility of distal joints
  - Characteristic radiologic findings[37]

- Minimal criteria suggestive for spEDS:
  - Major criterion (1): short stature
  - AND major criterion (2): muscle hypotonia

  Plus
  - Characteristic radiographic abnormalities and at least three other minor criteria (general or type-specific)

  Confirmatory molecular testing is obligatory to reach a final diagnosis
- Molecular basis

  spEDS is caused by either:
  - Biallelic mutations in *B4GALT7,* encoding galactosyltransferase I (β1,4-galactosyltransferase 7 or β4GalT7), which catalyzes the transfer of the first galactose to the xylose residue in tetrasaccharide linker region of glycosaminoglycans (GAGs).
  - Biallelic mutations in *B3GALT6*, encoding galactosyltransferase II (β1,3-galactosyltransferase 6 or β3GalT6), which catalyzes the transfer of the second galactose to the first galactose residue in tetrasaccharide linker region of GAGs.
  - Biallelic mutations in *SLC39A13*, encoding the homodimeric transmembrane Zrt/irt-like protein 13 (ZIP13) protein, a member of the SLC39A/ZIP family that regulates the influx of Zn into the cytosol.
- Verification of diagnosis

  Molecular screening by means of targeted resequencing of a gene panel that includes *B4GALT7, B3GALT6,* and *SLC39A13* is indicated. Such a gene panel may also include other genes associated with phenotypes that clinically overlap with spEDS, such as *PLOD1, FKBP14, ZNF469, PRDM5, CHST14,* and *DSE*. Alternatively, WES may be performed. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications in these genes.

  For definite proof of GAG deficiency (*B4GALT7* and *B3GALT6* mutations), biochemical methods to assess GAG synthesis in patients' cultured fibroblasts are currently available in many specialized laboratories [Talhaoui et al., 2010].

  The laboratory measurement of urinary pyridinolines, lysyl-pyridinoline (LP) and hydroxylysyl-pyridinoline (HP) quantitated by HPLC allows the detection of an increased ratio LP/HP to approximately 1, (compared to a normal values of approximately 0.2) in patients with mutations in *SLC39A13* [Giunta et al., 2008]. This fast and cost-effective method can also be used to determine the pathogenic status of a VUS (see also "verification of diagnosis" in kEDS-*PLOD1*).

  Absence of confirmatory genetic findings does not exclude the diagnosis of spEDS, as specific types of mutations (eg deep intronic mutations) may go undetected by standard diagnostic molecular techniques, and still other, yet to be discovered, genes may be associated with these phenotypes. In case no *B4GALT7, B3GALT6, or SCL39A13* mutations are identified, alternative diagnoses should however be considered.

[36]Reported radiographic features associated with biallelic *B3GALT6* mutations include: platyspondyly, anterior beak of vertebral body, short ilium, prominent lesser trochanter, acetabular dysplasia, metaphyseal flaring, metaphyseal dysplasia of femoral head, elbow malalignment, radial head dislocation, overtubulation, bowing of long bones, generalized osteoporosis, healed fractures. Craniosynostosis and radioulnar dysostosis has been reported in one patient.

[37]Reported radiologic findings associated with biallelic *SLC39A13* mutations include: mild to moderate platyspondyly, mild to moderate osteopenia of the spine, small ileum, flat proximal femoral epiphyses, short, wide femoral necks.

Musculocontractural EDS (mcEDS)

- Inheritance

  Autosomal recessive
- Major criteria
  1. Congenital multiple contractures, characteristically adduction-flexion contractures and/or talipes equinovarus (clubfoot)
  2. Characteristic craniofacial features, which are evident at birth or in early infancy[38]
  3. Characteristic cutaneous features including skin hyperextensibility[39], easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling
- Minor criteria
  1. Recurrent/chronic dislocations[40]
  2. Pectus deformities (flat, excavated)
  3. Spinal deformities (scoliosis, kyphoscoliosis)
  4. Peculiar fingers (tapering, slender, cylindrical)
  5. Progressive talipes deformities (valgus, planus, cavum)
  6. Large subcutaneous hematomas
  7. Chronic constipation
  8. Colonic diverticula
  9. Pneumothorax/pneumohemothorax
  10. Nephrolithiasis/cystolithiasis
  11. Hydronephrosis
  12. Cryptorchidism in males
  13. Strabismus
  14. Refractive errors (myopia, astigmatism)
  15. Glaucoma/elevated intraocular pressure

[38]Characteristic craniofacial features include: large fontanelle, hypertelorism, short and downslanting palpebral fissures, blue sclerae, short nose with hypoplastic columella, low-set and rotated ears, high palate, long philtrum, thin upper lip vermilion, small mouth, micro-retrognathia.

[39]For definition of skin hyperextensibility, see criteria for "Classical EDS."

[40]The phenotypic features in the three reported patients with EDS caused by DSE deficiency seem to be milder than those in patients with EDS caused by D4ST1-deficiency, but identification of additional patients with DSE-deficiency is needed to confirm this correlation.

- Minimal criteria suggestive for mcEDS:
  - At birth or in early childhood: Major criterion (1): Congenital multiple contractures AND (2) characteristic craniofacial features
  - In adolescence and in adulthood: Major criterion (1): Congenital multiple contractures AND (3) characteristic cutaneous features

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis
  mcEDS is caused by biallelic mutations in *CHST14,* encoding D4ST1, a single-exon gene encoding carbohydrate sulfotransferase 14 or dermatan 4-*O*-sulfotransferase 1, an enzyme involved in the biosynthesis of the GAG dermatan sulfate. It catalyzes 4-*O*-sulfation of *N*-acetylgalactosamine (GalNAc) in the sequence "L-iduronic acid (IdoA)-GalNAc," immediately after epimerization of D-glucuronic acid (GlcA) to IdoA by dermatan sulfate epimerase (DSE).

mcEDS is caused by biallelic mutations in CHST14, encoding D4ST1, a single-exon gene encoding carbohydrate sulfotransferase 14 or dermatan 4-O-sulfotransferase 1, an enzyme involved in the biosynthesis of the GAG dermatan sulfate.

  A few mutations have been identified in the *DSE* gene, encoding DSE, in patients with a similar phenotype.
- Verification of diagnosis
  Molecular screening by means of targeted resequencing of a gene panel that includes *CHST14* and *DSE* is indicated. Such a gene panel my also include other genes associated with phenotypes that clinically overlap with mcEDS, such as *PLOD1, FKBP14, ZNF469, PRDM5, B4GALT7, B3GALT6,* and *SLC39A13*. Alternatively, WES may be performed. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications in these genes.

  Absence of these confirmatory findings does not exclude the diagnosis of mcEDS, as specific types of mutations (e.g., deep intronic mutations) may go undetected by standard diagnostic molecular techniques. In case no *CHST14* or *DSE* mutations are identified, alternative diagnoses should be considered.

Myopathic EDS (mEDS)

- Inheritance
  Autosomal dominant or autosomal recessive
- Major criteria
  1. Congenital muscle hypotonia, and/or muscle atrophy, that improves with age[41]
  2. Proximal joint contractures (knee, hip, and elbow)[42]
  3. Hypermobility of distal joints
- Minor criteria
  1. Soft, doughy skin
  2. Atrophic scarring
  3. Motor developmental delay
  4. Myopathy on muscle biopsy
- Minimal clinical criteria suggestive for mEDS:
  - Major criterion (1): congenital muscle hypotonia that improves with age

  Plus
  - Either: one other major criterion
  - And/or: three minor criteria

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis
  mEDS is caused by heterozygous or biallelic mutations in *COL12A1,* encoding type XII *c*ollagen. The clinical phenotype highly overlaps with collagen type VI-related myopathies, that is, Bethlem Myopathy, and Ullrich Congenital Muscular Dystrophy. It is currently unknown whether other, yet to be discovered genes, are associated with this phenotype.
- Verification of diagnosis
  Molecular screening by means of targeted resequencing of a gene panel that includes *COL12A1* is indicated. Such a gene panel my also include other genes associated with phenotypes that clinically overlap with mEDS, such as *COL6A1, COL6A2, COL6A3*. Alternatively, WES may be performed. When no, or only one, causative mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications in these genes.

  Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations (eg deep intronic mutations) may go undetected by standard diagnostic molecular techniques, and other, yet to be discovered, genes may be associated with this phenotype. In case no *COL12A1* mutations are identified alternative diagnoses, especially collagen VI-related Ullrich Congenital Muscular Dystrophy and Bethlem Myopathy, should be considered.

Periodontal EDS (pEDS)

- Inheritance
  Autosomal dominant

[41]So far, five families have been reported: four with an autosomal dominant condition and one with an autosomal recessive condition. The affected siblings from the family with the autosomal recessive condition have a more severe form of the condition than patients with autosomal dominant inheritance [Zou et al., 2014].

[42]Muscle biopsy and skin fibroblast culture studies: the diagnosis can be suspected in patients that undergo a muscle biopsy and/or in whom a fibroblast line is established. In the autosomal recessive form in which there is no collagen XII produced, immunostaining has shown absence of collagen XII staining. In missense mutations that lead to autosomal dominant forms, collagen XII may be abnormally secreted. The myopathic pattern on muscle biopsy may be suggestive, but is not diagnostic. Recently, muscle MRI has been developed as an alternative, non-invasive technique to study muscle involvement, however it is not specific enough to confirm the diagnosis.

- Major criteria
  - Severe and intractable periodontitis of early onset (childhood or adolescence)
  - Lack of attached gingiva
  - Pretibial plaques
  - Family history of a first-degree relative who meets clinical criteria
- Minor criteria
  - Easy bruising
  - Joint hypermobility, mostly distal joints
  - Skin hyperextensibility[43] and fragility, abnormal scarring (wide or atrophic)
  - Increased rate of infections
  - Hernias
  - Marfanoid facial features
  - Acrogeria
  - Prominent vasculature
- Minimal criteria suggestive for pEDS:
  - Major criterion (1): severe and intractable periodontitis of early onset (childhood or adolescence)
  - OR major criterion (2): lack of attached gingiva

  Plus
  - At least two other major criteria and one minor criterion

  Confirmatory molecular testing is obligatory to reach a final diagnosis.
- Molecular basis

  pEDS is caused by heterozygous gain-of-function mutations in *C1R* or *C1S*, encoding subunits C1r and C1s of the first component of the classical complement pathway.
- Verification of diagnosis

  Identification of known or compatible mutations by sequence analysis of *C1R* and *C1S*. Large deletions or null mutations that completely remove C1r or C1s protein function do not cause pEDS.

  At present it cannot be stated whether absence of a *C1R* or *C1S* mutations excludes the diagnosis because the experience with the molecular diagnosis is limited.

CONCLUDING REMARKS

We hope that the revised International EDS criteria will serve as a new, albeit provisional, standard for the diagnosis of EDS. Our proposal has the aim of facilitating accurate and timely diagnosis, and improve the diagnostic uniformity for clinical and research purposes, genetic counseling, management, natural history studies, and identification of potential areas of research. Future revision of this EDS Classification will be planned within the framework of the International EDS Consortium and the Ehlers–Danlos Society.

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RESEARCH REVIEW

Ehlers–Danlos Syndrome, Classical Type

JESSICA M. BOWEN, GLENDA J. SOBEY, NIGEL P. BURROWS, MARINA COLOMBI, MARK E. LAVALLEE, FRANSISKA MALFAIT, AND CLAIR A. FRANCOMANO*

Classical EDS is a heritable disorder of connective tissue. Patients are affected with joint hypermobility, skin hyperextensibilty, and skin fragility leading to atrophic scarring and significant bruising. These clinical features suggest consideration of the diagnosis which then needs to be confirmed, preferably by genetic testing. The most recent criteria for the diagnosis of EDS were devised in Villefranche in 1997 [Beighton et al. (1998); Am J Med Genet 77:31-37].The aims set out in the Villefranche Criteria were: to enable diagnostic uniformity for clinical and research purposes, to understand the natural history of each subtype of EDS, to inform management and genetic counselling, and to identify potential areas of research. The authors recognized that the criteria would need updating, but viewed the Villefranche nosology as a good starting point. Since 1997, there have been major advances in the molecular understanding of classical EDS. Previous question marks over genetic heterogeneity have been largely surpassed by evidence that abnormalities in type V collagen are the cause. Advances in molecular testing have made it possible to identify the causative mutation in the majority of patients. This has aided the further clarification of this diagnosis. The aim of this literature review is to summarize the current knowledge and highlight areas for future research. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Ehlers–Danlos syndrome; classical type; cEDS; joint hypermobility; skin fragility; skin hyperextensibility

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INTRODUCTION

The Committee met by phone throughout 2015 to discuss the Villefranche diagnostic criteria for classical Ehlers–Danlos Syndrome (classical EDS) and how they might be modified to improve specificity and sensitivity. A comprehensive review of the literature was conducted, led by two of the authors

Jess Bowen is a registered genetic counsellor specializing in Ehlers–Danlos syndrome, with wide experience of all types of EDS. She has worked in the UK EDS National Diagnostic Service since its foundation. Together with colleagues in the service, Jess has developed an emergency card for patients with vascular EDS. Jess has a particular interest in the psychosocial outcomes and consequences of early and accurate diagnosis of rare disease.

Glenda J Sobey is co-founder of the Ehlers–Danlos Syndrome National Diagnostic Service in the UK and Honorary Senior Lecturer at the University of Sheffield. Her unit is responsible for the diagnosis of rare and atypical EDS, and together with cardiology colleagues she runs a specialist EDS cardiology clinic for patients at risk of blood vessel rupture. Dr. Sobey has published widely and plays an active role in teaching and lecturing both nationally and internationally. She is particularly interested in promoting early diagnosis in rare disease to allow optimal outcome for patients and families.

Dr. Nigel Burrows is a Consultant Dermatologist at Addenbrooke's Hospital, Cambridge, UK. He is on the medical advisory board for two UK EDS patient support groups (EDS Support UK and Annabelles Challenge). He is actively involved in the management of patients with EDS and, in addition to peer reviewed publications on EDS, he has written several book chapters and also lectures on national courses on EDS.

Marina Colombi is a full professor of Medical Genetics at the School of Medicine, University of Brescia, Italy. Her major interests are diverse heritable connective tissue disorders including Ehlers–Danlos syndromes, for which she has provided new insights in the molecular basis, phenotypic characterization, clinical spectrum, and pathogenesis.

Mark Lavallee is a board certified Family Medicine and Sports Medicine Physician. He joined the Ehlers–Danlos National Foundation in 1987, and served as a board member and founding chairman of their Professional Advisory Council. His career has focused on Ehlers–Danlos syndrome, including laboratory studies of the COL3A1 gene at Penn State University, and the founding of Ehlers–Danlos Clinics in Indiana and Pennsylvania. Dr. Lavallee has several publications and research projects in relation to EDS, specifically regarding the use of exercise to improve the quality of life in patients with connective tissue diseases.

Fransiska Malfait is a rheumatologist and clinical geneticist. She is an Associate Professor at the Centre for Medical Genetics at the Ghent University Hospital, where she directs the research, clinical service and laboratory facility for diagnosis and genetic testing for the Ehlers–Danlos Syndrome and other heritable disorders of connective tissue. She currently is the Chair of the Medical and Scientific Board of the Ehlers–Danlos Society.

Clair A. Francomano is a clinical geneticist with a long interest in the hereditary disorders of connective tissue. Her professional work in the last 10 years has centered on Ehlers–Danlos Syndrome. She is Director of Adult Genetics and of the Ehlers–Danlos Society Center for Clinical Care and Research at the Harvey Institute for Human Genetics, and Associate Professor of Medicine at Johns Hopkins University School of Medicine. She serves on the Executive Board and the Medical and Scientific Board of the Ehlers–Danlos Society.

Conflict of interests: None of the authors has a conflict of interest to report.

*Correspondence to: Clair A. Francomano, Greater Baltimore Medical Center – Harvey Institute for Human Genetics, 6701 N. Charles Street, Suite 2326, Towson, MD 21204. E-mail: cfrancomano@gbmc.org

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(Bowen and Sobey). The diagnostic criteria presented here represent the consensus of the group after review of the literature and considering the professional experience of each of the authors.

The committee agrees to retain the name "classical EDS."

METHODS

Each member of the committee carried out a literature search for classical EDS. The results were collated. All articles were reviewed for relevance and additional articles were identified from the literature. The articles were summarized and divided into themes. Themes that were suggested by the Steering Committee of the International Consortium on the Ehlers–Danlos syndromes were also included to assess where there were gaps in the literature. Each theme was written up to include the relevant literature in that area, focusing on information since the Villefranche nosology. The original list of articles was then reviewed to ensure all areas of the current literature had been covered.

Organ System Review

Musculoskeletal: Joint hypermobility is present. This will be evidenced by the presence of a Beighton score of 5 or greater, either on examination or historically. Joint instability complications may comprise sprains, dislocation/subluxation, temporomandibular joint dysfunction, pain and pes planus, dyspraxia, and early osteoarthritis. Mild muscle hypotonia, and some skeletal morphological alterations (scoliosis, pectus deformities, elbow/genus/hallux valgus) are regularly observed. Pre-menopausal osteopenia or an increased bone fragility in the presence of a bone mineral density within the range may occur [Mazziotti et al., 2016].

Skin: The skin involvement is key to establishing the diagnosis of classical EDS. Skin is hyperextensible and soft, with severe atrophic scarring and haemosiderin deposition over the shins and extensor surfaces. Easy bruising is also a hallmark of classical EDS.

Cardiovascular: While aortic root dilation and mitral valve prolapse are seen in classical EDS, they are rarely clinically significant. Arterial aneurysm and rupture have been reported in a few individuals and families with *COL5A1* mutations.

Gastrointestinal: Gastrointestinal complaints are more commonly described in the hypermobile type of EDS, although they can be present in patients with classical EDS and may include: dysphagia, dyspepsia, reflux disease with or without hiatal hernia, irritable-bowel disease-like symptoms, unspecified abdominal pain, defecatory dysfunctions (constipation, diarrhea), and rectocele [Ritelli et al., 2013; Nelson et al., 2015].

Neurologic: Pain is a common feature of EDS. One report suggests that pain intensity in classical EDS patients is mild and less frequent compared to hypermobile EDS.

Literature Review

The literature was divided into 8 themes: The history of classical EDS, the mechanism of disease, clinical description, testing strategy, management, differential diagnoses, genetic counselling, and gaps/future research.

THE HISTORY OF CLASSICAL EDS

Classical EDS (OMIM #130000) is a heritable disorder of connective tissue characterized by skin hyperextensibility, poor wound healing, and joint hypermobility. Classical EDS was first noted to be a distinct type of EDS in the 1960s when Beighton reviewed 100 patients and described a patient with distinct features which he termed EDS gravis [Beighton, 1968]. Patients were noted to have characteristic findings on electron microscopy, which helped to differentiate between EDS diagnoses [Vogel et al., 1979]. In 1988, gravis type was termed EDS type I and the milder, mitis type was labelled EDS type II [Beighton et al., 1988]. Type V collagen was implicated after mouse models with mutations in *COL5A2* showed features of the condition [Andrikopoulos et al., 1995]. This was shortly followed by the first reports of *COL5A1* mutations in patients with classical EDS [Nicholls et al., 1996; Wenstrup et al., 1996; De Paepe et al., 1997]. Linkage to *COL5A1* also suggested the EDS types I and II were phenotypic variation of the same condition [Burrows et al., 1996]. In 1996, a balanced translocation interrupting the *COL5A1* gene was identified and haploinsufficiency was suggested as the cause of the patient's EDS phenotype [Toriello et al., 1996]. The name classical EDS was given when the Villefranche nosology was written in 1997 [Beighton et al., 1998]. Initially other genes were thought to be involved, as *COL5A1* and *COL5A2* mutations were only found to account for around half of classical EDS patients [Schwarze et al., 2000; Malfait et al., 2005]. Advances in molecular testing have allowed more type V collagen abnormalities to be identified, and recent reports indicate that the majority of patients with classical EDS do have a mutation in either *COL5A1* or *COL5A2* [Symoens et al., 2012; Ritelli et al., 2013].

Classical EDS (OMIM #130000) is a heritable disorder of connective tissue characterized by skin hyperextensibility, poor wound healing and joint hypermobility. Classical EDS was first noted to be a distinct type of EDS in the 1960s when Beighton reviewed 100 patients and described a patient with distinct features which he termed EDS gravis.

THE MECHANISM OF DISEASE

Reduction in the amount of type V collagen is central to the pathogenesis of

classical EDS [Symoens et al., 2008; De Paepe and Malfait, 2012]. Type V collagen has a regulatory function in fibrillogenesis. The phenotype is caused by disturbance in the regulatory function of type V collagen [Symoens et al., 2012].

Type V collagen is a fibrillar collagen present in small amounts in a wide variety of tissues [Malfait and De Paepe, 2005]. It is mainly found in vertebrate tissues as the heterotrimer $\alpha1(V)_2\alpha2(V)$ [Viglio et al., 2008]. Type V collagen and type I collagen come together to form collagen fibrils. *COL5A1* haploinsufficiency is, therefore, a limiting factor for an adequate production of heterotrimers, hence compromising the regulatory role in fibrils assembly. Most of the $\alpha1(V)_2\alpha2$ (V) heterotrimer is embedded within the fibril, apart from the amino-terminal propeptide domain which remains exposed on the surface and has a role in fibril assembly and regulating fibril diameter [Birk, 2001].

The *COL5A1* gene encodes the $\alpha1$ chain and is located at 9q34.2-q34.3. The *COL5A2* gene encodes the $\alpha2$ chain and is located at 2q31. Both genes are large, comprising 66 and 52 exons, respectively. The majority of patients have mutations in *COL5A1*. A report of 93 gene positive patients found 73 had *COL5A1* mutations, 13 had *COL5A2* mutations, and in 7 cases the mutation could not be identified; however, *COL5* null allele testing confirmed the abnormality was in type V collagen [Symoens et al., 2012]. In this series two thirds of the mutations were found to be de novo. A series of 40 patients achieved a mutation detection rate of 93% [Ritelli et al., 2013]. Both studies confirmed that *COL5A1* and *COL5A2* are the major, if not the only genes involved.

The most common molecular defects result in nonsense mediated decay of the mutated *COL5A1* mRNA [Schwarze et al., 2000]. Whilst haploinsufficiency is seen most often, dominant-negative mutations are also reported [Wenstrup et al., 2000]. In general genotype–phenotype correlations are not found, but there are a couple of possible exceptions. Mutations in the highly conserved amino-terminal propeptide domain of $\alpha1(V)$ that cause atypical splicing outcomes have been associated with a more severe classical EDS phenotype with kyphoscoliosis and retinal detachment [Symoens et al., 2011]. There is one report that questions whether mutations involving glycine substitutions near the C-terminal end cause an increased arterial risk [Monroe et al., 2015]. Although numbers are still limited, *COL5A2* gene mutations are thought to result in a phenotype at the more severe end of classical EDS spectrum [Symoens et al., 2012].

CLINICAL DESCRIPTION

The Villefranche criteria list three major criteria for classical EDS [Beighton et al., 1998]:

(1) Skin hyperextensibility
(2) Widened atrophic scars (manifestation of tissue fragility)
(3) Joint hypermobility

In addition, there are a number of minor criteria which show less diagnostic specificity:

(1) Smooth velvety skin
(2) Molluscoid pseudotumours
(3) Subcutaneous spheroids/spherules
(4) Complications of joint hypermobility (e.g., sprains, dislocations/subluxations, pes planus)
(5) Muscle hypotonia, delayed gross motor development
(6) Easy bruising
(7) Manifestations of tissue extensibility and fragility (e.g., hiatus hernia, anal prolapse in childhood, cervical insufficiency)
(8) Surgical complications (postoperative hernias)
(9) Positive family history

The Villefranche criteria are still considered relevant for classical EDS. A study of 126 suspected classical EDS patients found that 93 out of the 102 that demonstrated all three major Villefranche criteria for classical EDS were found to have a type V collagen abnormality [Symoens et al., 2012]. They suggested making the diagnostic criteria more stringent as fulfilling all three major criteria was seen to be a reliable indicator of a type V collagen mutation. Another review of 40 patients also found that these three major criteria are considered to still be useful for clinical diagnoses in the majority of patients [Ritelli et al., 2013].

A study of 126 suspected classical EDS patients found that 93 out of the 102 that demonstrated all three major Villefranche criteria for classical EDS were found to have a type V collagen abnormality.

There have been a number of typical case histories of classical EDS described. These suggest that investigations into childhood bruising are often the first presentation to medical professionals, and if skin hyperextensibility and joint hypermobility are noted at this time, the diagnosis is generally made [De Paepe and Malfait, 2012; Byers, 2013; Morais et al., 2013; Sobey, 2014]. Bruising is generally a feature seen when children start to crawl and walk, with the characteristic scarring becoming apparent after knocks and bumps around the same time. Hypermobility may delay motor development, but intellectual development is unaffected.

Skin Features

Skin hyperextensibility has been shown to be a reliable and reproducible feature of classical EDS [Remvig et al., 2010]. This group confirmed that patients with classical EDS show extensibility beyond the normal range (Fig. 1). However, they found skin consistency to be an unreliable test and concluded that skin consistency should not be included in the diagnostic criteria for classical EDS.

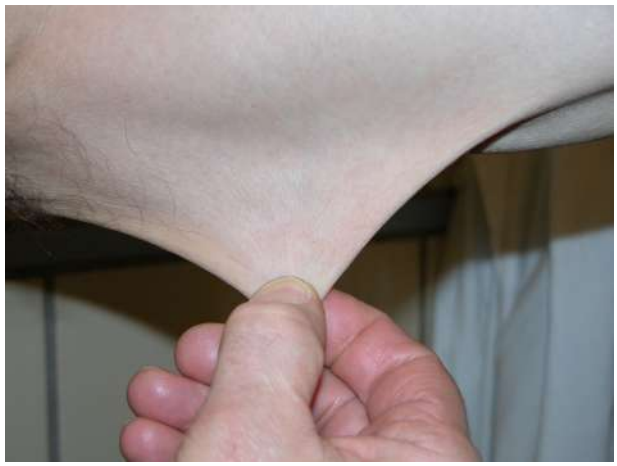

Figure 1. Hyperextensible skin in Classical Ehlers-Danlos Syndrome.

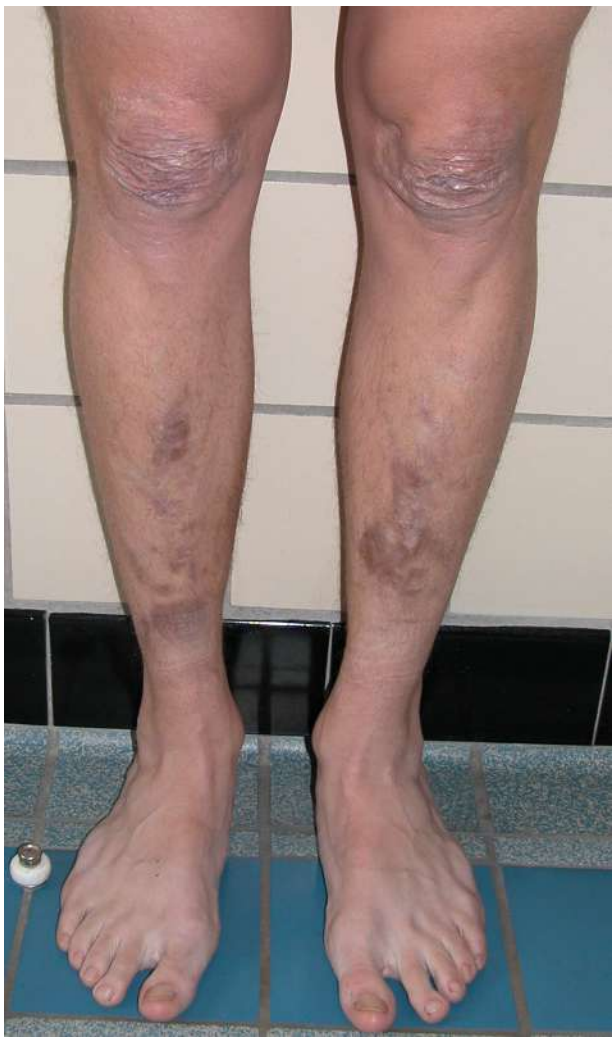

Figure 2. Typical scarring in classical EDS.

Other reports have also found skin hyperextensibility to be a good indicator for classical EDS, as it quite specific to this diagnosis [Heidbreder et al., 2008; Catala-Pétavy et al., 2009] Skin fragility with atrophic scarring and poor wound healing is a hallmark of the classical type of EDS [Beighton et al., 1998] (Fig. 2).

Cardiovascular Involvement

Nine patients (three in one family) have been reported to have molecularly confirmed classical EDS and vascular events [Monroe et al., 2015]. To determine whether there is any reporting bias it is helpful to compare these cases to the larger patient series that have been reported. Twenty-five patients with proven type V collagen abnormalities showed no vascular events at the time of writing [Malfait et al., 2005]. A series of 102 patients, 93 with collagen type V abnormalities, had two patients with vascular complications which included aneurysm and dissection of medium sized artery [Symoens et al., 2012]. They reported that severe or progressive cardiac-valvular disease was absent in their cohort. A report of 40 patients showed no patients with type V collagen abnormalities that had severe cardiovascular involvement [Ritelli et al., 2013].

The family of three are two brothers and their mother who were given a clinical diagnosis of vascular EDS [Monroe et al., 2015]. One brother died age 43 due to a subarachnoid bleed, after previously having a ruptured left subclavian artery age 15 years and a coeliac artery aneurysm was resected age 18 years with significant bleeding. His mother had died at age 28 while under anaesthesia for dental extraction; the post mortem revealed a renal artery tear. The other brother died age 34 following a right iliac artery rupture; his tissues were compared to rice paper in the operating theatre. They were all shown to have a *COL5A1* p.(Gly1537Val) mutation. This family represents the only report of familial vascular events with a *COL5A1* mutation. The authors wondered about modifying genes in the family or whether there could be a genotype–phenotype correlation. They speculated there could be increased arterial risk in cases involving glycine substitutions near the C-terminal end.

Another report of a patient with a glycine substitution at the C-terminal end of the triple helix domain had a symptomatic superior mesenteric artery aneurysm age at 9 years [de Leeuw et al., 2012]. This patient was said to fit clinically with a classical EDS diagnosis and was found to have a *COL5A1* p.(Gly1564Asp) mutation. Two further vascular events have been reported at young ages. One report is of a 13-year-old girl with classical EDS who had a superior mesenteric artery rupture and was found to have a *COL5A1* missense mutation c.1532G>T p.(Gly511Val) [Yasuda et al., 2013]. Another patient with a *COL5A1* p.(Gly922Asp) mutation was diagnosed with classical EDS at 4 years of age and presented at age 11 with a superior mesenteric artery aneurysm with thrombosis [Karaa and Stoler, 2013]. This patient was treated with anticoagulation, and a week later he ruptured his inferior mesenteric artery.

Two patients with classical EDS and hypertension have been reported following vascular events. A patient with a *COL5A1* mutation c.3184C>T p.(Arg1062*) who already had a clinical diagnosis of classical EDS went on to have a left common iliac artery rupture at age 42 years [Borck et al., 2010]. This patient had been diagnosed with hypertension at 40 and treated with clonidine, metoprolol and valsartan/hypochlorothiazide. The authors felt they could not exclude a chance association between the classical EDS diagnosis and the rupture, but felt a causal relationship was more likely. They considered whether the concurrent hypertension might have played a part, causing a second hit. However, their view was that a systematic counselling of the risk of arterial rupture in classical EDS should await confirmation of this association in larger series. Another patient with chronic hypertension (although well controlled) with a *COL5A1* nonsense mutation c2185C>T p.(Gln729*) had an iliac artery dissection whilst resistance training [Mehta et al., 2012]. This time the authors considered a triple hit effect; chronic hypertension, elevated vascular stress from resistance training, and his underlying weakened collagen matrix due to classical EDS. They suggested avoiding intense resistance training and/or tighter control of blood pressure.

Aortic root dilation has been reported in classical EDS [Wenstrup et al., 2002; McDonnell et al., 2006; Atzinger et al., 2011]. It appears to be more common in young patients and rarely progresses [Atzinger et al., 2011]. Mitral valve prolapse can occur in up to 6% of cases but tends to be of little clinical significance [Atzinger et al., 2011].

Newly recognized features

Features not mentioned in the Villefranche criteria that arise in the literature include premature rupture of fetal membranes, characteristic facial features, absence of striae, scoliosis, cardiac and blood vessel fragility. Premature rupture of fetal membranes can result in prematurity and this was reported to affect half of classical EDS patients, but is now thought not to be so common [Wenstrup et al., 2000]. The characteristic facial features described are; epicanthic folds, excess skin on eyelids, a prematurely aged appearance, and scars on the forehead and chin [Malfait and De Paepe, 2005]. Absence of striae has been noted in classical EDS patients [Sobey, 2014], although some patients with confirmed classical EDS have been seen to have striae. Three patients out of 40 were reported to have striae in one study [Ritelli et al., 2013]. Dual-energy X-ray absorptiometry (DXA) and quantitative vertebral morphometry were performed in 12 unrelated adult patients with classical EDS which showed bone mineral density below the expected range for age (osteopenia) in about 33.3% of patients and pre-menopausal osteoporosis in one patient. Giant bladder diverticula have been described in four cases, all male [Burrows et al., 1998]. In two reports the subtype of EDS was not given but the descriptions were compatible with classical EDS.

Gastrointestinal findings

Gastrointestinal (GI) manifestations were analyzed among a cohort of 73

unrelated adult patients with classical EDS. The most common upper GI symptoms were nausea (46.5%), vomiting (30.2%), and gastroesophageal reflux (30.2%); the most common lower GI symptom was chronic constipation (37.2%) [Nelson et al., 2015]. Gastroesophageal reflux and defecatory dysfunctions (i.e., chronic constipation) were also described in the cohort of 39 classical EDS patients reported in Ritelli et al. [2013].

Oral findings

Overall periodontal status in EDS is poor. One case of abnormal pulp shape and seven with pulp calcification were seen out of nine classical EDS patients examined [De Coster et al., 2005a]. It has been suggested that the absence of the inferior labial and lingual frenulae is a helpful marker for hypermobile and classical EDS, but the total numbers of classical EDS patients reported to date are too small to conclude that this is useful sign in this subtype [De Felice et al., 2001]. Pierro et al. [2006] reported on ligneous periodontitis in Ehlers-Danlos syndrome. Temporomandibular joint dysfunction is a common feature and a frequent cause of secondary headache in classical EDS patients with generalized joint laxity [De Coster et al., 2005b].

Ocular findings

Macro- and microstructural changes of the cornea were found in classical EDS patients [Villani et al., 2013]. Classical EDS patients have been shown to have thin, steep and transparent corneas as well as floppy eyelids [Segev et al., 2006; Villani et al., 2013]. Both studies found that these changes did not cause an increase in refractory errors (including astigmatism) nor an increase in keratoconus. This supports the lack of correlation between corneal thickness and refractive error. Villani et al. [2013] also found that the patients reported no complaints of ocular surface symptoms, despite having abnormal ocular surface symptoms and reduced tear secretion when compared to controls. One caveat concerning the report by Villani et al. [2013] is that the diagnosis of classical EDS was not supported by molecular testing in the reported population.

Pain and Neurological Features

Pain is considered a common feature in EDS patients, but it has been shown to be more prevalent and more severe in patients with hypermobile EDS than in those with classical or vascular EDS [Voermans et al., 2010]. The authors correlate pain intensity with the degree of joint hypermobility, dislocations, and previous surgery. A decrease in quality of life has been reported but found not to be significantly different between classical and hypermobile patients, provided they have been diagnosed and are under multidisciplinary management [Castori et al., 2010]. When compared to patients with vascular EDS and patients with homozygous and heterozygous TNXB mutations, the patients with classical EDS reported the most neuromuscular complaints [Voermans et al., 2009]. This study found mild, moderate or severe muscle weakness on examination of all of 10 classical EDS patients. They suggest that the neuromuscular involvement is due to the abnormal extracellular matrix within muscle and peripheral nerve. This is an alternative explanation to the view that it is exercise avoidance, for fear of dislocations and sprains, which leads to muscle weakness and fatigue. Rowe et al. [1999] reported an association between orthostatic intolerance, chronic fatigue, and Ehlers-Danlos syndrome. Autonomic burden has been reported to be lower in classical EDS than in hypermobile EDS, and classical EDS patients had levels more comparable to those reported by vascular EDS patients [De Wandele et al., 2014].

TESTING STRATEGY

The diagnosis of classical EDS can be confirmed by identifying the pathogenic causative mutation in COL5A1 or COL5A2. As the number of identifiable mutations has increased, molecular testing has been the main route for classical EDS testing. Testing strategies generally start with COL5A1 sequencing. If COL5A1 is negative, sequence COL5A2 and proceed to Multiplex Ligation-dependent Probe Amplification (MLPA) for COL5A1 [De Paepe and Malfait, 2012; Ritelli et al., 2013]. If the causative mutation is not identified, COL1A1 sequencing should be considered, at least in a subset of patients with vascular and/or valvular involvement, or history thereof [Ritelli et al., 2013; Colombi et al., 2016] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).

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Molecular investigations identify mutations in the majority, but currently not all, patients with the diagnosis [Symoens et al., 2012]. Pathogenicity must be determined and there is a registry of reported collagen gene variants [Dalgleish, 1998].

The pathogenicity of one reported variant remains unclear. The p.(Gly530Ser) variant in COL5A1 is reported to be potentially disease modifying in the heterozygous state and disease causing in the homozygous state [Giunta and Steinmann, 2000; Giunta et al., 2002]. However, there is still some uncertainty about whether this variant is disease causing, due to its frequency in the general population and the fact that not all molecular causes of classical EDS can currently be identified. Another study found the frequency of the

p.(Gly530Ser) variant to be similar in patients with classical EDS, vascular EDS, osteogenesis imperfecta (OI), and the three control groups they used as comparison [Mitchell et al., 2009]. They state that if homozygosity of this variant did cause classical EDS, 1 in 400 people would be affected. This is much higher than the current suspected frequency of classical EDS. Hence, they consider homozygosity of this variant is unlikely to cause classical EDS.

When a pathogenic mutation cannot be found, type V collagen abnormality can be sometimes be demonstrated by the COL5A1 null allele test [Greenspan and Pasquinelli, 1994; Schwarze et al., 2000; Mitchell et al., 2009; De Paepe and Malfait, 2012; Symoens et al., 2012]. The patient must be heterozygous for a polymorphic marker in COL5A1 gDNA. cDNA from a skin biopsy is then tested to look for the presence of one or both markers. If a marker is not expressed that allele is assumed not to be functional, that is, "null" [Malfait and De Paepe, 2005].

Typical frequent collagen flowers on electron microscopy (EM) of skin can be a helpful diagnostic tool for classical EDS, however collagen flowers are not unique to this condition. Electron microscopy of a skin biopsy can be used to direct testing [Sobey, 2015], and electron microscopy can aid diagnosis [Vogel et al., 1979; Hausser and Anton-Lamprecht, 1994]. The absence of typical collagen flowers would go against the diagnosis, as there are no reports of patients with type V collagen abnormalities without collagen flowers on EM [de Moraes et al., 2000; Proske et al., 2006; Symoens et al., 2012]. However, collagen flowers are not specific to classical EDS and have been reported in other connective tissue disorders including OI and Ullrich congenital muscular dystrophy (UCMD) [Kirschner et al., 2005; Hermanns-Lê and Piérard, 2007; Balasubramanian et al., 2015]. Collagen flowers on EM should be an indicator to look for COL1A1 mutations, when clinical features of classical EDS are present in the absence of a COL5 abnormality.

Collagen protein analysis of cultured fibroblasts is not an effective diagnostic tool for classical EDS as type V collagen is only synthesized at low levels [Malfait et al., 2010]. This analysis may be used to exclude alternative diagnoses in the absence of genetic confirmation and may be helpful for the confirmation of the mutation effect, that is, recognition of splice site mutations.

MANAGEMENT

The key management advice is fairly consistent and focuses on the skin and joints [Steinmann et al., 2002; Proske et al., 2006; Malfait et al., 2010; Sobey, 2014].

The advice on managing the skin is to:

Avoid undue trauma. Children are particularly prone to injury and benefit from protective pads and bandages. Custom made shin pads can be obtained from local appliance departments. Contact sports should be avoided.

Wounds should be expertly closed via sutures without tension. Patients should be known to their local plastic surgeons to enable access in emergencies. Stitches should be applied generously, in layers and left in place twice as long as usual. Tape can also help prevent stretching of the scar, but needs careful removal.

Wounds should be expertly closed via sutures without tension. Patients should be known to their local plastic surgeons to enable access in emergencies. Stitches should be applied generously, in layers and left in place twice as long as usual. Tape can also help prevent stretching of the scar, but needs careful removal.

Ascorbic acid (2 g/day for adults) may reduce bruising, but does not affect the basic clinical picture.

Surgery may be difficult due to tissue fragility and original problem may reoccur, for example, hernia.

Deamino-Delta-D-Arginine Vasopressin (DDAVP) may be useful to normalize bleeding time. Although bleeding is related to tissue and capillary fragility rather than clotting time, it may be beneficial in case of bruising, epistaxis or before procedures such as dental extractions.

Avoid excessive sun exposure to reduce the risk of premature skin aging.

Plastic surgery to remove molluscoid pseudotumors may be considered in presence of psychological/aesthetic issues.

The musculoskeletal management advice is:

Physiotherapy is beneficial for children with hypotonia and delayed motor development.

Light, non-weightbearing, muscle strengthening exercise such as isometric training and swimming are beneficial for hypermobile joints and pain management.

Competitive activities, such as gymnastics, repetitive heavy lifting, and sports that cause heavy joint stress, are not advisable. Mild strength training has shown benefit in joint stabilization and hypotonia.

Avoid "showing off" hypermobility and excessive stretching of the hypermobile joints.

Joint hypermobility is best managed by Rheumatology, Physiatry and Sports Medicine, together with physiotherapy, proprioception exercises, and occupational therapy (OT).

Ring splints, carefully considered bracing, and orthotics may be beneficial.

Skin fragility, muscle hypotonia, joint instability, and pain are key aspects of the condition and should be recognized and discussed with the patient. Lifestyle and professional choices may need to be adapted.

There are several articles giving contradictory advice on resistance exercise. One report found heavy

resistance training was both feasible and safe, although their numbers were small they saw an improvement in musculotendinous function and a reduction in fatigue [Møller et al., 2014]. Another report describes a case of iliac artery dissection following vigorous physical exercise [Mehta et al., 2012]. Schroeder and Lavallee [2006] offer guidance for athletes with EDS of all types.

The advice on pain management includes:

Anti-inflammatory drugs and pain medications using narcotics only as a very last resort.

Neurological assessment in patients with symptoms suggestive of neuropathic pain/compression neuropathy.

Regular, light, non-weightbearing exercise.

Relaxation techniques including mindfulness-based stress reduction and biofeedback.

Counselling support including cognitive behavioral therapy. See also "Pain Management in Ehlers-Danlos Syndrome" by Chopra et al., this issue.

Cardiac Management

Cardiac assessment including echocardiography to look for aortic root dilation and mitral valve prolapse. Mitral valve prolapse may need management. Aortic root size and mitral valve prolapse are increased in patients with classical EDS, but they tend to be of little clinical significance. Echocardiography may be warranted, but in symptom-free adults frequency can be reduced [Atzinger et al., 2011]. If this is normal in adulthood no follow up is required [Malfait et al., 2010].

Consider vascular imaging/use of blood pressure medication if the patient has a glycine substitution identified near the C-terminal end of the triple helix, or on the basis of their family history [Monroe et al., 2015].

Gastrointestinal Management

Endoscopy and colonoscopy should be performed with care due to a possibly increased risk of mucosal bleeding and tissue fragility.

Pregnancy Management

Follow up throughout pregnancy is warranted.

Preterm delivery is more likely when the fetus is affected and is mainly due to premature rupture of the membranes.

Breech presentation is more common if the baby is affected.

After delivery, extension of episiotomy incisions and pelvic prolapse leading to urinary/faecal incontinence may occur due to tissue fragility and extensibility. Treatment of symptomatic pelvic prolapse remains problematic in classical EDS.

DIFFERENTIAL DIAGNOSIS

There are a large number of conditions reported to be amongst the differentials when a diagnosis of classical EDS is being considered. One paper specifically on classical EDS gives a detailed description of 18 differential diagnoses [Malfait et al., 2010]. Another highlights the need to distinguish hyperelastic skin from the redundant skin seen in cutis laxa syndromes and Menkes disease [Malfait and De Paepe, 2005].

A paper describing the differential diagnoses for connective tissue diseases in general, mentions features similar to those of classical EDS in four other conditions [Murphy-Ryan et al., 2010]:

(1) Cardiac-valvular EDS—In this condition, patients sometimes present with the skin and joints of classical EDS but have an increased risk of cardiac valvular complications and autosomal recessive inheritance (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(2) Classical-like EDS due to complete tenascin X deficiency—can present with a phenotype similar to classical EDS but without the typical scarring, and with autosomal recessive inheritance (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(3) Spondylodysplastic EDS due to SLC39A13 mutations—a rare recessive condition caused by mutations in SLC39A13, which presents with atrophic scarring similar to that seen in classical EDS, in addition to fragile skin which appears prematurely aged on hands and feet. Muscle atrophy, pes plans, postnatal growth deficiency, and small joint contractures are also characteristic [Giunta et al., 2008] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(4) Loeys–Dietz syndrome—which can present with a whole spectrum of features including the translucent and velvety skin and joint laxity seen in classical EDS, but also craniofacial features and vascular tortuosity not typical of cEDS.

A review on the differential diagnoses of joint hypermobility syndrome (JHS)/EDS hypermobile type (hEDS) includes classical EDS [Colombi et al., 2015]. In a small number of cases, patients with classical EDS and those with JHS/hEDS can present similarly. In one study, two adult patients with confirmed classical EDS were reported to have no atrophic scars [Ritelli et al., 2013]. Another study reported hEDS patients with hyperextensible skin [Castori et al., 2015].

Also to be included in the differential diagnosis of classical EDS is the dermatosporatic type of EDS, which is an autosomal recessive disorder characterized by extreme skin fragility with congenital or post-natal skin tears. Typically the skin is redundant, with excessive palmar wrinkling and severe bruisability with a risk of subcutaneous hematomas and haemorrhage Postnatal growth retardation with short limbs, hand and feet, which are not typically features of cEDS, are seen in the dermatosporatic type (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).

A review of case reports and patient series reveals a number of incidences where a clinical diagnosis of classical EDS was altered after genetic testing identified an alternative diagnosis. In all cases, they all involved mutations in type I collagen.

There are currently three reported forms of type I collagen abnormality that can present with EDS features:

(1) Cardiac valvular EDS—an autosomal recessive condition caused by total absence of α2(1) collagen chain [De Paepe and Malfait, 2012]. The condition was named because three patients were reported to have aortic or mitral valve requiring replacement surgery in adulthood [Schwarze et al., 2004]. A review of all reported cases concludes that loss of function mutations result in a phenotype similar to hEDS or classical EDS but with cardiac valve disease in adulthood while gain of function mutations lead to a severe OI phenotype [Malfait et al., 2006] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(2) "Classic EDS-like with a propensity for arterial rupture"/"vascular-like classical EDS" are two names that have been used for the condition caused by COL1A1 mutations involving substitutions of arginine for cysteine. This condition can present as classical EDS with an increased risk for arterial dissection [Malfait et al., 2007; Ritelli et al., 2013; Gaines et al., 2015]. Three patients were described who had arginine to cysteine substitutions in the pro-alpha (l) collagen chain and one had presented as classical EDS [Malfait et al., 2007]. They suggest that this shows the need to differentiate COL1 patients (given the phenotypic similarity) as there is vessel fragility in patients with COL1A1 arginine to cysteine mutations. The molecular characterization of 40 patients with classical EDS showed that one patient had a COL1A1 p.(Arg312Cys) mutation [Ritelli et al., 2013]. This patient was reported to be similar to the other classical EDS patients except that he had vascular involvement (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(3) OI/EDS overlap syndrome.

Patients with mutations at the N-terminal end of both COL1A1 and COL1A2, which are seen to affect the processing of the N-propeptide, can present phenotypically as EDS rather than OI [Malfait et al., 2013]. This is in contrast to patients with mutations in the same region who do not show delayed type I procollagen N-propeptide processing on SDS–PAGE analysis, who present with an OI phenotype. The potential risk for vascular rupture associated with these mutations means they need to be diagnosed correctly, particularly given the clinical overlap. This again highlights the need to consider type I collagen in patients presenting with EDS features. The authors recognized that the further work was needed to fully characterize this phenotype, but suggest being aware of the potential for vascular aneurysm or rupture at a young age and recommend caution and consideration of the risk of vascular fragility in event of surgical or other invasive procedures.

GENETIC COUNSELING

Classical EDS is inherited in an autosomal dominant pattern. Affected individuals have a 50% chance of passing on the condition in each pregnancy. For siblings of an affected person it will depend on whether one of the patents is also affected. If a parent is affected the other children will have a 50% chance of being affected. Intrafamilial variability has been reported [Burrows et al., 1996]. About 50% of cases are thought to be de novo [Malfait et al., 2010]. If the parents are unaffected there is a theoretical risk to the other children due to gonadal mosaicism, however, this has not yet been reported [Malfait et al., 2010].

Once the molecular cause is known for a patient, cascade testing is possible to confirm or exclude the diagnosis in relatives who may have a milder phenotype [Ritelli et al., 2013]. Prenatal testing and preimplantation genetic diagnosis are possible once the mutation is known; however, requests for these are not common for conditions that do not affect intellect or life span [Malfait et al., 2010].

Diagnostic Criteria

After review of the literature, and considering the clinical experience of the authors, we recommend the following diagnostic criteria:

Major criteria

(1) Significant skin hyperextensibility and atrophic scarring.
(2) Generalized joint hypermobility.

Minor criteria

(1) Easy bruising.
(2) Soft, doughy skin.
(3) Skin fragility (or traumatic splitting).
(4) Molluscoid pseudotumours.
(5) Subcutaneous spheroids.
(6) Hernia (or history thereof).
(7) Epicanthal folds.
(8) Complications of joint hypermobility (e.g., sprains, dislocation/subluxation, pain, pes planus).
(9) Family history of a first degree relative who meets clinical criteria.

Minimal criteria suggestive for a diagnosis of classical EDS

Major criteria (1)—Skin hyperextensibility and atrophic scarring

Plus

Either: Major criteria (2)—generalized joint hypermobility

Or: three of the nine minor criteria

Comments

Skin is hyperextensible if it can be stretched over a standardized cut off in the following areas: 1.5 cm for the distal part of the forearms and the dorsum of the hands; 3 cm for neck, elbow and knees; 1 cm on the volar surface of the hand (palm).

Abnormal scarring can range in severity. Most patients have extensive atrophic scars at a number of sites. A minority of patients are more mildly affected. The relevance of surgical scars should be considered with caution in classical EDS, they can appear normal in patients with classical EDS if well managed. Atrophic surgical scars can be found in the general population due to mechanical factors and site of the incision.

Joint hypermobility (JHM) is evaluated according to the Beighton score; a

Beighton score of >5 is considered positive for the presence of generalized joint hypermobility. Since joint hypermobility decreases with age, patients with a Beighton score <5/9 may be considered positive based on their historical observations.

Easy bruising can occur anywhere on the body, including unusual sites. The pretibial area often remains stained with hemosiderin from previous bruises.

Subjective abnormality of the skin texture is appreciable by touching the skin.

Molluscoid pseudotumors are fleshy lesions associated with scars, found over pressure points (e.g., elbow, fingers).

Subcutaneous spheroids are small spherical hard bodies, frequently mobile and palpable, on the forearms and shins. Spheroids may be calcified and detectable radiologically.

Epicanthal folds are often seen in childhood but may also be seen in adults.

Verification of clinical diagnosis

Confirmatory analysis is recommended for any patient meeting the above clinical criteria.

Molecular analysis of COL5A1 and COL5A2 genes identifies a causal mutation in more than 90% of the patients [Symoens et al., 2012; Ritelli et al., 2013]. Molecular screening by means of targeted resequencing of a gene panel that includes at least the *COL5A1*, *COL5A2*, and *COL1A1* gene, or by WES or WGS is indicated. When no mutation is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications.

If genetic testing is not available, electron microscopy findings of collagen flowers on skin biopsy can support the clinical diagnosis.

Absence of these confirmatory findings does not exclude the diagnosis; however, alternative diagnoses should be considered in the absence of a type V collagen gene mutation or electron microscopy findings.

GAPS/FUTURE RESEARCH

A study of the management of vascular complications in EDS described 15 patients with clinical diagnoses of classical EDS with two having thoracic aortic aneurysm repair and two having abdominal aortic aneurysm repair [Brooke et al., 2010]. The authors recognized that they were limited by reliance on clinical criteria for diagnosis when biochemical and genetic testing is more accurate. The evidence that COL1 mutations have an increased vascular risk raises this particular question for these patients. This highlights the benefit of molecular confirmation of patients for research purposes.

A large proportion of the current literature on patients that have had molecular testing focuses on confirming the diagnosis, while the literature on clinical features and management is often not based on molecularly characterized populations. Further studies of associated features in confirmed classical EDS patients is warranted. There are some recent large patient reviews that have helped to develop the understanding of classical EDS. There is huge potential for research using these large patient groups with molecularly confirmed diagnoses.

Mutations in COL5A2 account for a relatively small number of cases. As more mutation analysis is carried out, genotype-phenotype correlations may become more apparent.

Large scale studies on vascular risk and cardiac features would aid management. A few cases studies may be skewing the data and further clarification of this would be helpful for patients with type V collagen mutations. However, it is clear that in the absence of molecular testing, the potential for a type I collagen mutation with an increased risk of arterial rupture cannot be ruled out.

Another question that would benefit from further research is whether a lack of striae can be used as a good indicator for classical EDS and help to direct molecular testing.

Literature is lacking on the frequency of dysautonomia, chronic fatigue syndrome, gastrointestinal involvement, Chiari and cranio-cervical instability in this patient population.

Pregnancy and delivery in classical EDS is another area that would benefit from clear management guidelines.

More data are needed in regard to mild, persistent strength training in relation to the treatment of the hypotonia seen in some cases of classical EDS. The role of fitness, exercise, and rehabilitation in the functional ability and quality of life measure in those with classical EDS is an area for further investigation.

Finally, there is a lack of good prevalence and natural history data for classical EDS.

SUMMARY

A diagnosis of classical EDS is indicated by the well-described triad of hyperextensible skin, atrophic scarring, and hypermobile joints. Although a set of clinical criteria has predominated diagnosis, other conditions do present similarly. Confirmation of diagnosis informs management and is vital for research purposes. Much of the early literature on classical EDS is limited by the lack of laboratory confirmation of diagnoses.

The diagnosis of classical EDS can be confirmed by identifying the pathogenic causative mutation in COL5A1 or COL5A2. Molecular investigations identify mutations in the majority, but currently not all patients with a clinical picture compatible with the diagnosis. Where genetic confirmation has not been possible, a type V collagen abnormality can sometimes be demonstrated by the COL5A1 null allele test. Typical frequent collagen flowers on electron microscopy (EM) of skin can be a helpful diagnostic tool for classical EDS, however, collagen flowers are not unique to this condition. Collagen flowers on EM should be an indicator to test COL1A1 and COL1A2 when clinical features of classical EDS are present in the absence of a COL5 abnormality. Patients with a type 1 collagen abnormality can present with a similar initial clinical appearance to classical EDS, but they have a higher risk of vascular events and need appropriate management.

The management advice for classical EDS has remained consistent over a number of years. There are now a large number of patients with molecularly confirmed classical EDS and these provide a basis for further research on management. Further evidence on cardiac risks, skin care management, exercise potential, and associated features would aid the understanding and management of the condition.

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ARTICLE

Diagnosis, natural history, and management in vascular Ehlers–Danlos syndrome

PETER H. BYERS,* JOHN BELMONT, JAMES BLACK, JULIE DE BACKER, MICHAEL FRANK, XAVIER JEUNEMAITRE, DIANA JOHNSON, MELANIE PEPIN, LEEMA ROBERT, LYNN SANDERS, AND NIGEL WHEELDON

Vascular Ehlers Danlos syndrome (vEDS) is an uncommon genetic disorders characterized by arterial aneurysm, dissection and rupture, bowel rupture, and rupture of the gravid uterus. The frequency is estimated as 1/50,000–1/200,000 and results from pathogenic variants in COL3A1, which encodes the chains of type III procollagen, a major protein in vessel walls and hollow organs. Initial diagnosis depends on the recognitions of clinical features, including family history. Management is complex and requires multiple specialists who can respond to and manage the major complications. A summary of recommendations for management include: Identify causative variants in COL3A1 prior to application of diagnosis, modulate life style to minimize injury, risk of vessel/organ rupture, identify and create care team, provide individual plans for emergency care ("vascular EDS passport") with diagnosis and management plan for use when traveling, centralize management at centers of excellence (experience) when feasible, maintain blood pressure in the normal range and treat hypertension aggressively, surveillance of vascular tree by doppler ultrasound, CTA (low radiation alternatives) or MRA if feasible on an annual basis. These recommendations represent a consensus of an international group of specialists with a broad aggregate experience in the care of individuals with vascular EDS that will need to be assessed on a regular basis as new information develops.

KEY WORDS: Ehlers–Danlos syndrome; vascular EDS; aterial rupture

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INTRODUCTION

Vascular Ehlers–Danlos syndrome (vascular EDS, vEDS, or VEDS, previously known as Ehlers–Danlos type IV) is a dominantly inherited disorder that results from mutations in *COL3A1,* the gene that encodes the chains of type III collagen [Pope et al., 1975; Pepin et al., 2014; Frank et al., 2015a]. The initial diagnosis is usually suspected on the basis of family history, or a clinical history of arterial rupture, dissection or aneurysm, rupture of the large intestine, or pregnancy complications at young ages. Because of clinical overlap with some forms of Loeys–Dietz syndrome, Marfan syndrome, and familial arterial aneurysm and dissection syndromes, the diagnosis should be confirmed by identification of pathogenic variants in *COL3A1* to allow for appropriate surveillance, treatment, and family studies. Type III collagen is a major protein in the walls of blood vessels and hollow organs, which explains increased bruising, arterial and bowel fragility, and uterine, cervical and vaginal fragility during pregnancy and delivery. Mutations in *COL3A1* are currently the only explanation for the vascular EDS phenotypic spectrum. The clinical spectrum (see below) is explained, in part, by

Dr. Peter H. Byers, Departments of Pathology and Medicine (Medical Genetics), University of Washington, Seattle, Washington.
Dr. John Belmont, Department of Human and Molecular Genetics, Baylor College of Medicine, Houston, Texas.
Dr. James Black, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland.
Dr. Julie De Backer, Department of Human Genetics, Ghent University, Ghent, Belgium.
Dr. Michael Frank, AP-HP, Centre de Référence des Maladies Vasculaires Rares, Hôpital Européen Georges Pompidou, Paris, France.
Prof. Xavier Jeunemaitre, AP-HP, Centre de Référence des Maladies Vasculaires Rares, Hôpital Européen Georges Pompidou, Paris, France.
Dr. Diana Johnson, Sheffield Children's Hospital, Western Bank, Sheffield, Yorkshire, United Kingdom.
Melanie Pepin, Departments of Pathology and Medicine (Medical Genetics), University of Washington, Seattle, Washington.
Dr. Leema Robert, Department of Clinical Genetics, Guy's and St Thomas Hospital NHS Foundation Trust, London, United Kingdom.
Lynn Sanders, EDSCares, Milwaukee, Wisconsin.
Dr. Nigel Wheeldon, South Yorkshire Cardiothoracic Center, Northern General Hospital, Sheffield, United Kingdom.
*Correspondence to: Peter H. Byers, M.D., Department of Pathology, Center for Precision Diagnostics, University of Washington, P.O. Box 357655, Seattle, WA 98195-7655. E-mail: pbyers@u.washington.edu
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striking allelic heterogeneity. Clinical heterogeneity among individuals with the same pathogenic variant is probably explained by other genetic modifiers. About half of the probands identified have no family history of vascular EDS, which means the diagnosis is often made in the context of the major complications of the condition. Biallelic mutations have been found in less than 1% of all affected individuals [Plancke et al., 2009; Jorgensen et al., 2015].

Diagnostic Testing

Sequence analysis of *COL3A1* in a qualified clinical laboratory is very sensitive and is thought to identify the underlying pathogenic variant in more than 98% of individuals with vascular EDS. The sensitivity differs little among sequencing strategies so that analysis by Sanger sequencing, exome sequence analysis, or genome sequence analysis appear to be equally effective although genome sequence analysis could identify deep intronic mutations that result in splicing alterations. For individuals with clinical features consistent with vascular EDS in whom no *COL3A1* mutation has been identified, routine sequence analysis, genome sequence analysis, examination of mRNA from cultured fibroblasts, or genome sequence of the region can identify deep intronic variants that alter splicing. Whole exome sequencing is unlikely to uncover a *COL3A1* pathogenic variant in a patient who has previously been tested with a gene panel. In individuals with clinical features of vascular EDS in whom no *COL3A1* mutation has been identified, considerations should be given to analysis of other genes such as those that disrupt the TGFβ signaling pathways and may be referred for research studies to search for additional genetic alterations.

NATURAL HISTORY

The key element to the creation of an effective assessment and management plan for people with vascular EDS is a comprehensive knowledge of the natural history of the disorder. The most common presentation in childhood is easy bruising that may be accompanied by striking skin lucency and vascular visibility. There may be excessive bleeding with circumcision. In some instances, childhood bruising has been sufficient to raise the question of abuse [Roberts et al., 1984]. Other signs such as talipes, congenital hip dislocation, and the facial features are often recognized only in retrospect. There appears to be an increased risk of sudden death under the age of 20, as a consequence of vascular rupture in males [Pepin et al., 2014]. The reason for the selective effect in males is not clear but does not appear to be related exclusively to sporting injuries. In most instances, the diagnosis in these individuals had not been identified prior to death, so that, in part, because they had no family history of the disorder, the diagnosis was made post-mortem. Usually, in the absence of family history, the diagnosis of vascular EDS is rarely considered in childhood, even in the face of unexplained bruising.

The key element to the creation of an effective assessment and management plan for people with vascular EDS is a comprehensive knowledge of the natural history of the disorder.

In the absence of a family history, the diagnosis of vascular EDS is often not considered until after a vessel or hollow organ rupture. Additional features which can raise concern about the diagnosis include with less severe consequences which should raise the suspicion of vascular EDS include unusual bruising without identified cause, acrogeria, recurrent pneumothorax talipes, early onset varicose veins, and characteristic facial features with prominent eyes.

Life Span and Predictors

At present, the life span for affected individuals is a median age of about 51 years (49 for males and 53 for females) but with a very large range (roughly from 10 to 80 years) [Pepin et al., 2014; Frank et al., 2015a]. The major cause of death is arterial dissection or rupture with organ failure. The nature of the underlying mutation in *COL3A1* influences life expectancy. Splice site mutations that lead to exon skipping have the lowest median survival although numbers with this mutation type are small. Substitutions of bulky residues (arginine, aspartic acid, glutamic acid, and valine) for triplet glycine residues in the triple helical domain (Gly-Xaa-Yaa) are usually less severe than splice site mutations, but more consequential than substitutions by smaller residues (alanine, serine, cysteine). Pathogenic variants that alter sequences in the carboxyl-terminal propeptide of the chains can have the full range of effects. Heterozygosity for *COL3A1* null alleles (which accounts for less than 5% of recognized mutations) delays onset of complications on average by almost 2 decades. In some instances, individuals in those families may have few clinical manifestations, even into the 9th decade even though the family was ascertained through an individual with a typical presentation, which emphasizes that life span estimates are population estimates and not strictly applicable to the individual. Knowledge of the familial mutation facilitates care choices, assists with reproductive options, and may be important in the choice of treatment modalities.

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family was ascertained through an individual with a typical presentation, which emphasizes that life span estimates are population estimates and not strictly applicable to the individual.

Bowel rupture is uncommon in early childhood, begins to be recognized in the late childhood, and continues as a risk into adulthood. Bowel rupture ultimately affects about 25–30% of individuals but rarely leads to death.

Spontaneous pneumothorax can also occur during the late childhood with a high risk of recurrence. Active interventions that range from simple needle aspiration to chest drain are often needed and surgical pleurectomy, bleb removal, or chemical pleurodesis may be necessary to control recurrent pneumothoraces.

Pregnancy

The Kaplan–Meier survivals of women who have been pregnant and those who have not are similar [Murray et al., 2014]. However, disease-related complications during pregnancy remain the most common cause of death in women of childbearing age. Pregnancy is associated with death in about 5% of women and first pregnancies seem to account for 50% of those maternal pregnancy-related deaths [Pepin et al., 2014], but only a small number have complications that lead to death that are pregnancy specific (e.g., uterine rupture). The remainder die from arterial complications that are similar to those seen in non-pregnant women. Complications occur in about half the pregnancies and include premature rupture of membranes with preterm delivery, rare uterine rupture during labor, severe perineal tears, and antepartum and post-partum hemorrhage. Some of these complications may be avoided by delivery by cesarean.

OVERALL MANAGEMENT

Life Style—Sense and Sensibility

The goals of medical management are to minimize the likelihood of adverse events and to assure that quality of life is minimally impaired. The general approach to medical management includes the creation of an informed care team, the avoidance of activity choices that are likely to cause adverse effects, and the management of ordinary medical conditions where there is additional risk in individuals with vascular EDS such that this risk is minimized

In general, most of the usual aspects of daily living and recreational activities are within the expected possibilities. Collision sports and isometric activities are generally discouraged. There are examples of individuals who have played football, rugby, soccer, and water polo with only bruising occurring during the activity. However, there are rare deaths that can be attributed directly to the involvement in these activities. The increase risk for early death in young males does not seem to be explained by athletic activities in most individuals. The two concerns in high level sports activities are that the trauma of collisions can lead to vascular rupture and that rapid and recurrent increase in blood pressure and rate can compromise normal vascular structure and lead to dissection or rupture. Specific limits on the extent of activity are difficult to establish. The concept that to retain the capacity to converse with a partner during activity, good breath control while lifting, and light weights to retain tone and strength rather than building mass seem like appropriate guidelines. Weight limits depend not only on previous strength and fitness, but also on history of joint hypermobility, pain, and dislocations. Shoulder, hip, and knee injuries can be minimized by use of light resistance and/or weights. Aerobic fitness through mild to moderate conditioning exercises are encouraged, but with use of pools, stationary bicycle, elliptical trainers, or well cushioned treadmills. Running on hard surfaces and for long distances may exacerbate foot, ankle, knee, and hip pain. Activities with rapid acceleration/deceleration should be discouraged as these may increase the risk of vessel dissection.

Creation of a Care Team

A frequent concern is that the physician does not know anything about this type of EDS. Given the rarity of vascular EDS, outside of medical geneticists, vascular surgeons, and cardiologists few clinicians would be expected to have had significant (any) experience with people with the disorder. With this in mind, at the time of diagnosis, an affected individual should be referred to a center in which there is both experience and expertise. The referral pattern will vary depending on the geographic region. In some settings, centers of excellence have been established and referral patterns institutionalized. This is the case in France and the United Kingdom and in European countries in which reference networks have been set up. In others, the search for an expert may be ad hoc and success not guaranteed. Consultation with the national or international peer groups or University Medical Centers or large free-standing clinical centers with large referral populations may help to identify clinicians with experience and knowledge.

Each individual with vascular EDS should have a primary physician, who acts as the care coordinator, and who is linked to a geneticist or other specialist with detailed knowledge of the disorder. The care team should include the primary care practitioner, a vascular surgeon, and a general surgeon. A genetic consultation will help in identifying possible affected relatives who should be offered cascade testing. The psycho–social impact of the disease is too often neglected and often requires psychological care. It is helpful to have backups, and the team members should be introduced to the patient and family. This team exists to care for the affected individual in the case of major complications, such as bowel rupture, arterial dissection or rupture. A clear protocol

should be created, the local emergency room or rooms should have data about the individual and both the affected individual and relevant family members should know the protocol for contact. A protocol for the emergency room evaluation needs to be established and the on-call caretakers must recognize the needs of the patient. Each affected individual should have letter or "passport"/Emergency Care Card to be carried and provided to the ER physicians at the time of consultation. Copies of such documents are available from several resources once the diagnosis has been established by genetic testing. For younger women planning pregnancy, a high risk team should be assembled that includes experienced obstetricians and vascular surgeons.

Each individual with vascular EDS should have a primary physician, who acts as the care coordinator, and who is linked to a geneticist or other specialist with detailed knowledge of the disorder. The care team should include the primary care practitioner, a vascular surgeon, and a general surgeon.

Surveillance

The objective of surveillance is to identify the potential for complications before they occur and substitute a planned elective procedure in an experienced setting for an ad hoc approach that may occur in the closest available resource. Currently there are no guidelines for surveillance that have been created on an evidence-based formula and, as a consequence programs and institutions vary in their approach. These approaches range from no interim evaluations other than routine and directed physical examination following an interim medical history with perhaps some imaging of the aorta, to detailed assessment of the arterial tree by MRA or CTA on a periodic basis, usually yearly. Even in the latter settings, the criteria for intervention have not been well established and the use of endovascular stenting compared to open surgical replacement of arterial segments remains uncertain. It is hoped that data emerging from established centers with broad experience will provide well-vetted protocols for surveillance and intervention.

TREATMENT

Medical Intervention

The major target of medical intervention has been the maintenance of blood pressure in the normal or low normal range and prevention of surges in blood pressure with the intent to minimize the likelihood of arterial dissection or rupture. Over time, a variety of medications have been suggested that include diuretics, β-adrenergic blockers, angiotensin processing blockers or receptor blockers, and other antihypertensive agents that may depend on knowledge and experience of the clinician. Reports of only one systematic investigation of efficacy of any of these drugs is available, a trial of the mixed β1 antagonist and β2 agonist, celiprolol [Ong et al., 2010]. The study suggests that treatment of individuals with vascular EDS with the drug extends the time to vascular complications compared to those not treated. Selection of subjects was made on clinical grounds and the allocation to treatment or control was based on demographic and clinical criteria for the whole group. Part way through the study it was determined that for about a third of participants no COL3A1 mutation could be identified. Although individuals with COL3A1 mutations who were treated appeared to benefit in the secondary prevention of vascular events, the failure to determine if the comparison groups were equivalent compromises the ability to come to clear conclusions whether treatment with the drug can delay or prevention of vascular events in people with vascular EDS. The drug has been used in this population in Europe and Great Britain (it is not yet available in the US) and it is hoped that analysis of those individuals can clarify whether and under what circumstances there is benefit.

Surgical Intervention

Arterial events

Many symptomatic arterial events are dissections that are self-limiting and may not require radiologic intervention or surgery. In the case of arterial rupture, urgent repair by any possible means is required.

Not all dissections are symptomatic. Indeed, it is not uncommon to discover silent arterial defects during routine arterial monitoring [Frank et al., 2015a]. Symptoms of arterial dissection may be pain secondary to the tear in the arterial wall, to capsular stretch, or related to ischemia in organs or limbs located distal to the dissection. Locations that are commonly symptomatic are iliac and femoral arteries, mesenteric and celiac vessels, renal arteries, aorta (any location), and peripheral arteries of the limbs. Acute management of symptomatic dissection requires pain control, blood pressure control, and monitoring for signs of deterioration in case of ischemia. Anticoagulant or antiplatelet therapy may be required when there is a high risk of ischemia due to narrowing of the vessel or peripheral embolization. Given the risk of complication due to these therapies, their use is generally limited to a short period of time.

In the event of arterial rupture, interventional therapy may be indicated. Anatomically contained (partial) ruptures may be treated medically but require close monitoring to detect recurrent bleeding. Non-contained ruptures or clinically unstable aneurysms (pre-rupture) or false aneurysms most often require intervention. According to the location, interventional radiology or open surgery may be indicated, although invasive procedures may be more likely to provoke further morbidity. The nature of

treatment depends on the location of the arterial rupture. Often occlusion by embolization of the bleeding artery is necessary.

The best setting for vascular surgery is the planned repair of aneurysms and dissecting aneurysms, especially those affecting the aorta or iliac vessels. Open intervention however requires specific repair techniques because of the inherent vessel friability and should be avoided as much as possible.

Repeated arterial events

Patients with symptomatic arterial events may present during the acute phase of their dissection/rupture with repeated arterial accidents in distant arterial territories in the hours/days following the initial event. The risk of secondary accidents may increase with the severity of the initial event, the length of the hospital stay, the invasive character of treatment, and the extent of fluid overload. No specific causal factors have been formally identified to explain these events.

We suggest a protocol of "permissive hypotension" in which hypotension is permitted as long as it does not compromise intellectual or other organ function, the avoidance of inotropic agents, and the judicious use of IV fluids to increase pressure. Additional precautions are required with indwelling catheters because of the risk to the integrity of vascular or organ walls.

Evaluation

Evaluation at the time of emergency referral depends on the signs and symptoms. In general, non-invasive evaluation of the abdomen, chest, and head are preferred using MRI, CT, and venous angiographic approaches to understand blood loss. Use of arteriography with high pressure injection is generally avoided because of the risk of further vascular injury. Some vascular events can be dealt with effectively with embolization [Brooke et al., 2010; Okada et al., 2014]. Although covered stents are being placed in life-threatening situations to forestall active bleeding, it is not known if and how arteries will withstand the pressure of the stents over the long course. Aneurysmal dilation may occur in some while others may require open surgical intervention.

Bowel rupture almost always requires surgical intervention and usually leads to isolation of the distal bowel, removal of the ruptured segment, and creation of a colostomy. Repair of colostomy has become more commonplace and is frequently successful. Recurrent surgery may be associated with ilio-colic fistula formation and subtotal colectomy may prevent further colonic ruptures [Frank et al., 2015a]. This possibility could be discussed at the time of the first colonic rupture if the diagnosis of vascular Ehlers–Danlos syndrome has been established.

ORGAN SYSTEM INVOLVEMENT

Cardiac

There is no increased risk of cardiac valvular abnormalities or structural cardiac defects. Mitral valve prolapse probably occurs at the same frequency as in the general population. There is an increased risk of coronary artery dissection and, as a consequence, myocardial infarction [Pepin et al., 2014]. In the event of myocardial infarct, there is an increased risk of ventricular rupture and pericardial tamponade with sudden death. Non-MI related mitral valve papillary muscle rupture has been described in vascular EDS patients.

Gastrointestinal

The most common complication is spontaneous rupture of the colon, usually the sigmoid [Pepin et al., 2014; Frank et al., 2015a]. The clinical presentation is one of rapid crescendo of unremitting pain, generally in the lower left quadrant. Treatment is similar to that in individuals without vascular EDS and generally leads to colostomy which can be successfully reversed a few months after the initial event without further complications. Recurrence is more frequent than in the non-EDS population and may lead to partial colectomy. Awareness of the genetic diagnosis may help to shape care.

Small bowel rupture appears to be less common and may in some result from intramural hemorrhage and in others as a consequence of adhesions from previous surgery. Fistula formation is not uncommon following abdominal surgery and may lead to rapid transit time and problems with nutrition. Surgical intervention with partial bowel resection can be successful.

Esophageal and gastric rupture have also been reported [Reis et al., 1998].

Pulmonary

Spontaneous pneumothorax is seen in 12% of individuals, often as a first manifestation. It is not clear if there is a male predominance as there is with the idiopathic presentation. Rupture of pulmonary blebs is probably the major cause of pneumothorax.

Spontaneous pneumothorax is seen in 12% of individuals, often as a first manifestation. It is not clear if there is a male predominance as there is with the idiopathic presentation. Rupture of pulmonary blebs is probably the major cause of pneumothorax.

Spontaneous pulmonary hemorrhage resulting in hemoptysis is a rare complication and can result from rupture of small pulmonary vascular nodules or arteriovenous fistulae [Ishiguro et al., 2009; Kawabata et al., 2010].

Treatment of this complication follows the same pathways as for those without vascular EDS.

Vascular

Superficial venous insufficiency (SVI) is more prevalent in patients with vascular EDS than in the general population (37% vs. 17–23%; Frank et al., 2015b). SVI is characterized by its precocity (44% of patients with SVI declare their venous disease before the age of 20 years; Frank et al., 2015a) and is characterized by the early presence of significant (>3 mm) varicose veins (stage C2 CEAP). Vein stripping may result in extensive vascular damage (femoral vein/artery rupture) and/or in uncontrolled bleeding and should therefore be avoided. Commonly however, the early onset of SVI competes with the first vascular EDS-related events and thus the genetic diagnosis of the patient's condition. Because of this, it is not rare that the diagnosis of vEDS is suspected after an unusually complicated surgical stripping. Therapy primarily consists in medical compression. Endovenous laser or radiofrequency endovenous thermal ablation have been successfully reported in patients with vEDS [Okada et al., 2014; Frank et al., 2016]. In countries where it is available, foam sclerotherapy may also be a complementary or alternate treatment.

Skin

Although thin skin with readily visible venous patterning is one of the typical features described in individuals with vascular EDS, it is often a subtle finding and bruising that is not explained by trauma is more common. Acrogeria is uncommon and usually accompanies mutations that appear near the carboxyl-terminal end of the triple helical domain. Bruising may increase with aspirin or non-steroidal anti-inflammatory medications and certain in the presence of anti-coagulant treatment. Alopecia occurs inconstantly but can be striking in some women.

Musculoskeletal

Height varies through the normal range although small for family may be more common. Congenital hip dislocation is increased as is congenital talipes and limb reduction defects (perhaps secondary to amputations by amniotic bands) [Young et al., 1985] when compared to the average population but these alone are generally insufficient to warrant diagnostic testing.

Distal joint contractures occur in a small proportion of individuals, these are progressive and can be disabling.

There also appears to be an increase in the relative frequency of muscle and tendon rupture, but these data have not been aggregated.

Ocular

Carotid cavernous fistula: Globe protrusion as a consequence of retrograde arterial flow through the venous system around the globe occurs as a result of "carotid-cavernous sinus fistula" formation and is a medical emergency. This may be recognized by the affected individual because of sudden onset of a swishing sound in the temporal region of the head followed by injection of the veins of the eye, pain around the eye, and protrusion with slow loss of visual acuity. The only treatment is closure of the fistula, usually by an arterial catheter and coiling or occlusion of the carotid proximal to the fistula [Halbach et al., 1990; Linfante et al., 2015].

Subtle globe protrusion is also a common feature of the "characteristic facial appearance" and may result in failure to completely close the lids during sleep with recurring conjunctivitis.

Keratoconus, thinning of the cornea, is a very rare feature of vascular EDS but the frequency has not been determined. The diagnosis requires measure of the corneal thickness and architecture. It can lead to sufficient visual distortion that cannot be well treated with contact lenses so that the only effective remedy is corneal transplant, which has been successful. Retinal disorders do not appear with increased frequency. Keratoconus, globe rupture, and blue sclerae are features of a different type of EDS that results from mutations in two separate genes (*ZNF469* and *CHST14*) [Rohrbach et al., 2013; Kosho, 2016]. Globe rupture is not a feature of vascular EDS. Isolated keratoconus is a rare disorder that does not appear to result from mutations in *COL3A1* or the other Ehlers–Danlos-related genes. Isolated keratoconus may be more frequent than vascular EDS.

Oral

The most common oral problem is gum fragility with bleeding after brushing or flossing [Ferré et al., 2012]. In some individuals, there is marked loss of gingival tissue with recession that can lead to tooth loss. This may lead to confusion about the diagnosis and raise the concern of the periodontal form of EDS [Kapferer-Seebacher et al., 2016]. Therapy is limited to fastidious oral hygiene but even that may not be sufficient to safe guard gingival integrity.

Hyperlaxity of the temporomandibular articulation can also result in repetitive subluxations and pains.

Renal

Intrinsic renal disease is not increased. The major renal concern results from renal artery dissection that may lead to diminished renal blood flow, loss of renal parenchyma, and renal hypertension. In some instances, stenting of the stenotic vascular regions can restore flow and result in normalization of blood pressure (unlikely approach in these patients in clinical practice). In others, appropriate and aggressive treatment of blood pressure to maintain the normal range is indicated, in first instance with a blocker of the renin angiotensin system (ACEI, ARB).

Genitourinary

There do not appear to be specific genitourinary complications. Iatrogenic bladder perforation has been reported during C-section.

ANIMAL MODELS

Currently there are two available mouse models for vascular EDS, both are homozygous or heterozygous nulls which represent only about 5% or less of all known instances of human vascular EDS [Liu et al., 1997; Cooper et al.,

2010; Smith et al., 2011]. In these models, a very small proportion of the homozygotes survive until birth and then they uniformly develop arterial ruptures and died by about 6 months of age. Hypertension converts an asymptomatic heterozygote to one that develops large arterial rupture. In one model, use of doxycycline to inhibit matrix metalloproteinases appeared to change the arterial topography but the effect on aortic rupture was unclear. Animal models with missense and splicing mutations are currently under investigation.

FUTURE NEEDS

Vascular EDS is an uncommon genetically homogeneous, but with substantial allelic heterogeneity, disorder (perhaps as frequent as 1/50,000) that results from pathogenic variants in *COL3A1*. There is no consensus on the best practice for medical surveillance, for medical intervention, or for surgical intervention. In part, these limitations result from the rarity of the disorder, the difficulty in assembling clinical data, and the relative paucity of natural history data. The following pathways may lead to better diagnosis, management, and treatment:

- make educational materials about the disorder available to the medical community: Undergraduate medical education, medical and surgical teaching programs, and ER facilities,
- collect all sequence data from testing laboratories and facilitate contact with all individuals with pathological variants and those with VUS for follow-up,
- create centers of excellence to provide expert periodic evaluation to develop standardized care, surveillance, and intervention,
- assist in the provision of local "care teams" for each individual identified,
- create an international web-based registry of individuals with vascular EDS with permission to contact and re-contact for both clinical information and involvement in clinical trials,
- promote international cooperation and collaboration through yearly scientific/clinical meetings in revolving venues,
- use registry and other clinical data to provide clear natural history descriptions,
- create animal models with common types of mutations—heterozygous substitutions for glycine in the triple helical domain and splice site mutations,
- identify or develop "biomarkers" for surveillance (enrollment closed),
- develop clinical trials for small molecular intervention (enrollment about to begin), and
- develop models for genetic intervention.

Summary of Management Recommendations

- identify causative variants in COL3A1 prior to application of diagnosis,
- modulate life style to minimize injury, risk of vessel/organ rupture,
- identify and create care team,
- provide individual plans for emergency care ("vascular EDS passport") with diagnosis and management plan for use when traveling,
- centralize management at centers of excellence (experience) when feasible,
- maintain blood pressure in the normal range and treat hypertension aggressively, and
- surveillance of vascular tree by doppler ultrasound, CTA (low radiation alternatives) or MRA if feasible on an annual basis.

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ARTICLE

Hypermobile Ehlers–Danlos Syndrome (a.k.a. Ehlers–Danlos Syndrome Type III and Ehlers–Danlos Syndrome Hypermobility Type): Clinical Description and Natural History

BRAD TINKLE,* MARCO CASTORI, BRITTA BERGLUND, HELEN COHEN, RODNEY GRAHAME, HANADI KAZKAZ, AND HOWARD LEVY

The hypermobile type of Ehlers–Danlos syndrome (hEDS) is likely the most common hereditary disorder of connective tissue. It has been described largely in those with musculoskeletal complaints including joint hypermobility, joint subluxations/dislocations, as well as skin and soft tissue manifestations. Many patients report activity-related pain and some go on to have daily pain. Two undifferentiated syndromes have been used to describe these manifestations—joint hypermobility syndrome and hEDS. Both are clinical diagnoses in the absence of other causation. Current medical literature further complicates differentiation and describes multiple associated symptoms and disorders. The current EDS nosology combines these two entities into the hypermobile type of EDS. Herein, we review and summarize the literature as a better clinical description of this type of connective tissue disorder. © 2017 Wiley Periodicals, Inc.

KEY WORDS: joint hypermobility; joint hypermobility syndrome; Ehlers–Danlos syndrome type III; Ehlers–Danlos syndrome hypermobility type

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INTRODUCTION

Hypermobile Ehlers–Danlos syndrome (hEDS; previously known as EDS type III according to the Berlin nosology [Beighton et al., 1988] and EDS hypermobility type in the Villefranche nosology [Beighton et al., 1998]) is a heritable connective tissue disorder (HCTD) primarily identified as having generalized joint hypermobility (GJH), related musculoskeletal manifestations, and a milder involvement of the skin, which lacks the degree of cutaneous features typically observed in the classical and vascular types of EDS. Since the Villefranche nosology, the clinical description of hEDS in the medical literature has expanded considerably to include more features, such as chronic pain, chronic fatigue, dysautonomia, and anxiety among other associated symptoms.

Since the Villefranche nosology, the clinical description of hEDS in the medical literature has expanded considerably to include more features, such as chronic pain, chronic fatigue, dysautonomia, and anxiety among other associated symptoms.

Brad Tinkle is a clinical geneticist with interests in connective tissue disorders and is Division Head of Clinical Genetics at the Advocate Children's Hospital.

Marco Castori is a Clinical Geneticist with focus on the diagnosis and management of hereditary connective tissue disorders, particularly Ehlers–Danlos syndromes. He is a co-author of more than 130 papers in international journals and 14 book chapters.

Britta Berglund is an associated researcher in nursing research in Uppsala University, retired but active.

Helen Cohen is in the Department of Rheumatology at Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex.

Rodney Grahame is at Centre for Rheumatology, University College London and the Hypermobility Unit at Hospital of St John & St Elizabeth, London.

Hanadi Kazkaz is in the Rheumatology Department, University College Hospital, London.

Howard Levy is an Associate Professor at Johns Hopkins University. He is a primary care internist and a medical geneticist, with particular interest and experience in Ehlers–Danlos syndrome and other hereditary disorders of connective tissue.

*Correspondence to: Brad Tinkle, M.D., Ph.D, Division of Clinical Genetics, Advocate Children's Hospital, 1875 Dempster St, Suite 285, Park Ridge, IL 60068. E-mail: brad.tinkle@advocatehealth.com

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In a similar timeframe, joint hypermobility syndrome (JHS; also called hypermobility syndrome or benign joint hypermobility syndrome) has been further delineated since its original description [Kirk et al., 1967; Grahame et al., 2000]. The clinical spectrum of JHS is often clinically indistinguishable from hEDS according to an international panel of experts [Tinkle et al., 2009]. Subsequently, Castori et al. [2014] demonstrated the evolving natural history by studying multi-generational pedigrees and applying the then current diagnostic criteria for each (hEDS and JHS) concluding that both disorders may co-exist in the same pedigrees and could not be distinguished in the familial cases. It is, therefore, the consensus of the authors on behalf of the International Consortium on the Ehlers–Danlos Syndromes, based on the present state of our knowledge, that the two conditions are part of the same clinical spectrum ranging from apparently symptomatic GJH to the most disabled individuals fitting the new diagnostic criteria for hEDS.

Grouping all phenotypes comprised in this spectrum under the same heading may be misleading on both nosologic and therapeutic perspectives. Although it is reasonable that the congenitally "double-jointed" gymnast and the chronically disabled hEDS patient may share a strong genetic and pathophysiological background, to date, we have not any proof unequivocally demonstrating that they carry the same genetic trait, unless, perhaps, they are linked by a close blood relationship. But also in this case, as the molecular bases of these phenotypes remain unknown, we cannot exclude that these two individuals share a part only of the causative genetic milieu (i.e., oligogenic/polygenic disorder) in the absence of shared additional clinically or structurally relevant signs.

The new criteria of hEDS are stricter than the old Villefranche nosology [Beighton et al., 1988] and the Brighton criteria [Grahame et al., 2000]. This is intended to define a more homogeneous phenotype shared among patients who require long-term medical attention for hEDS and to facilitate scientific identification of the underlying genetic cause(s) of the condition. Accordingly, some patients meeting the old Villefranche and Brighton criteria will not meet the new hEDS criteria. For all these individuals not showing a sufficiently convincing hEDS phenotype, some alternative labels within the above-mentioned spectrum are presented elsewhere in this issue (see "A Framework for the Classification of Joint Hypermobility and Related Conditions" by Castori et al., this issue).

Given the extreme variability within this spectrum and the age-influenced progression of the phenotype, some of these patients will probably remain under a relaxed program of follow-up in order to promptly detect the possible evolution into a full-blown hEDS phenotype.

METHODS

The Committee on hEDS of the International Consortium on the Ehlers–Danlos Syndromes met by telepresence or through electronic correspondence throughout 2015 and 2016 to discuss the nosology and clinical description of hEDS. The following reflects extensive literature review and the professional experience of the committee members as well as insights from various contributing members of the international effort on EDS through the Consortium.

CLINICAL DESCRIPTION

The below sections of this paper describing the phenotype and natural history of hEDS are extracted by the literature available on EDS hypermobility type, EDS type III and JHS (old nomenclature). To date, we are not sure that all available data will stand true for the newly defined hEDS. However, they are considered a good proxy for the delineation of the hEDS phenotype. In the following sections, the acronym hEDS is used as a substitute for EDS hypermobility type, EDS type III, and JHS, unless the distinction between these phenotypes is necessary for reasons of clarity.

Prevalence

Accurate prevalence estimation studies are still lacking for hEDS. Steinmann et al. [2002] reported a minimum prevalence of 1/5,000 for all types of EDS collectively. As hEDS likely represents 80–90% of cases of EDS, the prevalence is presumed not lower than 1/5,000. A much higher prevalence of 7.5/1,000 to 20/1,000 (0.75–2%) for "symptomatic" GJH has been proposed, considering that about 10% of individuals with GJH may develop related symptoms in their lifetime [Hakim and Sahota, 2006]. Others confirmed such an estimation [Hamonet et al., 2015]. A much higher prevalence for the association of JH and widespread pain is reported by Mulvey et al. [2013] and Morris et al. [2016]. Based on data obtained from a large epidemiological study undertaken on a population of 12,853, 3.4% had joint hypermobility and widespread pain which was been used as a proxy for hEDS [Mulvey et al., 2013]. Accordingly, hEDS is likely the most common systemic inherited connective tissue disorder in humans which translates in approximately 2 million in the United Kingdom, 10 million in the United States, 17 million in Europe, and 255 million affected worldwide. However, the diagnostic criteria proposed herein are more selective than the Villefranche nosology for EDS hypermobility type and the Brighton criteria for JHS, so the prevalence of hEDS under these criteria may be somewhat lower than some of these estimates.

Genetics

hEDS, for the most part, is inherited as an autosomal dominant disorder of connective tissue but other patterns of inheritance can be seen in some families; however, this may be confounded by non-penetrance, sex-influence as well as genetic heterogeneity. Unfortunately, unlike the other types of EDS, hEDS has no known genetic etiology responsible for any significant portion of this population. JH itself is multifactorial with age, gender, weight, training, and other aspects that influence this

phenotype. Twin studies have determined that the concordance of JH among dizygotic twins was 36% in 472 female twin pairs, whereas monozygotic twins had a concordance rate of 60% in 483 female twin pairs suggesting a strong genetic trait with multifactorial influences [Hakim et al., 2004].

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Various studies have suggested that hEDS is a phenotypically and presumably genetically heterogeneous disorder [De Wandele et al., 2013; Pacey et al., 2015a]. A minority of cases have been reported to be due to a haploinsufficiency of tenascin X (*TNXB*) [Zweers et al., 2003]. However, the haploinsufficiency was not penetrant in males and only partially in females (9 out of 14). *TNXB* lies near *CYP21A2*, the gene associated with congenital adrenal hyperplasia (CAH). The region contains several pseudogenes including those for *TNXB* and *CYP21A2*. Intragenic recombination and resultant microdeletion is a common cause of CAH. Merke et al. [2013] reported in several CAH individuals, an hEDS-like phenotype due to chromosomal microdeletion and coined the syndrome CAH-X. More recently, a novel missense variant of *TNXB* was shown in 10 individuals of seven families and was associated with the hEDS phenotype [Morissette et al., 2015]. Tenascin-X is an extracellular matrix protein and potentially can affect connective tissue in its various forms. However, the exact physiologic process remains unknown and heterozygous tenascin-X deficiency accounts for only a small percentage of hEDS.

A few case reports have pointed to other genetic factors in hEDS. A collagen type III (*COL3A1*) variant was found in one family without the arterial or intestinal fragility typical of vascular EDS [Narcisi et al., 1994], but no subsequent reports of *COL3A1* mutation have been published in hEDS. More recently, a variant of the *LZTS1* gene was found in four families with a hEDS phenotype among 231 individuals evaluated, but the causal nature of these variants remains unexplored [Syx et al., 2015]. It is believed by many that the hEDS phenotype represents substantial genetic heterogeneity. With the wider use of whole exome or whole genome sequencing with strict phenotyping, it is expected that additional hEDS-related genes will be identified. Eventual identification of validated genetic etiologies will allow objective clinical testing and better delineation of the full phenotype.

The Evolving Natural History

The Villefranche criteria for EDS hypermobility type and Brighton criteria for JHS were originally conceived for the diagnosis of two conditions perceived as distinct. However, they were subsequently recognized as separate tools for describing a single disorder [Tinkle et al., 2009; Castori and Colombi, 2015]. Such a dichotomy likely reflects the protean progression of the same entity. Anecdotally, many families were identified that had diagnoses of EDS hypermobility type and JHS in various family members usually segregated on age. The clinical identity between EDS hypermobility type and JHS was provisionally demonstrated in a single multiplex family with affected individuals fitting alternatively the Villefranche and Brighton criteria [Hermanns-Lê et al., 2012].

Definitive support to such a clinical overlap in families with EDS hypermobility type and JHS came from a study in 23 Italian pedigrees [Castori et al., 2014]. In these families, the formal diagnosis was influenced by age, with children usually meeting the Villefranche criteria only and the elderly mostly ascertained by the Brighton criteria alone, while both diagnoses often coexisted in young adults and middle-aged affected members. This implied that the mean Beighton score, frequency (and distribution) of musculoskeletal pain, manifestations of skin involvement, and appearance of other complications were strongly influenced by age. Such a phenomenon seems not limited to the items included in the Villefranche and Brighton criteria, but also extends to other disease manifestations not originally considered, such as the gastrointestinal involvement [Castori et al., 2015a].

In an Italian study on disease progression with 21 hEDS patients, the existence of three "discrete" disease phases was proposed: a "hypermobility" phase, a "pain" phase, and a "stiffness" phase [Castori et al., 2010a]. Subsequent observations and speculations on the same ethnic group reinforced the concept and smoothed the rigid approach on three separate phases [Castori et al., 2011a, 2013, 2015b]. The three-step model can remain a prototypical description of the potential disease course, but not every patient experiences all three phases and the rate of transition between phases can be highly variable. The decrease of the Beighton score in the symptomatic individual may be considered a proxy for disease evolution in hEDS [Castori et al., 2011a, 2015b]. In cross-sectional studies on patients with different ages at diagnosis, a tendency of the Beighton score to turn "negative" (i.e., <5) around the fourth decade of life has been identified [Castori et al., 2011a].

The "hypermobility" phase dominates the first several years of life with contortionism and propensity for sprains and dislocations. Pain is often limited to lower limbs (i.e., persistent "growing pains") but pain with fine motor or repetitive tasks such as handwriting is also commonly encountered [Gedalia et al., 1996; Murray and Woo, 2001]. Easy fatigability may be a feature, together with voiding dysfunction [Beiraghdar et al., 2013; Kajbafzadeh

et al., 2014]. Some hypermobile children experience developmental dyspraxia (or developmental coordination disorder), manifesting with mild hypotonia and non-specific developmental delay in gross and fine motor skills attainment [Adib et al., 2005; Kirby et al., 2005; Easton et al., 2014].

The "pain" phase is characterized by generalization and progressive chronicity of musculoskeletal pain, which is often diagnosed as fibromyalgia [Ting et al., 2012], summation of other forms of chronic pain, such as pelvic pain (in women) and headache, as well as exacerbation of fatigue. This phase typically starts in the second to the fourth decade of life and often associates with a variegated constellation of additional complaints, such as paresthesias, mixed and treatment-resistant functional gastrointestinal disorders, orthostatic intolerance, and pelvic dysfunction.

A generalized reduction of joint mobility dominates the "stiffness" phase, in which patients usually experience significant reduction in their functionality due to the combination of disabling symptoms (e.g., pain and fatigue) as well as motor limitations due to the coexistence of reduced muscle mass and weakness, defective proprioception, prior injuries, and arthritis. In this phase, observed in a few adults and elderly only, the symptomatology that appeared in the "pain" phase escalates and GJH is usually not appreciated.

hEDS is considered to be an autosomal dominant trait with variable expressivity. Yet, many studies point out a strong excess of affected females, at least in adults [Castori et al., 2010a]. The ratio ranges from 8–9:1 to ~2:1, depending upon how patients are selected. The lowest ratio was registered in familial cases only with the inclusion of affected relatives [Castori et al., 2014]. In early childhood, the male to female ratio of affected is similar. However, in the general population, as children enter puberty, joint mobility tends to increase in females and decrease in males [Fig. 1; Quatman et al., 2008]. The reason for the sex bias remains incompletely understood with speculation of a greater influence of female sex hormones [Wolf, 2009; Shultz et al., 2012; Boyan et al., 2013]. hEDS is best defined as an autosomal disorder "influenced by sex," with a predominance of symptoms in females. It should also be recognized that most chronic pain syndromes also have a female predominance, and this may be another contributing factor [Wijnhoven et al., 2006].

The phenotype of hEDS is one that evolves over time and has a gender bias that also changes over time. Previous attempts at diagnostic criteria (Villefranche and Brighton) have often not fully accounted for the natural transition from EDS hypermobility type to JHS with age within the above described disease evolution [Castori et al., 2013]. Such a nosological conundrum is solved by the use of unified diagnostic criteria.

Symptomatic Joint Hypermobility

Clinical problems associated with JH may present at any time of life. Syndromic or excessive JH can be difficult to diagnose in children, who are normally more flexible than adults [Tofts et al., 2009; Castori, 2012]. GJH is often diagnosed using the Beighton score (see also "Measurement properties of existing clinical assessment methods for local and generalized joint hypermobility—a systematic review," Juul-Kristensen et al., this issue), although this has major limitations in selected populations, such as the very young and the elderly [Dolan et al., 2003; Castori, 2012]. It can be asymptomatic, and is more common among dancers and elite athletes where it may confer a constitutional advantage [Day et al., 2011; Beighton et al., 2012]; however, it may predispose to higher injury rates [Briggs et al., 2009; Konopinski et al., 2015].

When symptomatic, it often manifests in childhood or adolescence, along with associated features, but is often poorly recognized [Engelbert et al., 2003]. Adults may recall being flexible as a child, and being able to perform "party tricks" with their joints. The two more common patterns of presentation are with: (1) a limited number of painful and/or unstable joints or (2) chronic widespread musculoskeletal pain (which may have been diagnosed as fibromyalgia). In the former group, the more common problematic or unstable joints often presenting with recurrent subluxations/dislocations or pain are the shoulder, knee, and ankle [Tobias et al., 2013]. Iliotibial band syndrome (sometimes called "snapping hip"

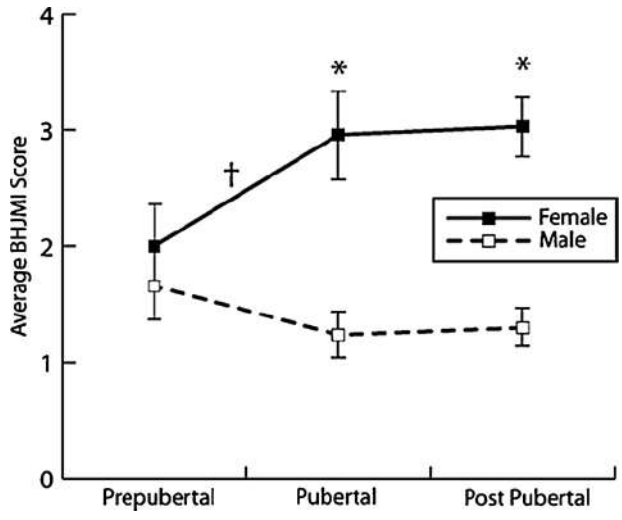

Figure 1. Gender and pubertal maturation status as compared to Beighton score (BHJMI) in a general population of male (N = 143) and females (N = 275). Beighton scores representing joint laxity increased during puberty in females and decreased in males. Published with permission [Quatman et al., 2008].

syndrome) is also common, and is frequently perceived by the patient as hip instability, even though the sense of motion occurs over the greater trochanters and not in the groin. In the group with chronic widespread musculoskeletal pain, the pain distribution and descriptions often overlap with fibromyalgia to such an extent that it can be virtually impossible to distinguish [Ofluoglu et al., 2006; Ting et al., 2012]. It is important to recognize that there are many causes for both localized and widespread joint or musculoskeletal pain, and that the presence of pain alone without associated JH is insufficient to establish a diagnosis of EDS. Over time, many patients lose their former joint laxity, while others remain hypermobile [Castori, 2012]. This reduction in JH over time further complicates the diagnostic evaluation of chronic pain patients over approximately age 40.

In common with other chronic pain syndromes, there may also be overlapping diagnoses such as chronic fatigue, irritable bowel syndrome, temporomandibular joint dysfunction, sleep disturbance, as well as depression and anxiety. The specific associated impairments and their severity can vary markedly, and are not necessarily associated with the degree of joint laxity. Higher rates of anxiety and depression have been noted in GJH, hEDS, and JHS since 1994 [Lumley et al., 1994; Mallorqui-Bagué et al., 2015]. Distress, kinesiophobia, and individuals' coping strategies and behavioral responses are more likely to predict impairment and quality of life (QoL) than the intensity of pain [Celletti et al., 2013]. Physical deconditioning can exacerbate joint laxity, contributing to an ongoing cycle of deconditioning, weakness, joint instability, and worsening pain [Castori, 2012].

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Pain

The specific underlying cause(s) and mechanism(s) of pain in EDS, and in particular hEDS, are not well understood, but both acute and chronic pain are common manifestations and often contribute to disability [Rombaut et al., 2010, 2011a,b, 2012; Voermans et al., 2010a,b; Castori et al., 2012a; Murray et al., 2013]. Nociceptive pain directly related to affected muscles, joints, and connective tissue is frequent. Neuropathic pain, characterized by allodynia and/or typical quality descriptors, such as electrical, burning, numb, or tingling, is also common. Anatomic imaging (e.g., for impingement of the central spine or foraminal nerve roots) and functional electrodiagnostic studies (e.g., nerve conduction studies or electromyography) are often negative even in the face of subjective symptoms highly suggestive of a neuropathic etiology. Skin biopsy may reveal reduction of intradermal nerve fiber density, suggestive of small fiber neuropathy [Cazzato et al., 2016].

Some potential etiologies of pain include spasm of muscles, tendons, and other connective tissue; direct trauma due to joint instability; and nerve entrapment [Granata et al., 2013]. Osteoarthritis, secondary to joint instability, is also a likely factor. Central sensitization, generalized hyperalgesia, chronic regional pain syndrome, and similar systemic or regional pathogenic mechanisms may contribute in later stages [Castori et al., 2013; Rombaut et al., 2015; Scheper et al., 2015, 2016a; Di Stefano et al., 2016]. See also "Pain Management in the Ehlers–Danlos Syndromes" by Chopra et al., this issue.

Skin and Fascia

The Ehlers–Danlos syndromes are primarily due to disorders of connective tissue matrix proteins, in particular, but not exclusively collagen (see also "The Ehlers–Danlos Syndromes: The New" by Malfait et al., this issue). It is presumed that the genetic determinants of hEDS are also likely of collagen or collagen-related genes. The dermis comprises 70% dry-weight collagen so that the skin presents itself as a visible, palpable, and readily accessible organ for the study of collagen-related genetic aberrations. The skin in hEDS is different from normal skin and these differences constitute an important aid to diagnosis. In hEDS, the skin texture is characteristically soft, silky, or velvety to the touch. It may be semi-transparent so that veins and tendons are more easily visible than normal, but this is subtle in comparison with the skin transparency of vascular EDS.

The skin in hEDS is also hyperextensible. The technique used is important in obtaining reliable results. The stretchiness is subtle in hEDS and can easily be overlooked if the clinician is anticipating the degree of stretch seen in classical EDS. The "rubber glove skin test" may distinguish between hEDS skin and normal, by raising a skin fold on the dorsum of the hand in patients with hEDS, the skin is seen to stretch over a much wider area than is normal, extending to the wrist and beyond. However, the clinical evaluation of skin laxity follows that outlined in the new diagnostic criteria for hEDS (see also "The 2017 International Classification of the Ehlers–Danlos Syndromes" by Malfait et al., this issue).

The hEDS skin is more fragile than normal, but much less so than in the other types of EDS. Easy bruising is common but poorly defined. Wound healing may be impaired with the production of mildly atrophic scars, which may be wider than the original wound and/or sunken below the

surface of the surrounding skin. Again, the degree of atrophic scarring in hEDS is less severe than in and usually distinguishable from the other types of EDS (Fig. 2). However, its occurrence may be exacerbated by the use of local or systemic steroids [Jacks and Zirwas, 2016].

Striae atrophicae often appear during the adolescent growth spurt usually between the ages of 11–13 years and not necessarily associated with rapid weight gain; however, this can also be seen in adolescents without an underlying connective tissue disorder as well [Feldman and Smith, 2007]. By contrast, striae gravidarum may be minimal or nonexistent in some as skin of the mature hEDS female is inherently stretchy so that the elastic limit is never reached despite the enlarging maternal abdomen.

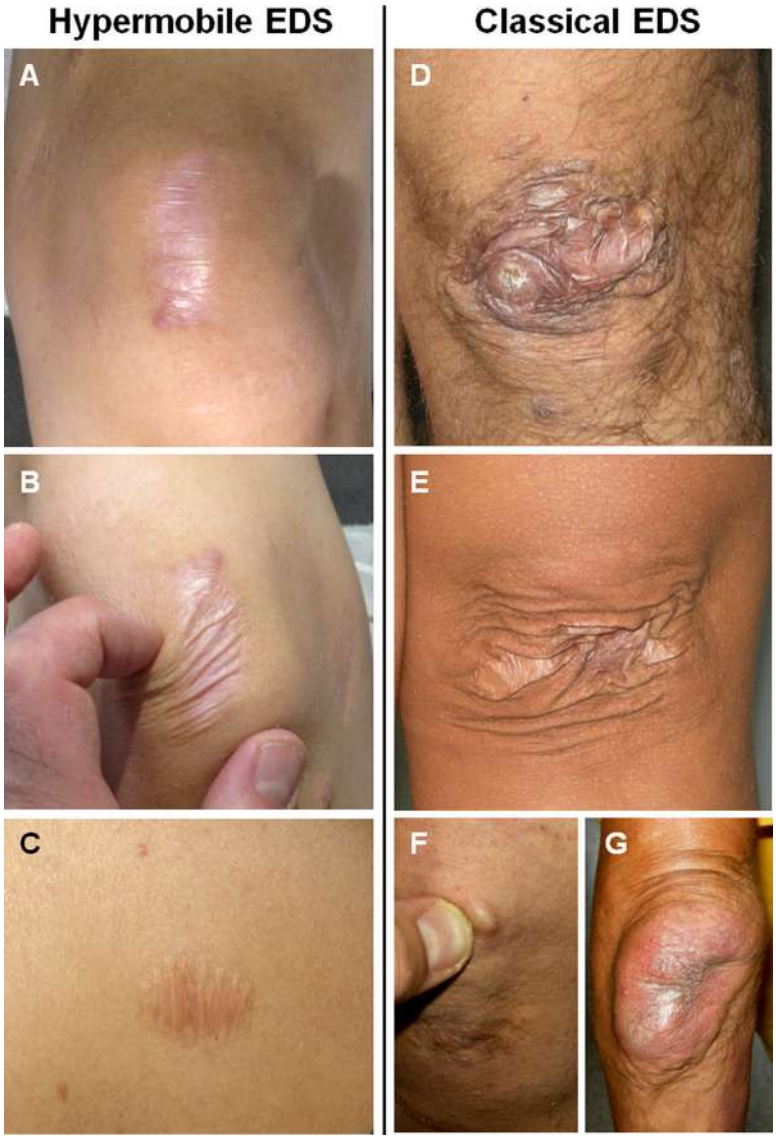

Figure 2. Comparison between abnormal scarring and satellite cutaneous signs in hEDS and classical EDS due to mutations in *COL5A1/COL5A2/COL1A1*. hEDS (A–C). **A**: Post-traumatic mildly atrophic scarring of the knee in a boy. **B**: Dermal hypotrophy is more evident by stretching between the observer's fingers. **C**: Post-surgical enlarged scar in a young woman. Classical EDS (D–G). **D**: Typical papyraceous and hemosiderotic scar of the knee in a man. **E**: A milder scar in a young woman; in comparison with A and B, the atrophic nature of the scar is appreciable without passive skin stretching and the surrounding skin is redundant with a cutis laxa-like appearance. **F**: The typical, though rare, subcutaneous spheroid. **G**: An enlarged molluscoid pseudotumor of the elbow in a man.

Other important collagen-bearing tissues may also fail in hEDS due to their inherent fragility. Cerebrospinal fluid (CSF) leaks, spontaneous or induced, are a possible cause of orthostatic headaches. One case-control study of patients with spontaneous CSF leak reported a greater than expected frequency (16/50) of patients with classical EDS, hEDS, or an unclassified hereditary disorder of connective tissue [Reinstein et al., 2013], while a similar study found no increase in features of hereditary connective tissue disorders between patients with spontaneous intracranial hypotension and controls [Liu et al., 2011].

Both of the musculotendinous support of the diaphragm and the pelvic floor can fail mechanically leading to hiatal hernia [Nelson et al., 2015] or pelvic floor weakness further leading to uterine/rectal prolapse, rectocele, cystocele, and/or enterocele [Veit-Rubin et al., 2016]. Fascial weakness can lead to hernias in the inguinal, femoral, or umbilical areas or at sites of previous surgical incisions as after abdominal surgery [Nazem et al., 2013].

Fatigue

Fatigue is common among adolescents in general, affecting approximately one-third of the general population and can interfere with activities of daily living including school performance and attendance [Kizilbash et al., 2014; Sleep Working Group et al., 2014]. However, chronic fatigue defined as fatigue lasting longer than 6 months, occurs in ~1% of adolescents in the general population [Werker et al., 2013]. The entity chronic fatigue syndrome (CFS) occurs more commonly in women and particularly in those over 45 years of age but is often underdiagnosed [Yancey and Thomas, 2012; Wright Clayton, 2015]. It can be associated with impaired memory, cognitive deficits, muscle pain, joint pain,

headaches, non-restorative sleep, post-exertional malaise, as well as psychological issues [Fossey et al., 2004; Nijs et al., 2006; Meeus et al., 2007]. The etiology of the chronic fatigue (syndrome) is multifactorial and includes infectious agents, immune dysregulation, allergies, endocrinopathy, nutritional deficiency, and abnormally low blood pressure often associated with postural orthostatic tachycardia syndrome (POTS) or neurally mediated hypotension (NMH) [Kanjwal et al., 2010; Werker et al., 2013; Kizilbash et al., 2014].

Fatigue is one of the most common complaints among those with hEDS [Gazit et al., 2003; Maeland et al., 2011; De Wandele et al., 2013; Murray et al., 2013]. Chronic fatigue in hEDS includes bodily and mental fatigue which only minimally improves with rest and often fits well into the diagnostic criteria of CFS [Castori et al., 2011b]. In a small series of 12 EDS patients (six classical EDS; six hEDS), Rowe et al. [1999] characterized that all had chronic fatigue, post-exertional malaise, and unrefreshing sleep, whereas 92% had impaired cognition/memory; 83% with polyarthralgia and headache; and 58% with muscle pain. Sore throat and lymphadenopathy occurred in the minority at 25%. In a subsequent study of 58 consecutive children with CFS, Barron et al. [2002] described GJH was significantly more common in the CFS population than in healthy controls. In 273 EDS patients, pain and fatigue comprised 31% of the functional impairment with fatigue having a slightly greater impact overall [Voermans et al., 2010a].

The fatigue in hEDS, as in the general population, is under recognized [Rombaut et al., 2015] and may increase in prevalence with age [Castori et al., 2011a]. Like in the general population, fatigue in hEDS is multifactorial with contributing factors including pain, sleep disturbance, dysautonomia, medications, and/or allergies. It has been associated with greater pain, functional impairment, and psychological distress as well as decreased QoL [Voermans et al., 2010b; Ali Zekry et al., 2013; Scheper et al., 2013; Pacey et al., 2015a, b; Hershenfeld et al., 2016].

Fatigue may also be a factor in musculoskeletal pain and injury. Exercise to the point of physical fatigue has been shown to alter kinematics, postural stability, and coordination, which may increase the risk of direct injury and also the risk of falls causing secondary injury [Sparto et al., 1997; Dickin and Doan, 2008]. A study of 30 EDS patients, five of whom had hEDS, showed correlation between fatigue and objectively measured muscle weakness [Voermans et al., 2011]. Exercise-induced fatigue increases knee laxity [Skinner et al., 1986], which may also increase the risk of knee injury. Fatigue is also associated with reduced ground reactive force during gait, suggestive of decreased proprioception [Celletti et al., 2012], which could also increase the risk for falls and injury. Severity of fatigue also correlated with kinesiophobia in hEDS and, therefore, became an activity-limiting factor [Celletti et al., 2013].

In conclusion, fatigue and especially chronic, debilitating fatigue is common in hEDS. Fatigue decreases muscle control and coordination, can inhibit physical activity, and may increase risk for injury. The fatigue is mental as well as physical, leading to impaired cognition and memory recall. It is also associated with multiple comorbidities linked to pain, sleep disturbance, anxiety and depression, as well as decreasing function and QoL. See also "Guidelines on the Assessment and Management of Chronic Fatigue in Ehlers–Danlos Syndrome" by Alan Hakim et al., this issue.

Cardiovascular

Mild dilation of the aortic root may develop in up to one-third of children or young adults [Wenstrup et al., 2002; McDonnell et al., 2006; Atzinger et al., 2011], but is unlikely to progress and typically does not require any specific treatment [Atzinger et al., 2011]. Baseline echocardiography is not recommended based on these findings alone but depend on other symptoms and differential diagnoses upon presentation.

POTS, NMH, and orthostatic intolerance are common manifestations in hEDS [Rowe et al., 1999; Gazit et al., 2003; Mathias et al., 2011]. Head-up tilt test may or may not establish a specific etiology, but often does not affect therapeutic decision-making and, therefore, may not be necessary. See also "Guidelines on the Assessment and Management of Cardiovascular Dysregulation in Ehlers–Danlos Syndrome" by Hakim et al., this issue.

Mitral valve prolapse (MVP) was previously considered a common feature of EDS and many other HCTDs, but that was prior to the establishment of more rigorous criteria for the diagnosis of MVP. Since then, some studies show no increase in the frequency of clinically significant MVP [Dolan et al., 1997, McDonnell et al., 2006, Atzinger et al., 2011] and others show an MVP frequency of 28–67% among hEDS patients [Camerota et al., 2014; Kozanoglu et al., 2016]. Increased prevalence of mitral and tricuspid insufficiency has also been reported [Camerota et al., 2014]. Since the mitral valve relies upon collagen for its tensile strength, and myxomatous MVP is characterized by disruption of the collagen layer with expansion of glycosaminoglycans within the middle layer of the valve [Delling and Vasan, 2014], it is reasonable to still consider MVP as a potential clue for hEDS, but the true clinical significance is not yet known.

Gastrointestinal Disorders

Systematic attention on gastrointestinal involvement in hEDS started in 2004 with the study by Hakim and Grahame [2004], who found a wide range of functional complaints in adults. The relevance of gastrointestinal manifestations in hEDS is increasing in both scientific and clinical perspectives. In fact, while the link between a congenital laxity of the soft connective tissue and gut diseases is still unclear as is the role of comorbidities and concurrent medications, its better understanding will certainly help better delineate patients' complaints, which remain without specific management protocols. In a recent

review on this topic, a total of 42 works were identified exploring the relationship between hEDS or GJH with gastrointestinal disorders [Castori et al., 2015a]. Among them, 12 were specifically addressed for better defining the spectrum of gastrointestinal symptoms in syndromic patients [Manning et al., 2003; Hakim and Grahame, 2004; Castori et al., 2010b, 2011a; Zarate et al., 2010; Danese et al., 2011; Mastoroudes et al., 2013a; De Wandele et al., 2013, 2014a; Kovacic et al., 2014; Fikree et al., 2015; Pacey et al., 2015b], and various clinical reports on single complications and/or surgical treatment in EDS [Douglas and Douglas, 1973; Defuentes et al., 2004; Sardeli et al., 2005; Chen and Jao, 2007; Reinstein et al., 2012; Dordoni et al., 2013; Fogel, 2013; Plackett et al., 2014].

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Based on these publications, gastrointestinal involvement in hEDS may have functional and morphological manifestations, although most papers were focused on the former. Collectively, functional features may be observed in 1/3 to 3/4 of the patients with an increasing rate by age. Manifestations variably include gastroesophageal reflux, heartburn, bloating, recurrent abdominal pain, irritable bowel syndrome, constipation, and diarrhea [Maeland et al., 2011]. Dysphagia may be a further common complaint in hEDS, but the literature is scanty except for an early report highlighting a high prevalence of speech, voice, and swallowing disorders in a heterogeneous group of EDS patients [Hunter et al., 1998]. Zarate et al. [2010] provisionally identified dysphagia in 14.3% of their JHS patients.

Constipation with or without other features of voiding dysfunction is usually the earliest sign of gastrointestinal involvement, which tends to manifest with multiple, sometimes severely disabling symptoms at any age. Repeated evidence indicates that gastrointestinal involvement aggregate with other chronic symptoms and, then, is more commonly encountered in the complex patient [De Wandele et al., 2013; Fikree et al., 2015; Pacey et al., 2015b]. Standard investigations are usually carried out without severe complications in hEDS, but they often have negative or inconsistent results. Functional tests, including esophageal manometry, 24-hr pH-metry, gastric emptying study, small bowel manometry, and colorectal transit study, may lead to positive results although these too are sometimes intermittent [Zarate et al., 2010].

More recently, rectal evacuatory disorder has been confirmed by anorectal manometry in 60% of the cases from a mixed population of 30 classical EDS, hEDS, and vascular EDS patients [Nelson et al., 2015]. Treatment of functional GI complaints in hEDS is problematic due to the absence of tailored strategies and an apparent resistance to pharmacologic treatments at standard dosages/regimens. The exclusion of common comorbidities, such as celiac disease, lactose intolerance, and *Helicobacter pylori* infection, is reasonable at first examination. Preliminary results suggest an increased rate of celiac disease [Danese et al., 2011; Laszkowska et al., 2016] and eosinophilic esophagitis [Abonia et al., 2013] in hEDS, but additional studies are required to determine the significance of these potential associations.

Morphological findings with a presumed higher rate in hEDS compared to the general population may include abdominal hernias, rectal prolapse, ptosis of internal organs, diaphragmatic hernias, and intestinal intussusceptions. Systematic data are available for abdominal hernias [Harrison et al., 2016] and rectal prolapse [Manning et al., 2003] only, while all other features are described in single reports only and their relationship with hEDS remains to be further scrutinized. Abdominal hernias occur in up to one-fifth of the patients; the chance of occurrence increases with age, and their surgical treatment seems effective under standard procedures [Harrison et al., 2016]. Rectal prolapse is observed in more than one tenth of women [Mastoroudes et al., 2013b]. It can occur in nulliparous women but its rate is highest in those who underwent episiotomy but has been associated with JH and pelvic floor dysfunction [Lammers et al., 2012]. The rate of rectal prolapse in men and children with hEDS remains unknown, as such an association has been reported in single case reports only [Douglas and Douglas, 1973; Chen and Jao, 2007]. See also "Gastrointestinal Involvement in the Ehlers–Danlos Syndromes" by Fikree et al., this issue.

Dysautonomia

The first evidence for a tight link between hEDS and autonomic dysfunction was published by Rowe et al. [1999], who studied eleven pediatric patients (classical EDS and hEDS) all showing either POTS or NMH. Four years later, Gazit et al. [2003] found orthostatic hypotension, POTS, and uncategorized orthostatic intolerance in 21 out of 27 (78%) JHS adults. More specifically, this study revealed a greater drop in systolic blood pressure during hyperventilation and a greater increase in systolic blood pressure after a cold pressor test in patients compared to controls. The authors suggested the existence of alpha- and beta-adrenergic hyper-responsiveness in hEDS. The concept was reinforced by Hakim and Grahame [2004], who demonstrated, for the first time, a significant increase of the rate of systemic dysautonomic symptoms in hEDS.

More recently, a study focused on hEDS found an increase of the physiological heart rate variability, a greater

blood pressure fall during Valsalva maneuver and a smaller initial systolic blood pressure increase during tilt in a cohort of 39 hEDS women compared to controls [De Wandele et al., 2014b]. This study also highlighted POTS as the most prevalent autonomic profile in hEDS and identified sympathetic neurogenic dysfunction as the most likely explanation for dysautonomia in this condition, although connective tissue laxity and vasoactive medication may also play a role.

Cardiovascular dysautonomia can easily explain orthostatic intolerance, palpitations, tachycardia, and atypical chest pain, as well as a series of neurological secondary manifestations, including fatigue, dizziness, fainting, syncope, memory, and concentration troubles. A primary sudomotor involvement was recently demonstrated in hEDS with a significant reduction of sweat volume production [De Wandele et al., 2014b]; a finding than can explain dry skin and mucosa. A possible wider involvement of the autonomic nervous system could contribute to other relatively common features of hEDS that affect the gastrointestinal and urinary systems, such as gut dysmotility and underactive/overactive bladder. The link between abdominal symptoms and dysautonomia, possibly via an increased visceral sensitization, still needs additional research [Farmer et al., 2014]. Dysautonomia could be also a pathogenic contributor to selected psychological traits of hEDS, as recently proposed [Eccles et al., 2015]. General assessment strategy and treatment of POTS are available in Mathias et al. [2011]. Minor adaptations specifically addressed for hEDS were also published [Castori et al., 2012a]. See also "Guidelines on the Assessment and Management of Cardiovascular Dysregulation in Ehlers–Danlos Syndrome" by Hakim et al., this issue; as well as "Gastrointestinal Involvement in the Ehlers–Danlos Syndromes" by Fikree et al., this issue.

Bone Mass

Osteoporosis and osteopenia are considered features of the rare kyphoscoliotic and arthrochalasis types of EDS as well as the classic-like EDS with propensity to arterial rupture [Beighton et al., 1998]. See also "Ehlers–Danlos Syndomes: Rare Types" by Malfait et al., this issue. Reports of reduced bone mass in the more common EDS variants, mainly classical and hypermobile types, remains controversial.

Coelho et al. [1994] described four adults with classical EDS and bone mineral density (BMD) values persistently below 1 standard deviation consistent with osteopenia. In this very limited series, they found that bone mass appears reduced in EDS, predominantly affecting trabecular bone, but the degree of involvement is less marked than other HCTDs. In the same year, Deodhar and Woolf [1994] reported EDS as a diagnosis among seven adults referred for low bone density (one with classical EDS and the others with less defined phenotypes which may have included hEDS). Similarly, reduced bone mass was also demonstrated at the calcaneum by ultrasound and previous fractures were 10 times more common in EDS than general population (86.9% vs. 8.7%) [Dolan et al., 1998]. In this work, the cause of reduced bone mass in EDS was considered multifactorial with a possible contribution of reduced mobility and proprioceptive defect. However, Carbone et al. [2000] did not confirm this finding in 23 hEDS adults. The authors also noted that the femoral neck BMD was significantly reduced as compared to controls but once age, weight and activity-level were corrected for, the difference became not significant. More recently, Mazziotti et al. [2016] found no significant difference in BMD among 52 EDS patients (37 hEDS). However, a urrogate radiographic marker for vertebral fracture was more prevalent in the EDS group as compared to controls. If the fractures are true (patients only report chronic low back pain) then this observation is not likely due to reduced BMD but mechanical stress of the hypermobile spine. Critics of the above-mentioned studies have speculated that those patients with EDS were often less active and this should be taken into account in comparing bone density. Overall, there is no convincing evidence that hEDS is associated osteoporosis or fragility fractures, especially in children. Such persons should be evaluated for other underlying disorders as outlined in the American Academy of Pediatrics Guideline [Flaherty et al., 2014]. The bone fragility disorder, osteogenesis imperfecta, as well as the EDS/osteogenesis imperfecta overlap (see EDS rare types, this issue), have JH and may be mistaken for hEDS [Castori, 2015].

The association between GJH and BMD was further investigated in three additional studies. Reduced BMD by ultrasound and lower excretion of urinary hydroxylysylpyridinoline cross-links and lysylpyridinoline cross-links were demonstrated in 15 children with "symptomatic" GJH compared to 95 healthy prepubertal children [Engelbert et al., 2003]. By contrast, another study suggests that a high Beighton score may be a marker of fitness, reduced rate of knee osteoarthritis and increased (rather than reduced) hip BMD in postmenopausal women [Dolan et al., 2003]. A third study showed reduced BMD (mild osteopenia) in 23 premenopausal hypermobile women compared to controls by DXA at some sites but not others [Gulbahar et al., 2006].

As expected from the early literature and the nosologic confusion among EDS, GJH, and JHS, the published data may be hard to apply to "pure" hEDS and, then, translated in clinical practice. In the above-mentioned studies, it is unclear if hEDS is associated with osteoporosis in adults, especially premenopausal women. An increase in fractures or risk of bone fragility fractures was not well-established. There is no evidence at present to suggest that children or infants have a lower bone mass in hEDS nor that they are predisposed to fragility fractures.

Osteoarthritis

Osteoarthritis (OA) has been postulated as a long-term consequence of JH [Scott et al., 1979]. It is possible that an increase in the prevalence of OA is due to the same underlying collagenopathy or by repetitive trauma that commonly occurs in JH and altered joint mechanics

[Bird et al., 1978; Grahame, 1989; Klemp, 1997]. Knee hypermobility is common among patients with knee OA [Dolan et al., 2003; van der Esch et al., 2006; Gürer et al., 2016]. In a study of 34 patients with severe thumb (carpometacarpal) OA, 62% had generalized JH [Jonsson and Valtysdottir, 1995]. In a small series of 24 EDS patients with a mean age of 16 years, 16% already had radiographic evidence of trapezial-metacarpal OA [Gamble et al., 1989]. In that same study, 66% had evidence of subluxation and 29% with dislocation. This association adds evidence that joint hypermobility and presumably altered joint biomechanics may increase the susceptibility of such joints to OA [Wolf, 2009].

Headaches

Much like headaches in the general population, headaches in hEDS vary by type and severity [Jacome, 1999; Murray et al., 2013; Neilson and Martin, 2014; Castori et al., 2015c]. Headache itself has been show to occur in a larger portion of EDS patients (multiple types of EDS) as compared to historical controls [Sacheti et al., 1997]. It is a frequent complaint among those having hEDS as well [Jacome, 1999; Maeland et al., 2011; Murray et al., 2013; Hamonet et al., 2015]. More specifically, migraines were seen at a greater frequency and disability compared to a control population [Hakim and Grahame, 2004; Bendik et al., 2011; Puledda et al., 2015].

Rozen et al. [2006] described new daily persistent headaches in a series of 12 patients of which 11 demonstrated cervical spine hypermobility. Further work revealed that 10 of the 11 with cervical spine hypermobility showed GJH. Headache due to CSF leak has been demonstrated in a few case reports and affects a very small minority of hEDS patients but can cause significant disability [Reinstein et al., 2013]. Craniocervical junction instability is thought to be linked to cervicogenic and Chiari-like headaches [Milhorat et al., 2007]. This instability or simply the musculature strain throughout the upper body can cause widespread spasms and muscular tension leading to headaches as well. Temporal headaches, unilateral or bilateral, may again be related to muscular dysfunction but involving the temporomandibular joint. Such headaches can be associated also with ear symptoms such as pain, sense of fullness, or tinnitus. Those patients with dysautonomia, orthostatic intolerance, or POTS can also complain of intense pounding headaches. Medications and medication-overuse can also be responsible for headaches in this population. As in the general population, individual patients often suffer from more than one type of headache, making both the etiology of the headache and the intervention less certain.

Temporomandibular Joint and Dental Issues

Several studies have linked temporomandibular joint (TMJ) hypermobility to temporomandibular joint dysfunction (TMD), including in children [Adair and Hecht, 1993]. Nosouhian et al. [2015] characterized 69 patients with TMJ hypermobility and found that a maximal mouth opening (MMO) of <55 or >65 mm, was associated with more TMJ discomfort than an intermediate degree of MMO. TMJ hypermobility was more common in women than men, and increased MMO was also correlated with more TMJ sounds ("clicks" or "pops") and more pain in the masticatory muscles. The jaw in hEDS is often also hypermobile until such time that damage occurs in the TMJ, which will further limit MMO. Jaw sounds, locking, dislocation, bruxism, and temporal headaches are also frequently described in this population. Indeed, Murray et al. [2013] found that a significant portion of 466 adults with hEDS self-reported TMD as a major issue.

Westling [1992] studied 360 patients with TMD. Among that group, a subset analysis of 74 females with GJH were compared to 73 age and gender matched controls. Using stepwise regression analysis, the study was able to show a significant association of GJH and TMD.

In a recent national study in Finland involving 6227 participants, TMJ pain was often associated with palpable pain of the neck and shoulder musculature, widespread pain, chronic illness, and female gender [Sipilä et al., 2011]. Given that those with hEDS often have most if not all of the additional variables, it would suggest that TMD in this population is complex, common, and must use a more holistic approach to treat.

The oral mucosa in hEDS is often friable and easily injured giving rise to episodes of painless bleeding [Hagberg et al., 2004; Berglund and Björck, 2012]. The lingual or labial frenulum may be hypoplastic or altogether absent [Machet et al., 2010]. Periodontitis may also be common. However, periodontal disease with early-onset and widespread tooth loss is thought to represent another form of EDS, the periodontal type [Rahman et al., 2003], that has been recently associated with defects in complement type 1 [Kapferer-Seebacher et al., 2016] (see also "Ehlers–Danlos Syndromes: Rarer Types" by Malfait et al., this issue). Many patients report being less responsive to local anesthetics during dental procedures [Arendt-Nielsen et al., 1990; Hakim et al., 2005]. A Swedish study utilizing a self-reported oral health questionnaire showed that mucosal problems in different areas of the body were reported by 206/223 (92%) women, and that 75% of respondents with hypermobility type self-reported problems with their oral mucosa [Berglund and Björck, 2012].

The teeth in hEDS are described with slightly altered morphology with higher cusps and deeper fissures of the premolars and molars with shortened roots. Enamel hypoplasia has also been described as well as tooth fracture (unclear if fracture intrinsic to the tooth or due to bruxism or similar mechanical pressures) [De Coster et al., 2005]. With the use of orthodontia, it is a common anecdotal experience that the teeth will migrate faster than expected and, unfortunately, migrate back toward their pre-treatment location after the removal of the orthodontic appliance. See also

"Oral and Mandibular Manifestations in Ehlers–Danlos Syndrome" by Mitakides and Tinkle, this issue.

Spine

Postural kyphosis is commonly encountered in those with hEDS [el-Shahaly and el-Sherif, 1991]. This is thought to be primarily due to loose ligamentous structure and poor postural ergonomics. Scoliosis is also common occurring in up to half of all patients [Ainsworth and Aulicino, 1993; Stanitski et al., 2000; Adib et al., 2005; Czaprowski, 2014; Stern et al., 2016]. The scoliosis is acquired, often mild as well as flexible and may continue to progress beyond the adolescent period but most do not require intervention.

The spine is a series of joints, the most mobile of which involves the craniocervical junction. Multiple connective tissue disorders have been reported to have craniovertebral instability including Marfan [Herzka et al., 2000], Loeys-Dietz [Rodrigues et al., 2009], and EDS [Milhorat et al., 2007]. Cervical hypermobility has been associated with headaches and hEDS [Rozen et al., 2006]. In a large series of patients presenting with signs of Chiari type I (neck pain, gait disturbance, numbness and tingling of the hands and feet, dizziness, dysphagia, and speech difficulties), Milhorat et al. [2007] described nearly 13% had features consistent with hEDS. Compared to the other patients with Chiari-like symptoms, the patients with hEDS were more likely to have a reduction of the basion-dens interval, clival-axial angle, clival-atlas angle, and the atlas-axial angle as well as an enlargement of the basion-dens interval—all of which are concerning for excessive laxity or instability. There was also an increase in retro-odontoid pannus formation, a pathophysiologic process thought to represent abnormal stress of the transverse ligament. A portion of these patients did not have radiologic findings of Chiari and were labeled as Chiari Type 0, a controversial label. Moreover, the Chiari-like symptoms of headache and dysautonomia are common in hEDS and the vast majority are not likely attributable to dysfunction at the craniocervical junction. See also "Neurologic Manifestations in the Ehlers–Danlos Syndrome" by Henderson et al., this issue.

Similarly, laxity of the lumbar spine increases movement and decreases stability. Kim et al. [2013] showed that young males with GJH had excessive lumbar segmental motion which was associated with increased low back pain, disability, and limited physical activity. Lumbar hypermobility is also an underlying risk factor for degenerative disc disease [Nef and Gerber, 1998] and facet fractures [Mazziotti et al., 2016].

Gynecologic Issues

Gynecologic complaints from patients with hEDS are commonly encountered. In a study with 223 women with EDS, 67% self-reported mucosal problems with their genital area [Berglund and Björck, 2012]. Heavy menstrual bleeding (menorrhagia) was reported by 26–76% of hEDS females [Ainsworth and Aulicino, 1993; Hugon-Rodin et al., 2016]. Painful intercourse was also reported by 30–57% of women with EDS and hEDS [McIntosh et al., 1995; Castori et al., 2010a; Hugon-Rodin et al., 2016].

Pelvic Dysfunction

Pelvic floor disorders include urinary incontinence (UI), pelvic organ prolapse (POP), and other sensory and emptying abnormalities. Childbirth has a very substantial impact on a woman's probability of developing pelvic floor disorders. It has been reported that about a third of women have UI after childbirth [Hallock and Handa, 2016]. In addition to parity, a positive family history of prolapse increases a woman's risk of prolapse, even among nulliparous women [Buchsbaum et al., 2006; Buchsbaum and Duecy, 2008].

Several case-control studies in the past suggested that hEDS is associated with pelvic floor disorders [Al-Rawi and Al-Rawi, 1982; Norton et al., 1995; McIntosh et al., 1996; Aydeniz et al., 2010]. However, most of these studies have not controlled for childbirth history or age and included patients affected by various types of EDS.

Castori et al. [2012c] found that POP represented a common late-onset complication in women with hEDS. Interestingly, most (90.9%) prolapses occurred in women with positive history for episiotomy. The reason(s) as to why episiotomy associates with POP in hEDS is unknown.

The largest prospective case-control study to date to address these issues was published in 2013 and involved 120 women [Mastoroudes et al., 2013a,b]. Sixty women diagnosed with JHS, according to the Brighton criteria, were recruited from a tertiary referral hypermobility clinic. Controls were recruited from hospital personnel. All women in the study group were matched with healthy control women according to age, parity and ethnicity. Both groups completed specific health and QoL questionnaires. Objective assessment of POP was undertaken. The prevalence of UI in those with hEDS were significantly higher than in controls (73.3% vs. 48.3%) as was voiding difficulties. The impact of UI on QoL was also statistically significant. Objective findings of prolapse of the anterior vaginal wall were more severe than in controls.

However, another recent study [Derpapas et al., 2015] reported a lack of strong association of JH with UI or POP. The study involved 270 women scheduled to undergo urodynamic investigations. JH was not assessed clinically but was based on the self-completed five-part JH questionnaire. Women underwent a full gynecological history and examination. The prevalence of reported JH in this study was 31.1%; however, the researchers did not find a strong association between JH and any UI subtype. They reported a trend toward higher prolapse staging in women with JH, which becomes significant only after adjustment for the confounding negative association between age and JH.

As childbirth has a very substantial impact on a woman's probability of

developing pelvic floor disorders, such as UI and POP, pregnancy remains a source of anxiety to patients and their doctors.

Pregnancy and Childbirth

Several pregnancy-related complications have been more commonly reported in women with hEDS in some studies but as often, not substantiated in others. In an online survey of EDS patients (N = 497), self-reported infertility was more commonly encountered in women with hEDS [Hurst et al., 2014] although this was not reproduced by others [Castori et al., 2012b; Hugon-Rodin et al., 2016; Sundelin et al., 2017]. Premature birth has been reported as more common among patients with EDS than in the general population, but this appears to be primarily among women with classic EDS; it is unclear if there is an increased risk for preterm birth specifically in the hEDS population as the few studies are conflicting [Sorokin et al., 1994; Lind and Wallenburg, 2002; Castori et al., 2012b; Hurst et al., 2014]. Some works report that miscarriage is increased in hEDS [Ainsworth and Aulicino, 1993; Hurst et al., 2014; Hugon-Rodin et al., 2016] but not in other studies [Sundelin et al., 2017].

In a comprehensive study, Castori et al. [2012c] collected a set of gynecological and obstetric features in 82 women with hEDS attending two Italian centers. All patients were originally assessed by physical examination and questionnaire administration focused on collecting information about selected aspects of their gynecological and obstetric history. Only postpubertal women meeting diagnostic criteria for the hypermobility type of EDS or JHS were included. Other HCTDs were excluded clinically. The study did not include gynecological examination. A total of 93 pregnancies were registered among the 82 women with at least one pregnancy. In this study, fertility was overall preserved, as were mean age at menarche and menopause, rate of pregnancy/woman and of spontaneous abortion that were comparable with those in the Caucasian population.

EDS-related symptom evolution during pregnancy seemed unpredictable as 40% of patients reported worsening symptoms (especially gastrointestinal complaints, asthenia, and pain), 13% of patients improved, and the symptoms were unchanged in the remaining 47%. Preterm delivery due to premature rupture of the membrane was reported in 10% pregnancies, which is not different from the general population, and none of which led to major complications. Rapid labor occurred in more than 1/3 of the cases.

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The risk of intra- and post-partum hemorrhages was 1/5 irrespective to the delivery modality. They reported a high rate of abnormal scar formation in both Caesarean and vaginal delivery with episiotomy. In all cases, hemorrhages were always successfully managed without life-threatening complications and no internal organ/vascular accidents were registered after Caesarean. It was reassuring that all delivery options showed a very limited number of local and systemic short-term complications. In this sample, the group did not find any life-threatening complication related to local and general anesthesia.

It has long been recognized that joint laxity increases over the course of pregnancy, allowing the bony pelvis to adapt to accommodate vaginal birth [Calguneri et al., 1982]. The same phenomenon occurs in women with hEDS, which may lead to increased joint instability later in pregnancy.

A large study was conducted to investigate the association between JH, obstetrical outcomes, and pelvic floor disorders [Knoepp et al., 2013]. It involved 587 parous women (participants in a longitudinal cohort study of pelvic floor disorders after childbirth). Their obstetrical histories were obtained from review of hospital records. Pelvic floor disorders were assessed using validated questionnaires and a structured examination for prolapse. JH and pelvic floor disorders were evaluated at enrollment (5–10 years after first delivery). The main weakness of this study was the inclusion criteria. The researchers defined JH as Beighton score $\geq$4 and did not use the Brighton or Villefranche criteria. They compared obstetrical outcomes and pelvic floor disorders between women with and without JH. JH was diagnosed in 46 women (7.8%) and was associated with decreased odds of caesarean after complete cervical dilation or operative vaginal delivery. In this study, anal sphincter laceration was less likely to occur in women with JH and was not associated with any pelvic floor disorder. Although this study did not address the issues related to hEDS specifically, the results are quite reassuring for women with asymptomatic hypermobility as JH seem to facilitate spontaneous vaginal birth but does not appear to be a risk factor for pelvic floor disorders in the first decade after childbirth.

Urinary System

De Kort et al. [2003] evaluated 89 families of children with GJH. The children with GJH showed an increase in daytime and nighttime urinary incontinence as well as urinary tract infections (UTIs). Voiding dysfunction was also significantly associated with GJH in children but this is unclear if this is secondary to constipation [Kajbafzadeh et al., 2014]. Adib et al. [2005] evaluated 125 children with a diagnosis of hEDS and catalogued their multisystem disorders. UTIs and urinary tract

dysfunction were more common in girls than controls. Vesicouretal reflux was also more common in children with hEDS as compared to the control population [Beiraghdar et al., 2013].

Sleep Disturbance

Sleep is a restorative process for the body. During the deeper stages of non-rapid eye movement sleep, the body regenerates tissue, builds bone and muscle, and positively affects the immune system. Sleep deprivation is considered unhealthy leading to fatigue, a decrease immune response, poor muscle coordination, susceptibility to injury, impaired cognition and memory, increased pain, moodiness, and depression [Owens, 2014]. Insomnia can be reported as delayed sleep (sleep-onset) or due to sleep fragmentation (sleep-maintenance). Sleep deprivation due to sleep maintenance insomnia has been related to impairment of the endogenous pain inhibitory function and therefore increases spontaneous pain and pain amplification [Smith et al., 2007].

Many patients with hEDS report poor sleep including insomnia and unrefreshing sleep [Verbraecken et al., 2001; Hakim and Grahame, 2004; Murray et al., 2013]. In a study of 115 patients with hEDS, Albayrak et al. [2015] found a significant decrease in sleep quality as compared to controls. Comorbid conditions such as restless legs syndrome and sleep apnea have been described in small series of patients with hEDS [Guilleminault et al., 2013]. However, of the 34 patients with EDS, only one was described as having hEDS but details on the diagnostic criteria were not described. Fibromyalgia is also a common comorbidity [Ofluoglu et al., 2006; Ting et al., 2012] and is strongly associated with sleep disturbance, including abnormal sleep architecture [Dauvilliers and Touchon, 2001; Besteiro Gonzalez et al., 2011]. Many other factors may also interfere with sleep in this population including pain, dysautonomia, poor sleep hygiene, and medications [Voermans et al., 2010b].

Mast Cell Activation Disorder

Mast cell activation syndrome (MCAS) refers to an increased number of mast cells, increased mast cell mediators (e.g., histamine, tryptase, etc.), or both. The clinical symptoms of MCAS include flushing, pruritis, hypotension, asthma, diarrhea, abdominal bloating, and cramping. The diagnosis of MCAS is increasingly recognized in the general population [Afrin et al., 2016] and is likely among those with hEDS as well. It remains unclear if MCAS is more common in hEDS or perhaps represents a phenocopy of hEDS (with similar joint laxity and multi-system involvement). Those with EDS report a higher incidence of food sensitivities suggestive of histamine reaction [Berglund, 2015]. Regardless of any possible association, the presence of MCAS in hEDS might complicate the known symptoms of POTS, chronic fatigue, and gastrointestinal manifestations. Elevated serum tryptase, a marker of MCAS, followed a dominant inheritance pattern that overlapped with a "hypermobile connective tissue phenotype" in eight of nine studied families [Lyons et al., 2014]. Subsequent evaluation of 35 families with elevated serum tryptase showed this phenotype to be due to increased copy number of the alpha-tryptase gene, *TPSAB1* [Lyons et al., 2016]. See also "Mast Cell Activation Syndrome in Ehlers–Danlos Syndrome" by Seneviratne et al., this issue.

Psychiatric

Psychological dysfunction and emotional problems, including depression, anxiety, affective disorder, low self-confidence, negative thinking, hopelessness, and desperation, are also common among those with EDS [Hagberg et al., 2004; Castori et al., 2010b; Baeza-Velasco et al., 2011; Branson et al., 2011; Rombaut et al., 2011a; Berglund et al., 2015; Sinibaldi et al., 2015; Hershenfeld et al., 2016]. These problems may exacerbate the pain experience, as well as other organ system manifestations (especially gastrointestinal and autonomic). This can lead to avoidance behavior, exacerbation of dysfunction and disability, and marginalization. Resentment, distrust, and hostility between the patient, family, and healthcare team may develop. To be ignored, being assigned a psychological and/or psychiatric explanation, not being respected and treated as an object could have consequences such as mistrusting health-care and create difficulties in encounters with care [Berglund et al., 2010]. Equally, to ignore or avoid confronting the presence of significant comorbid psychological problems can lead to suboptimal treatment. See "Psychiatric and Psychological Aspects in the Ehlers–Danlos Syndromes" by Bulbena et al., this issue.

Quality of Life

In a national cohort of 134 patients, functional gastrointestinal disorders correlated with a poorer QoL in EDS patients [Zeitoun et al., 2013]. When comparing SF-36 scores as a measure of QoL in EDS in a Swedish population study, the EDS group reported significantly lower scores [Berglund et al., 2015]. Also, probable anxiety on the Hospital Anxiety and Depression Scale was rated as 74.8% and probable depression was rated as 22.4%. Physical pain, psychological discomfort, and handicap has considerable impact on health-related QoL in EDS. Adults with hEDS reporting neck and shoulder pain had a significant association with generalized pain and a decreased health-related QoL [Johannessen et al., 2016]. Children with hEDS and fatigue experienced poor health-related QoL [Pacey et al., 2015b]. In 38 hEDS patients, baseline QoL was significantly reduced and worsened with experiences in physical therapy and iatrogenic injury [Bovet et al., 2016]. A recent meta-analysis revealed significant disability related to pain, fatigue, and psychological distress in hEDS [Scheper et al., 2016b]. These results indicate a lower quality of health in those with EDS than in the general population.

MANAGEMENT

Assessment of a person with or suspected of having hEDS is based on symptoms. Musculoskeletal symptoms should be approached conservatively. Physical therapy, education, and pacing are paramount [Simmonds and Keer, 2007]. "The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents and Adults Diagnosed with Joint Hypermobility Syndrome/Hypermobile Ehlers Danlos Syndrome" by Engelbert et al., this issue. Frank joint instability should be evaluated by orthopedics or other well-qualified personnel. Symptoms of orthostatic intolerance, tachycardia with palpitations, and/or near-syncope should be also treated conservatively by fluid and salt intake along with education and the appropriate exercise. Syncope should be evaluated further by specialists such as neurology or cardiology for concerns of arrhythmia, seizure disorder, cardiomyopathy, and so on.

The management of hEDS includes treatment of acute/emergency manifestations (e.g., dislocations), attenuation of chronic symptoms (e.g., pain and fatigue), as well as primary and secondary prevention of acute and chronic complications. Acute complications are usually managed far away from the reference center and treatment follows guidelines and procedures applied in the general population. As many patients with hEDS have multiple symptoms, a coordinated effort is required as other specialists (if needed) are incorporated into the medical team. The approach should be holistic focusing on the complications, the desire(s) of the patient, QoL and functionality, as well as the psychological aspects.

The management of hEDS includes treatment of acute/emergency manifestations (e.g., dislocations), attenuation of chronic symptoms (e.g., pain and fatigue), as well as primary and secondary prevention of acute and chronic complications.

Pain

Primary prophylaxis and treatment of nociceptive pain relies upon physical approaches to improve joint stability and prevent or reduce myofascial spasm. Although there is only limited evidence, avoidance of joint hyperextension may not be necessary [Pacey et al., 2013]. High impact and resistance exercise should be minimized, but regimens need to be individualized and this is not a strict contraindication. Myofascial release, stretching, and other mechanical techniques to reduce spasm can provide up to 24 hr of pain reduction. Joint stabilization is best achieved by working on muscle tone (the resting state of muscle contraction) and proprioception, with only gentle attention to strength (voluntary force exerted at will) [Simmonds and Keer, 2007; Palmer et al., 2014]. Exercises should be low resistance, with very gradual increase in repetitions but not resistance. Water-based exercise is often a good choice for some individuals because water reduces effective body weight and protects against impact. Exercise regimens are often initiated with formal physical therapy, but once learned by the patient, can and should be continued indefinitely, independent of formal instruction or supervision. It is important to understand that physical therapy should be done by experienced and learned professionals as many patients commonly report increased pain and decreased QoL with improper exercise regimens [Bovet et al., 2016]. It often takes several months of routine toning exercise to halt progressive deterioration in pain, and it may be several years before substantial reduction in pain is recognized.

Scheduled use of multiple medications together is often more effective than as-needed use of one or two medications at a time. Systemic non-opioid oral analgesics should be maximized first, including both acetaminophen and either a non-steroidal anti-inflammatory (NSAID) or cyclooxygenase-2 (COX2) inhibitor. NSAIDs may be helpful after episodes of dislocation or subluxation or as an addition during flares of pain. Topical agents such as lidocaine, NSAIDs and/or custom compounded creams can also be helpful. Where allowed by law, cannabinoids can be considered, but the treatment effect must be measured against potential long-term consequences [Mandelbaum and de la Monte, 2017]. Muscle relaxants may help to reduce myofascial spasm and nociceptive pain [Abdel Shaheed et al., 2017; Chou et al., 2016]. Benzodiazepines can be considered for cautious short-term muscle relaxation, but are poor choices for long-term use due to loss of muscle-relaxing effect over time, in addition to problems with tolerance, dependency, and sometimes addiction. Neuropathic pain often requires one or more of a tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor, and/or an anti-epileptic drug. Topical lidocaine and capsaicin may also provide some benefit. Opioids are rarely needed for the treatment of chronic musculoskeletal pain [NGC, 2013] and are no higher than third line agents for neuropathic pain [Finnerup et al., 2015]. Opioids and tramadol are best reserved for acute pain episodes or for patients whose pain is inadequately managed on all of the above medications, require close monitoring, and should be added on to the above regimen in the lowest possible doses rather than replacing the above medications. There are particular concerns regarding the risks of co-prescribing opioids and benzodiazepines [Babalonis and Walsh, 2015]. Recent guidance by the Centers for Disease Control recommends that providers should prescribe opioids only when benefits outweigh expected risks and that they should avoid prescribing opioids and benzodiazepines concurrently whenever possible [Dowell et al., 2016].

There is theoretical risk and anecdotal description that muscle relaxant

medications and/or too much stretching can exacerbate joint instability and ultimately increase nociceptive pain, but many patients tolerate these modalities well and treatment should be tailored to each individual's response. NSAIDs and COX2 inhibitors may exacerbate gastritis, bleeding and/or bruising, but are often well-tolerated. Chronic high dose NSAID therapy may also increase the risk of coronary artery disease and renal insufficiency; this risk needs to be weighed against the severity of the patient's pain and the patient should be encouraged to make his or her own choice about these risk and benefits. Many of the above pain medications increase serotonin levels, so patients should be monitored for signs and symptoms of serotonin syndrome.

Many patients with hEDS may develop chronic generalized pain which becomes their primary problem. This type of presentation should be considered as a centralized pain state belonging to the spectrum of chronic widespread pain, with additional superimposed musculoskeletal components. Some patients who continue to struggle to cope with their pain may need consideration of a multidisciplinary pain management program [Bathen et al., 2013].

The overall goal should be to maintain adequate control of pain to a tolerable level, not to completely eliminate pain. Such expectation management can help to reduce the overall subjective pain experience, even when objective somatic pain cannot be completely controlled. See "Pain Management in Ehlers–Danlos Syndrome" by Chopra et al., this issue.

Fatigue

Both mental and physical fatigue are as commonly encountered as pain in hEDS [Castori et al., 2011b]. It is often multifactorial. Stimulant medications are often effective for very short periods of time. However, the various contributors of fatigue should be considered such as anemia, nutritional deficiencies, deconditioning, medications, sleep disturbance, dysautonomia, and/or psychological aspects. Screening questionnaires should be used for diagnosis and ongoing monitoring. Fatigue, much like pain, often responds to treatment such as exercise therapy but only very slowly over time [Edmonds et al., 2004]. See "Chronic Fatigue in Ehlers–Danlos Syndromes" by Hakim et al., this issue.

Orthostatic Intolerance

Non-pharmacologic management includes avoidance of rapid orthostatic change or prolonged upright posture, lower extremity compression garments, and supplementation of water and electrolytes to maximize blood volume. Routine low resistance exercise increases both skeletal muscle and vascular tone, improving venous return to the heart. Beta adrenergic blockade often improves symptoms, perhaps by slowing the heart rate or perhaps by reducing autonomic sympathetic activity. Beta blockade is not strictly contraindicated in patients with low resting blood pressure, but does require close monitoring in such patients. Some additional medication options include midodrine, fludrocortisone, and pyridostigmine [Mathias et al., 2011]. See also "Autonomic Dysregulation in Ehlers–Danlos Syndromes," by Hakim et al., this issue.

Neuropsychiatric

Management starts with validation of the patient's symptoms and efforts to establish rapport and trust with the patient. Psychological counseling should focus on accepting and coping with chronic pain and chronic disease. Cognitive behavioral therapy is particular beneficial, if the patient is willing to actively engage in the process [Bathen et al., 2013]. Distraction, hypnosis, and judicious use of anti-depressant medication can also help.

Surgery and Anesthesia

In hEDS, surgical risks are generally lower that other EDS variants due to the only minor fragility of skin, vessels, and internal organs. The greatest surgery related issue of hEDS is the possibility of delay in wound closure and tissue repair. Hence, surgical procedures should be carried out with gentle dissection and use of mild lateral force during incisions, retraction and suturing. Skin closure should be performed in two layers with minimal tension, sufficient amount of sutures, deep stitches, and the support of steri-strips, by using proper distance to the incision in order to avoid sutures cutting through the fragile tissue, and without the use of skin clips. Finally, sutures should be left twice as long as normally recommended in order to avoid wound re-opening [Burcharth and Rosenberg, 2012].

Anesthesia and perioperative management may also deserve special care in hEDS. This is mostly influenced by some primary disease features, including mucosal fragility, propensity to ecchymosis, and the risk of hemorrhage (that are, however, usually limited in hEDS), the risk of orthostatic headache due to spinal anesthesia, but also by several common comorbidities, such as autonomic dysfunction, occipitoatlantoaxial joint instability, and spondylosis. A freely downloadable summary of recommendations concerning pre-surgical evaluation, patient monitoring and positioning, airway management, circulatory and bleeding issues, pharmacology, use of tourniquets, central venous catheterization, obstetrical, regional and local anesthesia, and other aspects, is available at the OrphanAnesthesia website (http://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/cat_view/61-rare-diseases/60-published-guidelines/89-ehlers-danlos-syndrome.html) or in the work by Wiesmann et al. [2014]. In both works, recommendations are offered for EDS in general, therefore, specific considerations for hEDS should be carefully extracted by the reader.

FUTURE DIRECTIONS

hEDS is a common clinical entity that affects many disciplines of healthcare. The precise description both in the diagnostic criteria as well as the natural history of hEDS need a great deal of further refinement. Management of this disorder has drawn many parallels to

other disorders as few large-scale studies have been performed in this patient population. The areas of future interest represent a limited partial set but those of higher priority.

hEDS Diagnostic Criteria

The new nosology will have to be applied to all populations and be determined where deficiencies and gaps lie within the criteria. This includes the evaluation of and validation of the modified Beighton scoring system. Formulation of such questions and addressing these concerns will need to be an ongoing mission.

As joint hypermobility is common in many disorders and may be the presenting sign, differentiating hEDS from other HDCTs, especially those with vascular involvement, is important. As hEDS is a clinical diagnosis, refinement of the diagnostic criteria is even more important as is the search for a genetic cause. In a systematic approach to pursuing a molecular diagnosis, Weerakkody et al. [2016] found 28 patients with pathogenic variants including one with suspected hEDS emphasizing the need for a systemic diagnostic approach to EDS that will need to be further refined.

Molecular Basis

hEDS remains the sole EDS major type without a known molecular defect. Such a lack of knowledge is likely due to various complexities. First, although hEDS is inherited as a dominant trait, that is, sex-influenced, this inheritance model may not explain all cases. Locus heterogeneity is very likely which may explain some of the cases with apparent different inheritance patterns. Second, the current diagnostic criteria are generally broad to cover what is suspected to be various phenotypic sub-groups. Therefore, the diagnosis of one individual may be ultimately attributable to a mutation of a particular gene while in another person with a similar or different phenotypic presentation may be due to mutation of another gene altogether. Without recognition and eventual separation of these sub-groups, efforts to define this group under a diagnosis of hEDS may complicate studies on an exomic or genomic basis. Last, as several factors play into the phenotype presentation such as gender, training, pain threshold, etc. multiple genetic and non-genetic factors may be contributing. It is obvious that there needs to be a broader recognition and recording of the features of hEDS (such as in a database registry) so that phenotypic patterns may emerge that can help the design and interpretation in the pursuit of the genetic etiology(ies).

Dysautonomia

The presence of orthostatic intolerance and POTS or NMH in the hEDS population needs further and large-scale validation. A full descriptive inventory of all of the dysautonomic symptoms also is in need. The link between abdominal symptoms and dysautonomia, possibly via an increased visceral sensitization, still needs additional validation [Farmer et al., 2014].

Bone Density

Due to a few small case reports and series, there is some concern for possible loss of bone density with hEDS. This has been popularized through social media and in the courts as a defense against charges of child abuse in the case of an infant with multiple fractures of unknown etiology. There is no credible studies demonstrating bone fragility fractures in hEDS. Subsequently, hEDS is not considered one of the bone fragility syndromes and the diagnosis of hEDS is far too subjective to rely on in these situations. Those infants with features of a connective tissue disorder and multiple unexplained fractures, should be considered for genetic testing [Byers et al., 2006; Flaherty et al., 2014]. Larger and well-controlled studies of bone density in hEDS are needed at all ages.

Physical Therapy Management

Physical therapy is considered the mainstay of management in hEDS. However, many questions remain including validation of physical therapy in the treatment of EDS. See "The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents and Adults Diagnosed with Joint Hypermobility Syndrome/Hypermobile Ehlers–Danlos Syndrome" by Engelbert et al., this issue.

Craniocervical Junction

As the cervical spine, and most especially the craniocervical junction, comprise a joint(s), it is also believed to be susceptible to the same strain and injuries as seen in other joints in EDS. As these joints protect the central nervous system, it is plausible that neurologic symptoms might also occur. Which symptoms, the proper imaging (and measurements) as well as management are not well-established. Although upright MRI reproduces a more physiologic strain on the craniocervical junction, its routine use has not been recommended [Health Quality Ontario, 2015]. Further studies about the prevalence as well as the symptoms, imaging, and management are needed.

Mast Cell Activation Syndrome

MCAS can complicate management of dysautonomia and may contribute to fatigue and decreased QoL. Further studies of MCAS in the hEDS population are needed to detail the possible comorbidity and its impact on disease manifestation and management.

SUMMARY

hEDS is a heritable connective tissue disorder without a clear etiology. It is common, representing up to 1–3% of the general population. It is multisystemic with primary musculoskeletal manifestations but various other comorbidities exist such as pain, fatigue, orthostasis, sleep disturbance, anxiety, and a poorer health-related quality of life. Much work in the area of diagnostics, prevalence of hEDS, and the associated comorbidities as well management specific to hEDS is needed.

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RESEARCH REVIEW

Measurement Properties of Clinical Assessment Methods for Classifying Generalized Joint Hypermobility—A Systematic Review

BIRGIT JUUL-KRISTENSEN,* KAROLINE SCHMEDLING, LIES ROMBAUT, HANS LUND, AND RAOUL H. H. ENGELBERT

The purpose was to perform a systematic review of clinical assessment methods for classifying Generalized Joint Hypermobility (GJH), evaluate their clinimetric properties, and perform the best evidence synthesis of these methods. Four test assessment methods (Beighton Score [BS], Carter and Wilkinson, Hospital del Mar, Rotes-Querol) and two questionnaire assessment methods (Five-part questionnaire [5PQ], Beighton Score-self reported [BS-self]) were identified on children or adults. Using the Consensus-based Standards for selection of health Measurement Instrument (COSMIN) checklist for evaluating the methodological quality of the identified studies, all included studies were rated "fair" or "poor." Most studies were using BS, and for BS the reliability most of the studies showed limited positive to conflicting evidence, with some shortcomings on studies for the validity. The three other test assessment methods lack satisfactory information on both reliability and validity. For the questionnaire assessment methods, 5PQ was the most frequently used, and reliability showed conflicting evidence, while the validity had limited positive to conflicting evidence compared with test assessment methods. For BS-self, the validity showed unknown evidence compared with test assessment methods. In conclusion, following recommended uniformity of testing procedures, the recommendation for clinical use in adults is BS with cut-point of 5 of 9 including historical information, while in children it is BS with cut-point of at least 6 of 9. However, more studies are needed to conclude on the validity properties of these assessment methods, and before evidence-based recommendations can be made for clinical use on the "best" assessment method for classifying GJH. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Beighton tests; Carter and Wilkinson; Rotes-Querol; Hospital del Mar; five-part questionnaire; self-reported; clinimetrics; quality assessment; COSMIN; best evidence synthesis

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INTRODUCTION

Generalized joint hypermobility (GJH) is relatively common, occurring in about 2–57% of different populations [Remvig et al., 2007b]. Important reasons for this may be the use of many different clinical assessment methods and criteria for classification and interpretation of GJH by these clinical assessment methods [Remvig et al., 2007a,b]. GJH is characterized by an ability to exceed the joints beyond the normal range of motion in multiple joints, either congenital or acquired [Remvig et al., 2011]. Many individuals with GJH are asymptomatic, which also makes it difficult to accurately estimate

Dr. Birgit Juul-Kristensen, Associate professor, PT, Department of Sports Sciences and Clinical Biomechanics, Research Unit of Musculoskeletal Function and Physiotherapy, University of Southern Denmark, Odense, Denmark.

Karoline Schmedling, M.Sc., PT, Department of Health Sciences, Institute of Occupational Therapy, Physiotherapy and Radiography, Bergen University College, Bergen, Norway.

Dr. Lies Rombaut, Postdoctoral researcher, PT, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

Dr. Hans Lund, Associate professor, PT, Department of Sports Sciences and Clinical Biomechanics, Research Unit of Musculoskeletal Function and Physiotherapy, University of Southern Denmark, Odense, Denmark; SEARCH (Synthesis of Evidence and Research), Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; Center for Evidence-Based Practice, Bergen University College, Bergen, Norway.

Dr. Raoul Engelbert, Department of Rehabilitation, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ACHIEVE, Faculty of Health, Center for Applied Research, University of Applied Sciences, Amsterdam, the Netherlands.

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*Correspondence to: Birgit Juul-Kristensen, Research Unit for Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark. E-mail: bjuul-kristensen@health.sdu.dk

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the number of people with this condition, as they are not recorded in the health system.

When GJH is accompanied with symptoms, it is defined as a health-related disorder, for example, Joint Hypermobility Syndrome (JHS) or the Ehlers–Danlos Syndrome—Hypermobile Type (hEDS) with several complications as described below. The two conditions (JHS and hEDS) have very close overlap to the point of being clinically indistinguishable [Tinkle et al., 2009; Remvig et al., 2011], and in the present study it is referred to as JHS/hEDS. The condition of JHS/hEDS can be defined as an under- and often misdiagnosed heritable connective tissue disorder, characterized generally by GJH, complications of joint instability, musculoskeletal pain, skin involvement, and reduced quality of life [Rombaut et al., 2010; Castori et al., 2014; Scheper et al., 2016]. Until now, JHS is diagnosed by the Brighton tests and criteria [Grahame et al., 2000], and hEDS by the Villefranche criteria [Beighton et al., 1998], both including the Beighton scoring (BS) system of nine tests for assessment of GJH [Beighton et al., 1973].

BS consists of four bilateral tests and one test including low back and lower extremities (first finger opposition, fifth finger extension, elbow extension, knee extension, and back forward bending), with scores ranging from 0 to 9. Influencing factors on BS are age, gender, ethnicity, and physical fitness [Remvig et al., 2007b; Tinkle et al., 2009]. For adults, a cut-point of 4/9 for GJH is included in the Brighton criteria for JHS [Grahame et al., 2000], while 5/9 for GJH is the criteria for hEDS in the Villefranche criteria [Beighton et al., 1998]. For children, there is no consensus on a specific cut-point for GJH, but cut-points of 5/9, 6/9, and 7/9 have been suggested [Jansson et al., 2004]. A previous review has listed different test assessment methods of which the Beighton score [Beighton et al., 1973] was most frequently used. The review concluded that reproducibility of Beighton or similar tests is good, but there is lack of evidence for the validity of this test assessment method [Remvig et al., 2007a].

For adults, a cut-point of 4/9 for GJH is included in the Brighton criteria for JHS, while 5/9 for GJH is the criteria for hEDS in the Villefranche criteria. For children, there is no consensus on a specific cut-point for GJH, but cut-points of 5/9, 6/9, and 7/9 have been suggested.

Further, also questionnaire assessment methods are used for classifying GJH, among which the five-part questionnaire (5PQ) [Hakim and Grahame, 2003; Mulvey et al., 2013]. The 5PQ, so far used only for adults, consists of five questions, including actual and historical information about joint hypermobility (forward bending of the back, first finger opposition, the ability to amuse friends with strange body shapes, dislocation of shoulder/knee, perception of being double-jointed). The 5PQ is claimed to have good reproducibility, in addition to satisfactory sensitivity and specificity [Hakim and Grahame, 2003]. However, clinimetric properties (reliability, different aspects of validity, and responsiveness) have not been described fully for BS, 5PQ, or other potential clinical assessment methods for classifying GJH.

Clear and valid diagnostic clinical assessment methods and criteria for classifying GJH with or without symptoms are essential, both for diagnosing JHS/hEDS and measuring treatment effects of JHS/hEDS, in children [Scheper et al., 2013] as well in adults [Palmer et al., 2014; Smith et al., 2014; Scheper et al., 2016]. In summary, there is lack of knowledge of clinimetric properties on clinical assessment methods for classifying GJH. Therefore, the purpose of this study was to perform a systematic review for identifying the clinical assessment methods for classifying GJH, to evaluate their clinimetric properties (reliability and validity), and finally to summarize the best evidence synthesis of these clinical assessment methods.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines, PRISMA, [Moher et al., 2009] and used the PICOS method to present the chosen research questions: Participants (humans with GJH and healthy controls, ranging from childhood to adults), Intervention (assessment methods for evaluation and classification of GJH), Comparison (e.g., healthy control groups), Outcomes (reliability/validity), and Study design (e.g., reliability/case control/longitudinal studies).

The overall method used in this review can be divided into four steps: (1) Compile an exhaustive list of assessment methods for GJH on the basis of an initial search (Search 1); (2) Additional search for studies including clinimetrics of the identified assessment methods from Search 1 (Search 2); (3) Critically appraisal of the methodological quality of the identified measurement properties in each study; and (4) synthesizing of the evidence as "a best evidence synthesis."

Selection Criteria

Search 1

With restrictions on the date of publication (January 01, 1965 to December 31, 2015), humans and English, the included articles had to meet the following criteria: (1) be originally published in peer-reviewed journals involving human participants; (2) include a clinical assessment method (test or questionnaire) to classify GJH; and (3) be reported in English. Studies were excluded if they: (1) contained other advanced assessment methods used as primary assessment method and not as a reference assessment; (2) were reviews, abstracts, theses, unpublished studies

("gray literature"); or (3) were animal studies.

Search 2

By using the names of the different assessment methods found in Search 1, Search 2 was initiated, and the articles were included if they: (1) explicitly outlined a purpose for evaluating clinimetric properties of an assessment method (test or questionnaire) for classifying GJH; and (2) included at least one of the clinimetric properties of reliability, validity, and responsiveness. To avoid confusion in relation to the terminology of clinimetric properties, this study relates to the COSMIN terminology, including reliability (reliability and measurement error), validity (criterion validity and hypotheses testing), and responsiveness [Schellingerhout et al., 2008; Mokkink et al., 2010].

Search Strategy and Data Sources

Search 1 (production of a list of clinical assessment methods)

The systematic review was performed by electronic and manual searches in CINAHL ($n = 153$), Embase ($n = 1{,}027$), SportDiscus ($n = 272$), and MEDLINE ($n = 833$). Furthermore, reference lists of relevant articles were hand-searched for additional literature, and the authors conferred with experts within the field of GJH, in order to make sure no relevant articles would be missing. In each of the four databases, the following search terms were used for the Electronic Search 1 for producing a method list: (joint*; hypermobility; instability; laxity; general*) AND (evaluation*; rating*; rate*; questionnaire*; test*; scale*; assess*; examin*; observ*; diagnos*; measure*) NOT (fracture*; surgical). The search terms were adjusted to the different databases where necessary. In all databases, the search fields included title, abstract, and keywords.

Search 2 (identifying clinimetric properties)

For the Electronic Search 2, using the same databases as described in Search 1, and with a total of six identified assessment methods at this point, a total of 24 searches were conducted; one in each database, on each assessment method. The following search terms were used, for retrieving studies with clinimetric properties on each of the six identified assessment methods: (psychometric*; clinimetric*; reproducibility; reliability; repeatability; responsiveness; sensitivity; specificity; validity; diagnos*; feasibility). When including the questionnaire assessment methods, the terms test* and tool* were left out. See PRISMA flow chart (Fig. 1) for the selection process.

Data Extraction and Quality Assessment

Two authors (KS/BJK) independently screened the titles and abstracts, and agreed upon a final list of assessment methods to be included in the current review. If there were any disagreements, the full paper was retrieved for detailed assessment, and consensus was achieved. A third reviewer (RHE) was included if disagreement still existed. The handling of data were performed with the use of EndNoteWeb (https://www.myendnoteweb.com/), for easy access and organizing of data. Screening for additional references were performed based on the retrieved articles.

Eligible studies for each of the retrieved assessment methods were evaluated by the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist for evaluating the methodological quality on clinimetric properties—reliability, validity, and responsiveness [Mokkink et al., 2010]. The COSMIN checklist is currently the only recommended standardized method [Terwee et al., 2012], and has been used in several different studies of clinical test assessment methods [Larsen et al., 2014; Kroman et al., 2014]. The complete COSMIN checklist includes 12 boxes, covering internal consistency, reliability, measurement error, validity, and responsiveness. The current study used the reliability and validity domains, in particular box B—reliability (14 items), box F—hypothesis testing (10 items), and box H—criterion validity (7 items). After inclusion of studies, these were grouped based on the clinimetric property assessed, in reliability (intra-, inter-tester and test-retest) and validity (hypothesis testing or criterion validity). No studies on the responsiveness domain were obtained.

A compiled list for the assessment of the item "minor methodological flaws" as used previously [Larsen et al., 2014] was included (no inclusion of the target population, only for reliability domain; only one trial per measurement/lack of information on repetition; no random order of investigators/measurements; no description of any training phase; inadequate description on demographic details). For the item "other important methodological flaws" an additional list was included (inadequately described/lacking of information about subject eligibility criteria; doubt regarding the site of measurement). Final scoring of the methodological quality of each items, evaluated on a four-point scoring system, (excellent, good, fair, and poor methodological quality) was based on the "worse score counts method" in the checklist [Terwee et al., 2012].

Finally, a best evidence synthesis was performed, by compiling the assessment of the methodological quality, the actual results of the included studies, the number of studies, and the total sample size, as outlined in connection to the COSMIN evaluation [Terwee et al., 2007], and as also performed in a previous study [Kroman et al., 2014]. The rating of the best evidence synthesis ranged from strong, moderate, limited, positive/negative, conflicting, or unknown. A note was made whenever a study was rated "poor" due to only one single item. In the reliability domain this mainly concerned the item "only one measurement" (in box B), as often used in clinical examinations and always in questionnaire studies; in the validity domain studies were mainly rated "poor" due to one rating based on the item "no information on the measurement properties of the comparator instrument(s)"; in addition, a note was made to studies rated "poor" due to "subject eligibility criteria inadequately described/lacking." Studies rated "poor" due to only one "poor" item were upgraded to "fair," in line with previous systematic reviews, describing the limitations of the COSMIN when used for clinical test assessment methods [Kroman et al., 2014; Larsen et al., 2014].

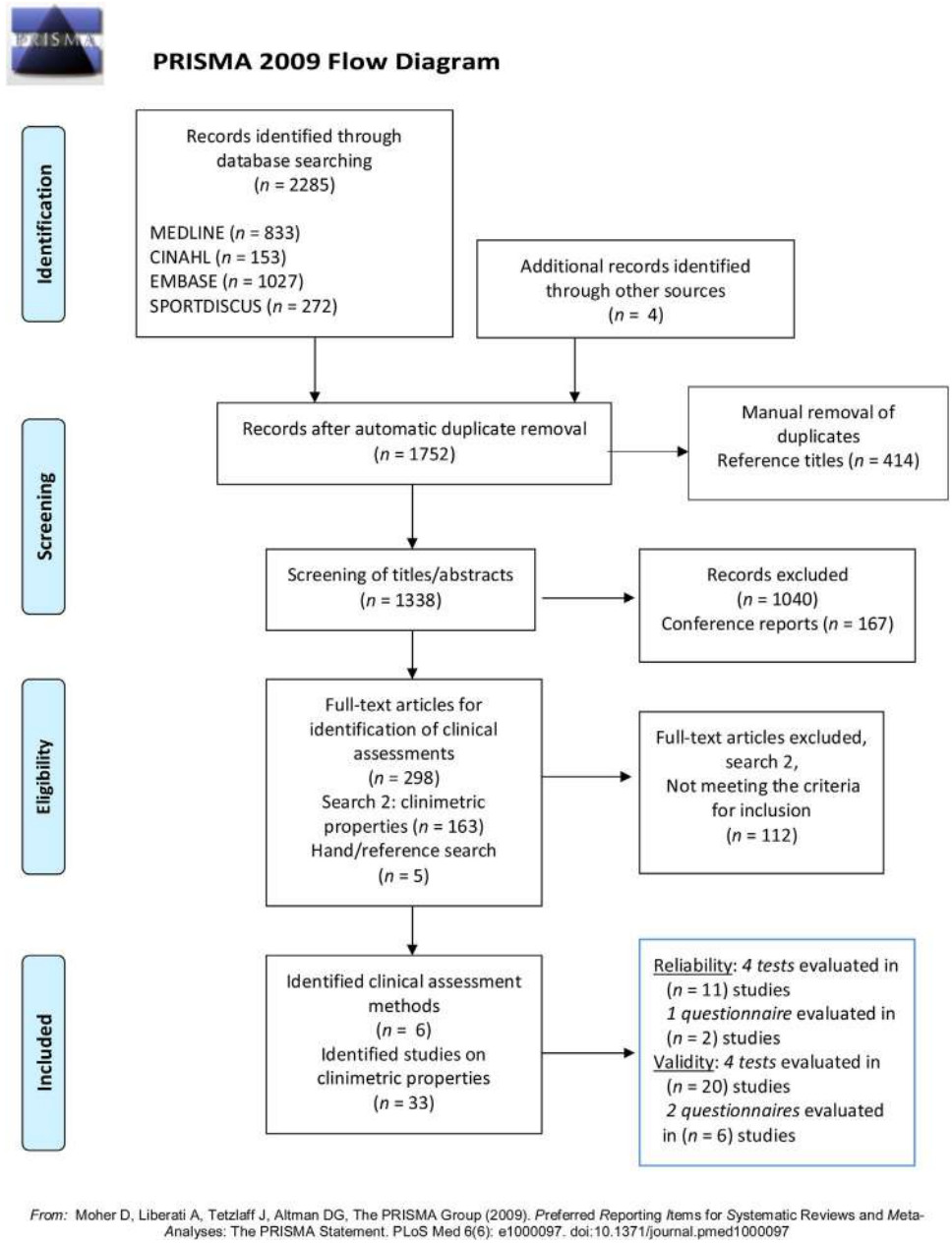

Figure 1. Flow diagram showing identification, screening, eligibility, and inclusion procedures.

Studies with more than one "poor"-rated item were omitted from the final evidence synthesis.

RESULTS

Identification of Clinical Assessment Methods

In total 2,285 references were identified, and after removal of duplicates 1,338 references were included in the screening procedure of titles and abstracts, of which 298 full-text articles were eligible according to the inclusion criteria. In Search 1, a total of six primary clinical assessment methods for classifying GJH were identified, corresponding to four test assessment methods (BS, Carter, and Wilkinson [CW], Hospital del Mar [HdM], Rotes-Querol [RQ]), and two questionnaire assessment methods (5PQ, Beighton Score self-reported [BS-self]). In Search 2, 163 references were identified, and after removal of duplicates 33 studies were identified describing the clinimetric properties of the six clinical assessment methods (Fig. 1).

Clinimetric Properties

Methodological quality in relation to reliability of the four test assessment methods (BS, CW, HdM, and RQ) was evaluated from eleven studies, and

reliability of one of the two questionnaire assessment methods (5PQ) was evaluated from two studies, while there were no reliability studies on BS-self (Table I).

Methodological quality in relation to validity of the four test assessment methods (BS, CW, HdM, RQ), was evaluated from twenty studies, and validity of the two questionnaire assessment methods (5PQ, BS-self) was evaluated from six studies (Table II).

All four tests were rated as having poor quality in all reliability studies, while 64% (7 of 11) for BS, and 50% (1 of 2) for RQ could be upgraded to fair quality, when one rating ("only one measurement") was omitted. Both studies of 5PQ were rated as having poor quality in test-retest reliability [Moraes et al., 2011; Bulbena et al., 2014], but both could be upgraded to fair. CW, RQ, and HdM were all rated as having fair quality (3/3), while for BS 82% (14/17) were upgraded and thus rated as having fair quality. All studies on validity for the two questionnaire assessment methods (for 5PQ: 5/5; for BS-self: 1/1) were upgraded, and therefore, rated as fair (Table III).

As seen in Tables I and II, all test assessment methods BS, CW, HdM, and RQ, have been tested for reliability, and for validity when compared with each other. BS has further been tested for different validity types, such as range of motion (ROM), associations with pain, injuries, and other diseases, whereas HdM has further been tested for validity on associations with shoulder injuries. 5PQ is the only one of the questionnaire assessment methods that has been tested for reliability, and for validity when compared with test assessment methods, associations with pain, diseases, and anxiety. BS-self has only been tested for validity compared with BS (Table III).

Best Evidence Synthesis: Levels of Evidence

Test assessment methods

Of the 11 reliability studies for test assessment methods, 5 studies had poor ratings on methodological quality [Bulbena et al., 1992; Mikkelsson et al., 1996; Hansen et al., 2002; Boyle et al., 2003; Aslan et al., 2006], and since they could not be upgraded to fair, they were not included in the best evidence synthesis. For the only two studies including intra-rater reliability on BS there was limited positive evidence [Erkula et al., 2005; Hirsch et al., 2007] (Table IV).

For inter-rater reliability four studies had limited positive evidence [Hicks et al., 2003; Erkula et al., 2005; Hirsch et al., 2007; Juul-Kristensen et al., 2007], while two studies had negative evidence [Karim et al., 2011; Junge et al., 2013], leaving the final evidence as limited positive to conflicting evidence. A total of four out of the eleven studies included children [Mikkelsson et al., 1996; Hansen et al., 2002; Erkula et al., 2005; Junge et al., 2013].

Validity of BS compared with other test assessment methods showed limited positive to conflicting evidence in three studies [Bulbena et al., 1992; Ferrari et al., 2005; Junge et al., 2013], while compared with ROM (trunk rotation, lower, and upper extremities) the validity in five studies showed limited negative to conflicting evidence (two on children) [Sauers et al., 2001; Erkula et al., 2005; Pearsall et al., 2006; Smits-Engelsman et al., 2011; Naal et al., 2014]. The validity for BS and the association with pain showed moderate positive to conflicting evidence in five studies (all on children) [El-Metwally et al., 2004, 2005, 2007, Tobias et al., 2013; Sohrbeck-Nøhr et al., 2014]. For the validity of BS and the association with injuries the validity showed conflicting evidence in three studies (one in children) [Rousel et al., 2009; Cameron et al., 2010; Junge et al., 2015]. For the validity of BS and the association with different diseases (Temporo-Mandibular Disorders, Chronic Fatigue Syndrome, Adhesive Capsulitis) there was limited positive to conflicting evidence in three studies [Nijs et al., 2004; Hirsch et al., 2008; Terzi et al., 2013].

CW (almost similar to the BS), and RQ had unknown evidence for both inter-rater reliability and validity compared with other test assessment methods [Bulbena et al., 1992], while HdM showed unknown evidence for inter-rater reliability and validity in the association with injuries, such as anterior shoulder dislocation [Bulbena et al., 1992; Chahal et al., 2010].

Questionnaire assessment methods

For reliability 5PQ showed conflicting evidence in the two studies [Moraes et al., 2011; Bulbena et al., 2014]. For the validity 5PQ showed limited positive to conflicting evidence compared with test assessment methods (BS, HdM) in the same two studies, while in the association with pain and tissue diseases (chronic widespread pain, JHS) 5PQ showed limited positive evidence in two studies [Hakim and Grahame, 2003; Mulvey et al., 2013], and with anxiety it showed unknown evidence [Sanches et al., 2014]. BS-self showed unknown evidence in the validity compared with BS in one study [Naal et al., 2014].

DISCUSSION

Four test assessment methods (BS, CW, HdM, RQ) and two questionnaire assessment methods (5PQ, BS-self) were identified for classifying GJH, in children and adults, with 33 studies reporting their measurement properties. The four test assessment methods and one of the questionnaire assessment methods (5PQ) reported measurement properties on both reliability and validity. Most studies were on BS, and only BS and 5PQ reported aspects of validity.

Four test assessment methods (BS, CW, HdM, RQ) and two questionnaire assessment methods (5PQ, BS-self) were identified for classifying GJH, in children and adults, with 33 studies reporting their measurement properties.

The majority of the reliability studies showed limited positive to conflicting evidence for BS, and thus, may seem acceptable to be used in clinical

TABLE I. Information From the Included Studies for COSMIN Scoring in the Reliability Domain

Ref/assessment method	Study sample/population	Registration/handling of missing data	Design	Time interval	Main result	Cut-off score	Methodological flaws
Beighton (5 items)							
Aslan et al. (2006) (BHJMI) (+goniometer for 5th finger, elbows, knees [lying])	$n=72$ Asymp. (mean age 20 yrs, range 18–25)	No information of registration/handling of missing data	Intra-/inter-rater	Intra-rater: mean 12.84 (+/− 7.41 days) Inter-rater: same day	ICC (mean) Intra: 0.92 Inter: 0.82 *% agreement* Intra: 86% (category scores) 43% (composite scores) Inter: 75%(category scores) 42% (composite scores)	Composite scores categorized (0–2: cat. 1) (3–4: cat. 2) (5–9: cat. 3)	Other important/minor methodological flaws (inadequately described/ lacking of info about subject eligibility criteria, asymp., no random order)
Boyle et al. (2003) (BHJMI) (+goniometer for 5th finger, elbows, knees [lying])	$n=42$ (intra) $n=36$ (inter) Asymp. (mean age 25 yrs, range 15–45)	No information of registration/handling of missing data	Intra-/inter-rater	Intra-rater: 1 day to 2 weeks apart Inter-rater: same day or within 6 days	*% agreement* Intra: 81% Inter: 89% Spearmans Rho (cont. score) Intra: 0.81 Inter: 0.87 ($P<.0001$) Spearmans Rho (cat. scores) Intra: .86 Inter: 0.75 ($P<.0001$)	Composite scores categorized (0–2: cat. 1) (3–4: cat. 2) (5–9: cat. 3)	Other minor methodological flaws (asymp., no random order, lacking demographic details)
Bulbena et al. (1992)	$n=30$ Symp. ($n=20$) (mean age 41 yrs) Control ($n=10$) (mean age 48 yrs)	Info on missing data provided, no info on the handling of the data	Inter-rater	No information	Kappa (range) 0.79–0.93	NS	Other minor methodological flaws (lack of info on repetition, no random order, inadequate demographic details)
Erkula et al. (2005)	$n=50$ Asymp. (children, mean age 10 yrs)	No information of registration/handling of missing data	Intra-/inter-rater	Reassessment after 2 weeks	Spearmans Rho Intra: 0.62 Inter: 0.86	≥7/9 (classified as sign. joint laxity)	Other important/minor methodological flaws (subject eligibility criteria inadequately described, asymp., no random order, no training phase, no blinding of results)

continued

TABLE I. (*Continued*)

Ref/assessment method	Study sample/population	Registration/handling of missing data	Design	Time interval	Main result	Cut-off score	Methodological flaws
Hansen et al. (2002) (4/5 selected tests included, no 5th finger)	$n=100$ Asymp. (children, 9–13 yrs)	Info on missing data provided, the handling of the data can be deduced	Inter-rater	No information	Kappa (range) 4 tests: 0.44–0.82 (experts) $\leq$0.40 (inexperienced/ parents)	NS	Other minor meth. flaws (asymp., no training phase, inadequate demographic details, no blinding)
Hicks et al. (2003)	$n=63$ Symp. (mean age 36 yrs, range 20-66)	No information of registration/handling of missing data	Inter-rater	15 min time-delay between raters	ICC (mean) Pair 1: 0.95 Pair 2: 0.76 Pair 3: 0.66	NS	Other important/minor meth. flaws (inadequately described/lacking of info about subject eligibility criteria, no random order, inadequate demographic details)
Hirsch et al. (2007) (+goniometer for elbows, knees)	$n=50$ Asymp. (mean age 38 yrs, range 20–60) (recruited from a general dental practice setting)	Info on missing data provided (1 subject), no info on the handling of the data	Intra-/inter-rater	An average of 24.6 days between first and follow-up exam	ICC (mean) Intra: >0.89 Inter: >0.84 Cronbach's alpha (intra- and inter-rater agreement) Mean 0.75 Median 0.77	$\geq$4/9	Other minor meth. flaws (asymp., no random order)
Junge et al. (2013) (2 different methods)	$n=39$ Asymp. (school children, aged 7–8 and 10–12 yrs)	No information of registration/ handling of missing data	Inter-rater	Approx. 30 min between testing sessions	% agreement 74–97% (method A) 72–97% (method B) $\geq$5/9: 82% (A), 80% (B) Kappa (range) 0.49–0.94 (method A) 0.30–0.84 (method B) $\geq$5/9: 0.64 (A), 0.59 (B)	$\geq$5/9	No other methodological flaws
Juul-Kristensen et al. (2007)	$n=40$ Symp. (mean age 34 yrs) Asymp.	No information of registration/ handling of missing data	Inter-rater	No information	Kappa (range) 0.34–1.00 (curr) 0.60–1.00 (curr/hist) $\geq$5/9: 0.66 (curr), 0.74 (curr/hist)	$\geq$5/9	No other methodological flaws

continued

TABLE I. (*Continued*)

Ref/assessment method	Study sample/population	Registration/handling of missing data	Design	Time interval	Main result	Cut-off score	Methodological flaws
	(mean age 46 yrs)				ICC (mean): 0.91(curr/hist)		
Karim et al. (2011)	$n = 30$ Contemporary Pro dancers (mean age 24 yrs, range 18–32)	No information of registration/handling of missing data	Inter-rater	No information/guideline available upon request	*% agreement* 54–100% Kappa (mean) 0.60	NS	Other minor methodological flaws (no random order, no description of blinding of results)
Mikkelsson et al. (1996)	$n = 29$ (inter) $n = 13$ (intra) Asymp. school children (mean ages 9 and 11 yrs)	No information of registration/handling of missing data	Intra-/inter-rater	Intrarater: within the same lesson (at the beginning and at the end) Inter-rater: during the same lesson	Kappa (mean) Inter: 0.78 Intra: 0.75 ICC (mean) Inter: 0.80 Intra: 0.84	≥6/9	Other minor methodological flaws (asymp., no random order, no training phase, inadequate demographic details)
Carter & Wilkinson (5 items, score 0–5)							
Bulbena et al. (1992)	$n = 30$ Symp. ($n = 20$) (mean age 41 yrs) Controls ($n = 10$) (mean age 48 yrs)	Info on missing data provided, no info on the handling of the data	Inter-rater	No information	Kappa (range) 0.68–0.92	NS	Other minor methodological flaws (lack of info on repetition, no random order, inadequate demographic details)
Hospital del Mar (9/10 items, score 0–9)							
Bulbena et al. (1992) (item testing)	$n = 30$ Symp. ($n = 20$) (mean age 41 yrs) Controls ($n = 10$) (mean age 48 yrs)	Info on missing data provided, no info on the handling of the data	Inter-rater	No information	Kappa (range) 0.61–1.00	NS	Other minor methodological flaws (lack of info on repetition, no random order, inadequate demographic details)
Rotès-Quérol (11 items, score 0–11)							
Bulbena et al. (1992)	$n = 30$ Symp. (n = 20) (mean age 41 yrs) Controls ($n = 10$) (mean age 48 yrs)	Info on missing data provided, no info on the handling of the data	Inter-rater	No information	Kappa (range) 0.44–0.93	NS	Other minor methodological flaws (lack of info on repetition, no random order, inadequate demographic details)
Juul-Kristensen et al. (2007)	$n = 40$ Symp.	No information of registration/handling of missing	Inter-rater	No information	Kappa (range) 0.32–0.79 (curr) 0.31–0.80 (curr/hist)		No other methodological flaws

continued

TABLE I. (*Continued*)

Ref/assessment method	Study sample/population	Registration/handling of missing data	Design	Time interval	Main result	Cut-off score	Methodological flaws
(3 items)	(mean age 34 yrs) Asymp. (mean age 46 yrs)	data			ICC (mean): 0.83 (curr/hist)		
5-part questionnaire (5 items, score 0–5)							
Bulbena et al. (2014)	$n = 33$	No information of registration/ handling of missing data	Test-retest	1 week	Tau-kendall index: 0.91 ICC (mean): 0.96	≥3/7	Other minor methodological flaws (no random order, inadequate description on demographic details)
5-part questionnaire (+2 questions)	Symp. (anxiety) (mean age 35 yrs)						
Moraes et al. (2011)	$n = 211$	Info on missing data implicit provided, the handling of the data can be deduced	Intra-group agreement	6 months	Kappa (mean) Q1: 0.63 Q2: 0.70 Q3: 0.65 Q4: 0.57 Q5: 0.48	≥2/5	Other minor methodological flaws (asymp., no random order, inadequate demographic details, no blinding)
5-part questionnaire	Asymp. (ages 17–24 yrs)						

BHJMI, Beighton and Horan Joint Mobility Index; NS, not stated; approx., approximately, Intra, intrarater; Inter, interrater; yrs, years; asymp., asymptomatic; symp., symptomatic; Q, question; cont., continuous; cat., category; curr, currently; hist, historically; ICC, intraclass correlation; sign., significant; rho, rank correlation co-efficient.

practice, provided that uniformity of testing procedures is included in testing procedures, in addition to historical information, especially in adults. However, there are shortcomings on studies for the validity of BS, while the three other test assessment methods lack information on both reliability and validity. For the questionnaire assessment methods, 5PQ was the most frequently used, however, only in adult population studies, and the reliability showed conflicting evidence. Concerning the validity there were shortcomings on studies for 5PQ, while for BS-self the validity showed unknown evidence in comparison with BS. More studies are needed to conclude on the measurement properties for BS-self.

Inter-rater reliability studies on test assessment methods were most frequently reported on BS, with the majority showing limited positive to conflicting evidence, and thus, may be acceptable for this assessment method. This may provide useful information for clinicians and researchers, in order to establish uniformity in carrying out the procedures. On the other hand, it also shows the need for more future comprehensive studies of this test assessment method, since unclear/vague or different descriptions of the procedures for performing the Beighton tests were used (e.g., thumbs apposition with straight or flexed elbow, knee extension in standing or supine lying). The procedures initially illustrated by photos for performing the Beighton tests [Beighton et al., 1973] are recommended for future clinical use, as described in detail in the appendix of one of the reliability studies [Juul-Kristensen et al., 2007], as they have satisfactory reliability.

Some of the studies did not include all nine tests as recommended, which especially is important when defining cut-points for classifying GJH, as discussed further below. Other test assessment methods, such as CW, RQ, and HdM showed unknown evidence on reliability in one single study [Bulbena et al., 1992], which is too limited to conclude on.

For the questionnaire assessment methods, most of the studies were

TABLE II. Information From the Included Studies for COSMIN Scoring in the Validity Domain

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
BS and other tests/different BS procedures							
Bulbena et al. •BS •CW (5 items) •RQ (11 items)	1992	$n=114$ (Symp.) $n=59$ (controls)	Info on missing data provided, the handling of data can be deduced	Agreement between BS, CW, and RQ criteria to define the HMS Multiple hypotheses formulated a priori	Pearson correlation BS vs. RQ:0.89 BS vs. CW: 0.97 CW vs. RQ:0.86 % agreement CW ≥3: 96–98% BS ≥5: 96–98% RQ ≥5: 95–96%	Different cutpoints are tested	Other important/minor meth. flaws (subject eligibility criteria inadeq. described/ lacking for the control group, 1 trial per measure., no random order, no training phase, inadequate demographic details, no blinding)
Ferrari et al. •BS •Lower Limb Assessment Score (LLAS) (12 items)	2005	1) $n=21$ (hyp.) 2) $n=88$ (possible hyp.) 3) $n=116$ (controls) (range: 5-16 yrs)	No info on missing data/handling provided	Agreement between BS and LLAS Hypotheses vague/not formulated, but possible to deduce what was expected	% agreement BS vs. LLAS 69% (1), 80% (3) Pearson correlation 0.43 (1), 0.79 (2), 0.79 (3)	≥5/9 (BS) ≥7/12 (LLAS)	Other minor methodological flaws (1 trial per measure. session, no random order, no training phase, inadequate demographic details, no blinding)
Junge et al. •BS method A •BS method B	2013	$n=103$ Asymp. (school children, aged 7–8 and 10–12 yrs)	Info on missing data provided, the handling of the data can be deduced	Agreement between preval. of GJH of Methods A and B Hypotheses vague/not formulated, but possible to deduce what was expected	McNemar sign probability test Prevalence on Method A and B No difference ($P=0.54$)	≥5/9 (BS A + B)	No other meth. flaws
BS and ROM							
Erkula et al. •BS	2005	$n=1273$	No info on missing data/handling	Agreement between joint laxity and trunk rotation	Chi2-test BS vs. scap.	≥7/9 (BS)	Other important/minor meth. flaws

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
•Trunk rotation/ asymmetry		Asymp. (mean age 10.4, range 8–15 yrs)	provided	Minimal hypotheses formulated a priori	asymmetry: ($P=0.008$) BS vs. left scap. elevation: ($P=0.028$)		(inadequately described subject eligibility criteria, only 1 trial per measure. session, no random order, no training phase, inadequate demographic details, no blinding)
Naal et al. •BS •Femoroacetabular impingement (FAI)	2014	$n=55$ Symp. (mean age 28.5 yrs, SD 4.1 yrs)	No info on missing data/handling provided	Agreement between BS and Hip ROM Hypotheses vague/not formulated, but possible to deduce what was expected	Spearmans correlation BS vs. Hipflex: 0.61 Int. rot: 0.56 Ext. rot: 0.44 (all with $P<0.01$)	≥4/9 (BS) ≥6/9 (BS)	Other minor methodological flaws (only 1 trial per measurement session, no random order, no training phase, no blinding)
Pearsall et al. •BS •Knee arthrometer (KT-2000) •Ankle arthrometer	2006	$n=57$ Asymp. (mean age 20.9 yrs, SD 1.45 yrs)	No info on missing data/handling provided	Agreement between BS and knee and ankle joint specific laxity Hypotheses vague/not formulated, but possible to deduce what was expected	Spearmans correlation BS vs. Kneelax: 0.37 ($P=0.110$) A/P ankle lax: 0.21 ($P=0.152$) Int-Ext rot ankle lax: 0.24 ($P=0.101$)	NS	Other minor meth. flaws (no random order, no training phase, no blinding)
Sauers et al. •BS (4/5 items, forward flexion not included) •Shoulder	2001	$n=51/102$ Asymp. (healthy shoulders)	No info on missing data/handling provided	Agreement between BS and glenohumeral joint laxity Hypotheses vague/not formulated, but possible to deduce what was expected	Pearsons correlation Bs vs. instr. AP lax score: (0.23, NS) Clin pass ROM:	NS (BS 0–8) assumed)	Other minor methodological flaws (only 1 trial per measure. session, no random order, no

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
arthrometer •Clinical passive ROM		(mean age 22 yrs, SD 2.8 yrs)			(0.01–0.48, NS)		training phase, inadequate demographic details, no blinding)
Smits-Engelsman et al. •BS •Goniometer	2011	$n=551$ Asymp. (mean age 8 yrs, range 6–12 yrs)	No info on missing data provided, but the handling of data can be deduced	Agreement between BS and 16 ROM Hypotheses vague/not formulated, but possible to deduce what was expected	Variance analysis Sign. diff in mean ROM between the 3 BS groups ($P<0.001$, except knee flex $P=0.02$; hip ext $P=0.06$)	BS: 0–4 (not hyp) 5–6 (incr. hyp) 7–9(hyp)	Other minor methodological flaws (only 1 trial per measure. session, no random order, no blinding)
BS and pain							
El-Metwally et al. •BS •Musculoskeletal pain	2004	$n=430$ Asymp. (mean age 9.8 and 11.8 yrs)	Info on missing data, and handling of data provided	Predictive baseline factors for persistence/recurrence of MSK pain, from childhood till adolescence Hypotheses vague and direction not formulated, but possible to deduce what was expected	Pain recurrence 4-yr follow-up (GLModels + RiskRatio): (RR = 1.35 [1.08–1.68])	≥6/9	Other minor methodological flaws (only 1 trial per measure, no random order, no training phase, inadequate demographic details)
El-Metwally et al. •BS •Lower limb pain (LLP)	2005	$n=1284$ Asymp. (mean age 9.8 and 11.8 yrs)	No info on missing data provided, but the handling of data can be deduced	Predictive baseline factors for persistence/recurrence of LLP, from childhood till adolescence Hypotheses vague and direction not formulated, but possible to deduce what was expected	LLP recurrence 4-yr follow-up (GLModels + OddsRatio) (OR = 2.93 [1.13–7.70])	≥6/9	Other minor methodological flaws (only 1 trial per measure, no random order, inadequate demographic details)
El-Metwally et al. •BS •Musculoskeletal pain	2007	$n=1113$ Asymp. (mean age 9.8 and 11.8 yrs)	Info on missing data provided, the handling of data can be deduced	Predictive baseline factors for incidenceof musculoskeletal pain, from childhood till adolescence Hypotheses vague and direction	Incidence 4-yr follow-up (GLModels + OddsRatio) BS vs. Non-traum. pain (OR:0.83 [0.44–1.56]) BS vs. Traumatic pain	≥4/9 ≥6/9	Other minor methodological flaws (only 1 trial per measure, no random order, inadequate

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
				not formulated, but possible to deduce what was expected	(OR: 0.70 [0.16–3.04]) NS		demographic details)
Sohrbeck-Nøhr et al. •BS •Pain (arthralgia)	2014	$n=301$ Asymp. (median age 14 yrs, range 13-15 yrs)	Info on missing data provided, described handling	Predictive baseline factors for incidence of arthralgia, from childhood till adolescence Hypotheses vague and direction not formulated, but possible to deduce what was expected	Arthralgia incidence 4 and 6-yr follow-up (Logistic Regress Models + Odds Ratio) BS ≥5/9 (OR: 3.00, [0.94–9.60])	≥4/9 ≥5/9 ≥6/9	Other minor methodological flaws (no random order)
Tobias et al. •BS •Musculoskeletal pain	2013	$n=2901$ Asymp. (mean age 13.8 yrs)	Info on missing data provided, the handling of data can be deduced	Predictive baseline factors for incidence of arthralgia, from childhood till adolescence Hypotheses vague and direction not formulated, but possible to deduce what was expected	Pain association 4-yr follow-up (Logistic Regress Models + Odds Ratio) Shoulder (OR1.68 [1.04–2.72]) Knee (OR 1.83 [1.10–3.02]) Ankle/foot (OR 1.82 [1.05–3.16])	≥6/9	Other minor methodological flaws(only 1 trial per measure, no random order, no blinding)
BS and injuries							
Cameron et al. •BS •Glenohumeral instability (GI, historic info)	2010	$n=714$ (soldiers, mean age 18.8 yrs, SD 1 yr)	Info on missing data provided, described handling	Relationship between BS and GI Hypotheses vague and direction not formulated, but possible to deduce what was expected	GI association (Logistic Regress Models + Odds Ratio) (OR 2.48 [1.19–5.20])	≥2/9	Other minor methodological flaws: (1 trial per measure, no random order)
Chahal et al. •HdM tests (10 items) + ext. rot >85° (GLL+ER) •Primary anterior shoulder dislocation (ASD)	2010	$n=57$(cases)/ 92(controls) (mean age 24 yrs, SD: 0.32)	No info on missing data provided, the handling of data can be deduced	Predictive risk factor of GLL + ER for AID Minimal number of hypotheses formulated, expected direction of correlation stated	AID association (Odds Ratio) All (OR: 2.79 [1.27–6.09]) GLL (OR: 3.6 [1.49–8.68]) GLL + ER Men: (OR: 7.43 [2.13–25.57])	Men: ≥4/10 Women: ≥5/10	Other minor methodological flaws (1 trial per measure, no random order, inadequate demographic details, no blinding)

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
					GLL (OR: 6.75 [1.92–23.36])		
Junge et al. •BS; Knee hypermobility (KH) •Knee injuries by SMS-track (KI)	2015	$n = 999$ (school children, 9–14 yrs)	Info on missing data provided, described handling	Predictive risk factor of BS + KH for KI Minimal number of hypotheses formulated, expected direction of correlation stated	KI association (Logistic Regress models + Odds Ratio) Traumatic Inj (OR: 1.56 [0.43–5.61]) BS TraumaticInj (OR: 2.22 [0.60–8.19]) BS + KH	≥5/9	Other minor methodological flaws (1 trial per measure, no random order, no training phase)
Roussel et al. •BS + goniometer •Pelvic injuries (PI), low back pain (LBP)	2009	$n = 32$ (dancers) $n = 26$ (students) (mean 20 yrs, SD: 2 yrs)	Info on missing data provided, described handling	Predictive risk factor of BS for PI and LBP Hypotheses vague and direction not formulated, but possible to deduce what was expected	PI/LBP (Spearman correlation: (Rho = − 0.03; $P = 0.89$) PI, LBP	BS: 0–3 (tight) 4–6 (hyp) 7–9 (extr. hyp)	Other important/minor meth. flaws(inadequately described subject eligibility criteria, 1 trial per measure, no random order, no training phase, inadequate demographic details, no blinding)
BS and diseases							
Hirsch et al. •BS •Temporo-mandibular sympt (TMs)	2008	$n = 895$ (mean age 40.6 yrs, SD: 11.6 yrs)	No info on missing data provided, but the handling of data can be deduced	Agreement between BS and TMs Hypotheses vague and direction not formulated, but possible to deduce what was expected	Association (Multiple log. Regress. Models + Odds Ratio) Joint click, reduced ROM (OR: 1.56 [1.01–2.39])	Category 0 (BS = 0) 1 (BS = 1–3) 2 (BS = 4–9)	Other minor methodological flaws (only 1 trial per measure.session, no random order, no training phase, inadequate

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
							demographic details, no blinding)
Nijs et al. •BS •Chronic fatigue syndrome (CFS)	2004	$n = 44$ Symp. (CFS) (mean age 40.2 yrs, SD: 9.11)	Info on missing data provided, but the handling of data can be deduced	Association between widespread pain in patients with CFS and BS Multiple hypotheses formulated a priori, direction and but magnitude not stated	Association between BS and CFS CFS: 63.6% Non-CFS: 36.5% (Fischers exact test: $P = 0.73$) CFS-APQ1: $P = 0.75$ CFS-APQ2: $P = 0.69$ (NS)	≥4/9	Other minor methodological flaws (only 1 trial per measure, no random order, no training phase, inadequate demographic details, noblinding)
Terzi et al. •BS •Adhesive capsulitis (AC) of the shoulder •Subacromial impingement syndrome (SIS)	2013	$n = 240$ (120 with AC, 120 controls/SIS) (mean age 53.9–54.08 yrs, SD: 8.21–10.68)	No info on missing data provided, but the handling of data can be deduced	Difference in GJH (BS) in AC vs. SIS Minimal number of hypotheses formulated, expected direction, but not magnitude of correlation stated	Chi-square GJH in AC vs. SIS: (0.8% vs. 7.5%, $P = 0.010$)	NS	Other minor methodological flaws (only 1 trial per measure, no random order, no training phase, no blinding)
Questionnaires (5-part) and other tests							
Bulbena et al. •5PQ (+2 questions) •HdM (10 items)	2014	$n = 191$ pt's (potential anxiety, mean age 35.5 yrs,	No info on missing data/handling provided	Agreement between 5PQ + 2Q and HDM Hypotheses vague and direction not formulated, but possible to deduce what was expected	Spearmans correlation 5PQ+2Q and HdM: (rho = 0.75; $P < 0.001$) 5PQ + 2Q and 5PQ: (rho = 0.86; $P < 0.001$)	≥3/7	Other important/minor meth. flaws (inadeq. described subject eligibility criteria, 1 trial per measure, no

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
		SD: 10.18 yrs)					random order, no training phase, inadeq. demographic details, no blinding)
Moraes et al. •5PQ (transl.) •BS 5-part Q and pain	2011	$n=394$ (university students, age 17–24 yrs)	Info on missing data provided, the handling can be deduced	Agreement between 5PQ and BS Hypotheses vague and direction not formulated, but possible to deduce what was expected Assumable that the criterion used (BS) can be considered a reasonable "gold standard"	% agreement 73.6% Sensitivity 70.9 (62.1–78.6) Specificity 77.4 (71.4–82.6)	≥2/5 (5PQ) ≥4/9 (BS)	Other minor methodological flaws (no random order, inadequate demographic details, no blinding)
Mulvey et al. •5-part questionnaire •Chronic widespread pain (CWP) 5-part Q and diseases	2013	$n=12{,}354$ (population, median age 55 yrs, range 25–107 yrs)	Info on missing data provided, registration/ handling described	Association between JH and musculoskeletal pain Minimal number of hypotheses formulated, expected direction of correlation stated	Relative risk ratio JH and CWP grade I: (RRR 1.2; $P=0.03$ – modest ass.) grade II: (RRR 1.2, $P=0.1$ – modest ass., not stat. sign.) grade III/IV: (RRR 1.4; $P=<0.001$)	≥2/5	Other minor methodological flaws (1 trial per measure., no random order, no training phase, inadequate demographic details, no blinding)
Hakim and Grahame •5PQ	2003	$n=269$ (212 BJHS, 57 controls) $n=220$ (170 BJHS, 50 controls) (range	No info on registration/ handling of missing data	Agreement between 5PQ and BJHS Hypotheses vague and direction not formulated, but possible to deduce what	Sens. (mean) 77-85% (1st and 2nd cohort) Spec. 80–89% (1st and 2nd cohort)	≥2/5	Other minor methodological flaws (1 trial per measure., no random order, no training phase,

continued

TABLE II. (*Continued*)

Ref/assessment method	Year	Study sample/population	Registration/handling of missing data	Construct validity hypotheses formulated/direction/criterion validity (adequate "gold standard")	Main results	Cut-off points	Methodological flaws (explicitly stated or lack of information)
		16–80 yrs)		was expected Assumable that the criterion used (BS) can be considered a reasonable "gold standard"			inadequate demographic details, no blinding)
Sanches et al. •5PQ •Anxiety	2014	$n=2300$ (university students, mean age 21 yrs, SD: 3.25)	Info on missing data provided, registration/handling can be deduced	Association between Beck Anxiety Inventory (BAI) and 5PQ Hypotheses vague and direction not formulated, but possible to deduce what was expected	Pearsons correlation 5PQ and BAI total score (Women: $r=0.11$, $P=0.007$, weak ass.) (Men: $r=0.04$, ($P=0.450$), not sign. ass.)	≥2/5	Other minor methodological flaws (1 trial per measurement, no random order, no training phase, inadequate demographic details, no blinding)
BS self-reported Naal et al. •BS •BS-self (from paper drawings) •Femoroacetabular impingement (FAI)	2014	$n=55$ Symp. (diagnosed with FAI) (mean age 28.5 yrs, SD: 4.1 yrs)	Info on missing data provided, registration/handling can be deduced	Agreement between BS-self and BS/agreement between BS and Hip ROM Hypotheses vague and direction not formulated, but possible to deduce what was expected	Kappa-values (L_w) Total 0.82 (0.72–0.91) Single tests range: 0.61–0.96 Spearmans correlation BS vs. Hipflex: 0.61 Int. rot: 0.56Ext. rot: 0.44 (all with $P<0.01$)	≥4/9 (BS) ≥6/9 (BS)	Other minor methodological flaws (1 trial per measure, no random order, no training phase, no blinding)

BS, Beighton Scale; CW, Carter & Wilkinson; HDM, Hospital del Mar; RQ, Rotès-Quérol; LLAS, Lower Limb Assessment Score; 5PQ, 5-part questionnaire; measure, measurement; meth, methodological; hyp, hypermobile; GJH, generalized joint hypermobility; HMS, hypermobility syndrome; GLL, generalized ligamentous laxity; JH, joint hypermobility; BJHS, benign joint hypermobility syndrome; MSK, musculoskeletal; scap, scapular; lax, laxity; ROM, range of motion; clin, clinical; pass, passive; incr, increased; diff, difference; sign, significant; ass, association; traum, traumatic; transl., translation; inadeq, inadequate; ER, external rotation; ASD, Primary anterior shoulder dislocation; KH, knee hypermobility; KI, knee injuries; PI, pelvic injuries; LBP, low back pain; TMs, Temporomandibular symptoms; CFS, chronic fatigue syndrome; AC, adhesive capsulitis; SIS, subacromial impingement syndrome; CWP, chronic widespread pain; BAI, Beck Anxiety Inventory; FAI, femoroacetabular impingement; A/P, anterior/posterior; SD, standard deviation; OR, odds ratio; RR, risk ratio; sens, sensitivity; spec, specificity; NS, non-significant; GLmodel, general linear regression model.

TABLE III. COSMIN Scoring of the Methodological Quality of Each Study on Measurement Properties (Reliability and Validity)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
Clinical tests									
Carter & Wilkinson (0–5) (4 bilateral BS tests + 1 ankle test)									
Bulbena et al. (1992)	$n = 30$ (mean age 41 yrs. [symp.], 48 yrs. [control])	Kappa: substantial/ almost perfect	–	Poor (only one measurement, lacking of info about subject eligibility criteria)			Hyp. test. (CW vs. RQ/BS) Pearson corr. High (CW vs. RQ) Very high (CW vs. BS) % agreement CW ≥3: 96–98%	–	Poor*** (other imp.meth. flaws: subject eligibility criteria inadeq. described/lacking for the control group)
Beighton (0–9)									
Erkula et al. (2005)	$n = 50$ (mean age 10 yrs)	Spearmans rho: Moderate (intra) High (inter)	≥7/9 (classif. as significant joint laxity)	Poor* (only one measurement)			Hyp. test. (BS vs. ROM) Chi^2-test: ($P = 0.008$) BS vs. scap. asymmetry ($P = 0.028$) BS vs left scap. elevation	≥7/9	Poor (no info on the measurement prop. of the comparator instr., other important meth. flaws - lacking of info about subject eligibility criteria)
Hirsch et al. (2007)	$n = 50$ (mean age 38 yrs, range 20–60)	ICC: Excellent (intra/inter)	–	Poor* (only one measurement)	Hirsch et al. (2008)	$n = 895$ (mean age 40.6 yrs, SD: 11.6 yrs)	Hyp. test (BS vs. TMDs) Odds Ratio: Joint click (OR: 1.56 (1.01–2.39)	Composite scores categoris.: (0: cat. 1) (1–3: cat. 2) (4–9: cat. 3)	Fair
Junge et al.	$n = 39$	Kappa:	≥5/9	Poor*	Junge et al.	$n = 109$	Hyp. test	≥5/9	Fair

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
(2013) (2 different BS methods)	(aged 7–8 and 10–12 yrs)	moderate/ substantial, substantial/ almost perfect (method A) Fair/moderate, substantial/ almost perfect (method B) ≥5/9: substantial (A), moderate (B)		(only one measurement)	(2013) Junge et al. (2015)	$n=999$ (range 9–14 yrs)	(BS vs. BS A + B) McNemar sign probability test Prevalence on Method A and B: No difference ($P=0.54$) Hyp. test. (BS vs. injuries) Odds Ratio: Traumatic inj (OR: 1.56 [0.43–5.61])	≥5/9	Poor** (inadequate info on the measurement properties of the comparator instrument)
Juul-Kristensen et al. (2007)	$n=40$ (mean age 34 yrs [symp.], 46 yrs [asymp.])	Kappa: substantial (curr), substantial (curr/hist) ICC: Excellent (curr/hist)	≥5/9	Poor* (only one measurement)	Sohrbeck-Nøhr et al. (2014)	$n=301$ (mean age 14 yrs, range 13–15 yrs)	Hyp. test. (BS and arthralgia): Odds Ratio: BS ≥5/9 (OR: 3.00, [0.94–9.60])	–	Fair
Mikkelsson et al. (1996)	$n=29$ (inter) $n=13$ (intra) (mean	Kappa: Substantial (intra/inter)	≥6/9	Poor (only 1 measure., small sample size, time interval not appropriate)	El-Metwally et al. (2004)	$n=430$ (mean age 9.8 and 11.8 yrs)	Hyp. test. (BS and pain) Risk Ratio: (RR = 1.35 [1.08–1.68])	≥6/9	Fair

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
	ages 9 and 11 yrs)				El-Metwally et al. (2005)	$n = 1{,}284$ (mean age 9.8 and 11.8 yrs)	Odds Ratio: (OR = 2.93 [1.13–7.70])	≥6/9	Fair
					El-Metwally et al. (2007)	$n = 1{,}113$ (mean age 14 yrs, range 13–15 yrs)	Odds Ratio: BS vs. non-traum. pain (OR: 0.83 [0.44–1.56]) NS Traumatic pain (OR: 0.70 [0.16–3.04]) NS	≥6/9	Fair
Aslan et al. (2006) (BHJMI)	$n = 72$ (mean age 20 yrs, range 18–25)	ICC: Excellent (intra/inter)	Composite scores categorized (0–2: cat. 1) (3–4: cat. 2) (5–9: cat. 3)	Poor (other important meth. flaws, inadequate statistics applied)		–	–	–	–
Boyle et al. (2003) (BHJMI)	$n = 36/42$ (mean age 25 yrs, range 15–45)	Spearmans rho: Excellent (intra/inter)	Composite scores categorized (0–2: cat. 1) (3–4: cat. 2) (5–9: cat. 3)	Poor (time interval not appropriate, inadequate statistics applied)		–	–	–	–
Bulbena et al. (1992)	$n = 30$ (mean age 41 yrs. [symp.], 48 yrs.	Kappa: Substantial/ almost perfect	–	Poor (only one measurement, lacking of info about subject eligibility			Hyp. test. (BS vs. CW/RQ) Pearsons corr. Very high (BS vs. CW) High (BS vs. RQ)	–	Poor*** (other imp. meth. flaws: subject eligibility criteria inadeq. described/lacking for the control group)

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
	[control])			criteria)					
Hansen et al. (2002) (4/5 tests, no 5th finger)	$n=100$ (range 9–13 yrs)	Kappa: Moderate/ substantial, substantial/ almost perfect (experts) Fair (inexp.)	–	Poor (only 1 measurem., test conditions not similar)	–	–	–	–	–
Hicks et al. (2003)	$n=63$ (mean age 36 yrs, range 20–66)	ICC: Fair/good, good/excellent	–	Poor* (only one measurement)	–	–	–	–	–
Karim et al. (2011)	$n=30$ (mean age 24 yrs, range 18–32)	Kappa: Moderate	–	Poor* (only one measurement)	–	–	–	–	–
–	–	–	–	–	Cameron et al. (2010)	$n=714$ (mean age 18.8 yrs, SD: 1 yr)	Hyp. test. (BS vs. injuries) Odds Ratio GJI (OR 2.48 [1.19– 5.20]) ($P=0.16$)	≥2/9 (95th percentile)	Fair
–	–	–	–	–	Ferrari et al. (2005)	$n=21(1)/88$ (2)/116 (3)	Hyp. test. (BS vs. other tests) % agreement BS vs. LLAS:	≥5/9	Fair

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
						(range: 5–16 yrs)	69% (1), 80% (3) Pearson correlation: Low (1), High (2), High (3)		
–	–	–	–	–	Naal et al. (2014)	$n=55$ (mean age 28.5 yrs, SD 4.1 yrs.)	Hyp. test. (BS vs. Hip ROM) Spearmans correlation BS vs. Hipflex: 0.61 Int. rot: 0.56 Ext. rot: 0.44 (all with $P<0.01$)	≥4/9 (BS) ≥6/9 (BS)	Poor* (inadequate info on the measurement prop. of comparator instr.)
–	–	–	–	–	Nijs et al. (2004)	$n=44$ (mean age 40.2 yrs, SD: 9.11)	Hyp. test. (BS vs. CFS) Association between BS and CFS CFS: 63.6% Non-CFS: 36.5% (Fischers exact test: $P=0.73$) CFS-APQ1: $P=0.75$ CFS-APQ2: $P=0.69$ (non-sign)	≥4/9	Fair
–	–	–	–	–	Pearsall et al. (2006)	$n=57$ (mean age 20.9 yrs, SD 1.45 yrs)	Hyp. test (BS vs. ROM) Spearmans correlation BS vs. Kneelax: 0.37 ($P=0.110$) AP ankle lax: 0.21, $P=0.152$ IE ankle lax: 0.24, $P=0.101$	–	Fair

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
–	–	–	–	–	Roussel et al. (2009)	$n=32/26$ (mean 20 yrs, SD: 2 yrs)	Hyp. test. (BS vs. injuries) PI/LBP (Spearman correlation: (Rho = −0.03; $P=0.89$) PI, LBP	Composite scores subgr.: (0–3: gr.1, tight) (4–6: gr.2, hyp.) (7–9: gr.3, extr. hyp.)	Poor (no info on the measurement prop. of comparator instr., other important meth. flaws - lacking of info about subject eligibility criteria)
–	–	–	–	–	Sauers et al. (2001)	$n=51/102$ (mean age 22 yrs, SD 2.8 yrs)	Hyp. test. (BS vs. ROM) Pearsons correlation BS vs. instrumented AP lax score: (0.23, Non-S) Clin pass ROM: (0.01 –0.48, Non-S)	–	Fair
–	–	–	–	–	Smits-Engelsman et al. (2011)	$n=551$ (mean age 8 yrs, range 6–12 yrs)	Hyp. test. (BS vs. ROM) Variance analysis: Sign. diff in mean ROM between the 3 BS groups ($P<0.001$, except knee flex $P=0.02$; hip ext $P=0.06$)	≥7/9	Poor (no description of the constructs measured by the comparator instr., no info on the measurement prop.)
–	–	–	–	–	Terzi et al. (2013)	$n=240$	Hyp.test. (BS vs. AC)	–	Poor** (no info on the

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
						(mean age 53.9–54.08 yrs, SD: 8.21–10.68 yrs)	Chi-square GJH in AC vs. SIS: (0.8% vs. 7.5%, $P = 0.010$)		measurement prop. of the comparator instr.)
		–	–	–	Tobias et al. (2013)	$n = 2901$ (mean age 13.8 yrs)	Hyp. test. (BS and pain) Odds Ratio: Shoulder (OR 1.68 [1.04–2.72]) Knee (OR 1.83 [1.10–3.02]) Ankle/ foot (OR 1.82 [1.05–3.16])	≥6/9	Poor** (no info on the measurement prop. of the comparator instr.)
Rotès-Quérol (0–11)									
Bulbena et al. (1992)	$n = 30$ (mean age 41 yrs. [symp.], 48 yrs. [control])	Kappa: Moderate/ substantial, substantial/ almost perfect	–	Poor (only one measurement, lacking of info about subject eligibility criteria)		Hyp. test. (RQ vs. CW/BS)	Pearson correlation High (RQ vs. BS) High (RQ vs. CW)	–	Poor*** (other imp. meth.flaws: subject eligibility criteria inadeq. described/lacking for the control group)
Juul-Kristensen et al. (2007) (3 tests)	$n = 40$ (mean age 34 yrs [symp.], 46 yrs [asymp.])	Kappa: Fair/ moderate, moderate/ substantial (curr) fair/ moderate, substantial/ almost perfect (curr/hist) ICC: Excellent	–	Poor* (only one measurement)	–	–	–	–	–

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result (curr/hist)	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
Hospital del Mar (0–10)				Design					
Bulbena et al. (1992)	$n=30$ (mean age 41 yrs. [symp.], 48 yrs. [control])	Kappa: Substantial/ almost perfect	–	Poor (only one measurement, lacking of info about subject eligibility criteria)	–	–	–	–	–
Chahal et al. (2010)	$n=57/92$ (Mean age 24 yrs, SD: 0.32)	–	–	–		Hyp. test. (HdM and injuries)	Odds Ratio: All GLL − (OR: 2.79 [1.27–6.09]) GLL + ER − (OR:3.6 [1.49–8.68]) Men GLL − (OR: 7.43 [2.13–25.57]) GLL + ER − [OR: 6.75 (1.92–23.36])	≥4/10 (men) ≥5/10 (women)	Fair
Questionnaires 5-part questionnaire (0–5)									
Bulbena et al. (2014) (+2Q)	$n=33$ (mean age 35 yrs)	ICC: Excellent Tau-kendall index: Very high corr.	≥3/7	Poor* (only one measurement)		Hyp. test. (5PQ vs. HdM)	Spearmans correlation 5PQ+2Q and HDM: (rho = 0.75; $P<0.001$) 5PQ + 2Q and 5PQ: (rho = 0.86; $P<0.001$)	≥3/7	Poor** (no info on the measurement prop. of the comparator instr.)

continued

TABLE III. (*Continued*)

		Reliability			Validity				
Assessment methods/ reference	Study (n)/ age	Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
Moraes et al. (2011)	$n = 211$ (range 17–24 yrs)	Kappa: Substantial (Q1, Q2, Q3) Moderate (Q4, Q5)	≥2/5	Poor* (only one measurement)	$n = 394$	Hyp.test. (5PQ vs. BS)	% agreement 73.6% Sens.(mean) 0.69 Spec.(mean) 0.75	≥2/5	Fair (other minor meth. flaws: inadequate description on demographic details, no blinding)
						Criterion validity			Fair (other minor)
–	–	–	–	Hakim and Grahame (2003)	$n = 212$ (range 15–80 yrs)	Hyp. test. (5PQ vs. BJHS)	Sens. (mean) 77–85% (1st and 2nd cohort) Spec. 80–89% (1st and 2nd cohort)	≥2/5	Poor** (no info on the measurement prop.of the comparator instr.)
						Criterion validity			Fair (other minor meth. flaws: inadequate description on demographic details, no description of blinding)
–	–	–	–	Mulvey et al. (2013)	$n = 2{,}354$ (median age 55 yrs, range 25–107 yrs)	Hyp.test. (5PQ vs. CWP)	Relative risk ratio: JH and CWP grade I: (RRR 1.2; $P = 0.03$ – modest ass.) grade II: (RRR 1.2, $P = 0.1$ – modest ass., not stat. sign.) grade III/IV: (RRR 1.4; $P = <0.001$)	≥2/5	Fair

continued

TABLE III. (*Continued*)

Assessment methods/ reference	Study (n)/ age	Reliability			Validity				
		Design/result	Cut-off score	COSMIN score	Reference	Study (n)/age	Design/result	Cut-off score	COSMIN score
–	–	–	–	Sanches et al. (2014)	$n = 2300$ (mean age 21 yrs, SD: 3.25)	Hyp.test. (5PQ vs. anxiety disease)	Pearsons correlation 5PQ and BAI total score (Women: $r = 0.11$, $P = 0.007$, weak ass) (Men: $r = 0.04$, $P = 0.450$, not sign ass)	≥2/5	Fair
Beighton self-reported (0–9)									
–	–	–	–	Naal et al. (2014)	$n = 55$ (mean age 28.5, SD: 4.1 yrs)	Hyp. test. (BS s-r vs BS)	Kappa-values (L_w) Total: 0.82 (0.72–0.91) Single tests (range): 0.61–0.96	≥4/9	Poor** (no info on the measurement prop. of the comparator instr.)

BS, Beighton Score; CW, Carter & Wilkinson; HDM, Hospital del Mar; RQ, Rotès-Quérol; LLAS, Lower Limb Assessment Score; 5PQ, 5-part questionnaire; measure, measurement; meth, methodological; prop, properties; GJH, generalized joint hypermobility, HMS, hypermobility syndrome; GLL, generalized ligamentous laxity; JH, joint hypermobility; BJHS, benign joint hypermobility syndrome; hyp, hypothesis; instr, instruments; scap, scapular; lax, laxity; ROM, range of motion; incr, increased; s-r, self-reported;p, persistent; r, recurrent; inc, incidence; classif, classified; cat, categorized; diff, difference; sign, significant; traum, traumatic; GJI, glenohumeral joint instability; ER, external rotation; ASD, Primary anterior shoulder

reported on 5PQ, which shows to be a promising assessment method for future population studies, where different domains of validity on GJH thus, can be studied more carefully. The additional questionnaire, BS-self, may also seem promising, as it contains illustrations of the test procedures for each of the BS tests. However, the questionnaire assessment methods need more evaluation before they can be used clinically, since very few studies have reported measurement properties on their reliability and validity.

The current review covers a wide range of populations, children, and adults (for adults comprising 64% [7/11] on reliability, and 62% [16/26] on validity), men and women (three studies on separately men or women), and different ethnic groups (mostly Caucasian, few on American/Canadian/Brazilian). For children, only BS has been used, while for adults, different test and questionnaire assessment methods have been used, though, still mostly BS, and 5PQ in population studies.

The current review demonstrates cut-points varying for the different clinical assessment methods. In the adult population, when using nine tests for BS, mostly one cut-point was used for classifying GJH varying between 4 and 6, but one study used 2/9 [Cameron et al., 2010]. However, also two cut-points were used, with a lower cut-point for "tight/not hypermobile" individuals varying between 1 and 4, and an upper cut-point for "hypermobile/extremely hypermobile" individuals varying between 4 and 7 [Boyle et al., 2003; Aslan et al., 2006; Hirsch et al., 2008; Roussel et al., 2009]. For the questionnaire assessment methods only one cut-point was used for classifying GJH, varying between 2 and 3 and with a different total score varying between 5 and 7 [Hakim and Grahame, 2003; Bulbena et al., 2014].

Generally, for adults, one cut-point, varying from 4 to 5 was used in BS (4/9 and 5/9), and 2/5 in 5PQ have been used. For children, one cut-point varying from 5 to 7 was used in

TABLE IV. Levels of Evidence of Included Studies

	Reliability			Validity		
	Intra/inter	Quality/(*n*)/pop		Hypothesis testing	Quality/(*n*)/pop	
Clinical assessment tools						
Beighton	Aslan[06]: ++	*P* (72)		vs. other tests:		
	Boyle[03]: ++	*P* (42/36)		(CW/RQ) Bulbena[92]: +	*P**** (173)	
	Bulbena[92]: +	*P* (30)		(LLAS) Ferrari[05]: +	*F* (225)	C
	Erkula[05]: ++	*P** (50)	C	(A/B) Junge[13]: −	*F* (103)	C
	Hansen[02]: −	*P* (100)	C	(+) to (+/−) Limited		
	Hicks[03]: +	*P** (50)		pos. to conflicting		
	Hirsch[07]: ++	*P** (50)				
	Junge[13]: −	*P** (39)	C	vs. ROM:		
	Juul-Kr[07]: +	*P** (40)		(Trunkrot.) Erkula[05]: −	*P* (1273)	C
	Karim[11]: −	*P** (30)		(Hip) Naal[14]: −	*P*** (55)	
	Mikkelss.[96]:++	*P* (29/13)	C	(k/a lax) Pearsall[06]: −	*F* (57)	
				(sh lax) Sauers[01]: −	*F* (51)	
	Ia			(gon) Smits-Eng[11]: +	*P* (551)	C
	(+) Limited pos.			(−) to (+) Limited neg. to conflicting		
	Ie					
	(+) to (+/−) Limited pos. to Conflicting			vs. pain:		
				(p/r) El-Metwally[04]: +	*F* (430)	C
				(LLP) El-Metwally[05]: +	*F* (1284)	C
				(inc) El-Metwally[07]: −	*F* (1113)	C
				(inc) Sohrb.-Nøhr[14]: +	*F* (301)	C
				(s/k/a)(inc/p)Tobias[13]:+	*P*** (2901)	C
				(++) to (+/−)		
				Moderate pos. to Conflicting		
				BS vs. injuries:		
				(GI) Cameron[10]: +	*F* (714)	
				(KI) Junge[15]: −	*P*** (999)	C
				(PI) Roussel[09]: −	*P* (58)	
				(+/−) Conflict		
				vs. diseases:		
				(TMs) Hirsch[08]: +	*F* (895)	
				(CFS) Nijs[04]: −	*F* (44)	
				(ACprev) Terzi[13]: +	*P*** (240)	
				(+)to (+/−) Limited pos. to conflicting		
Carter & Wilkinson	Bulbena[92]: +	*P* (30)		vs. other tests:		
	Inter: Unknown			(BS/RQ) Bulbena[92]: +	*P**** (173)	
				Unknown		
Rotès-Quérol	Bulbena[92]: +	*P* (30)		vs. other tests:		
	Juul-Kr[07]: + (3)	*P**(40)		(CW/BS) Bulbena[92]: +	*P**** (173)	
	Inter: Unknown			Unknown		
Hospital del Mar	Bulbena[92]: +	*P* (30)		(ASD) Chahal[10]: +	*F* (149)	
	Inter: Unknown			Unknown		

continued

TABLE IV. (*Continued*)

	Reliability		Validity	
	Intra/inter	Quality/(*n*)/pop	Hypothesis testing	Quality/(*n*)/pop
Questionnaires				
5-part Q.	Bulbena[14]: + Moraes[11]: − Retest: (+/−) Conflicting	*P** (33) *P** (211)	vs. other tests: (HdM) Bulbena[14]: + (BS) deMoraes[11]: −/+ (+) to (+/−) Limited pos. to Conflicting	*P*** (191) *F* (394)
	Criterion val. (BS) deMoraes[11]: − (BS) Hakim[03]:? Unknown	 *F* (394) *F* (489)	vs. pain/tissue diseases: (CWP) Mulvey[13]: + (BJHS) Hakim[03]: + (+) Limited pos.	*F* (2354) *P*** (489)
			vs. anxiety/psych. disease: (anx) Sanches[14]: − Unknown	*F* (2300)
BS-self-reported			vs. tests: (BS) Naal[14]: + Unknown	*P*** (55)

Ia, Intra-rater; Ie, Inter-rater; P, poor; F, fair; pop, population; BS, Beighton Score; CW, Carter & Wilkinson; HdM, Hospital del Mar; RQ, Rotès-Quérol; 5-part Q, 5-part questionnaire; LLAS, Lower Limb Assessment Score; k/a lax, Knee/ankle laxity; sh lax, Shoulder laxity; gon, goniometry; p, persistent; r, recurrent; inc, incidence; s/k/a, shoulder/knee/ankle; GI, Glenohumeral joint instability; Y, youth; C, children, AID, Primary traumatic anterior shoulder dislocation; KI, knee injuries; PI, pelvic injuries; TMs, Temporomandibular symptoms; CFS, chronic fatigue syndrome; ACprev, Adhesive capsulitis prevalence; ASD, Anterior Shoulder Dislocation; CWP, chronic widespread pain; BJHS, benign joint hypermobility syndrome; Anx, anxiety; [92], Superscripts shows year of publication.

*Reliability studies rated poor on the basis of one single rating, based on "only one measurement."

**Validity studies rated poor on the basis of one single rating "no information on the measurement properties of the comparator instrument(s)."

BS (5/9, 6/9, and 7/9). In one test assessment method the total score was 11 with a cut-point of 7/11 for classifying GJH based on only tests in the lower extremities [Ferrari et al., 2005], and another study used two cut-points the lower being 5/9 and the upper being 7/9 [Smits-Engelsman et al., 2011]. Since JHS and hEDS in the current review are recognized as one and the same condition, a specific cut-point needs to be decided, and 5/9 may be suggested for future use in adults. However, since joint mobility, and therefore, BS is known to decrease by age [Remvig et al., 2007b], there is a need for adults also to include additional historical information, as described in the appendix of the reliability study using the BS, with phrasing "can you now or have you previously been able to ... " [Juul-Kristensen et al., 2007], and in the study describing 5PQ [Hakim and Grahame, 2003].

Generally, for adults, one cut-point, varying from 4 to 5 was used in BS (4/9 and 5/9), and 2/5 in 5PQ have been used. For children, one cut-point varying from 5 to 7 was used in BS (5/9, 6/9, and 7/9).

Since children have individual growth periods, this may be the reason for using two cut-points (a lower and an upper) as recently suggested [Smits-Engelsman et al., 2011], and therefore, the upper cut-point is suggested to be at least 6/9 as used in previous population studies [El-Metwally et al., 2004, 2005, 2007; Tobias et al., 2013].

Warming-up before performing flexibility tests may influence the outcome of a test assessment method. However, almost no studies reported whether participants did warm-up, and

the influence of such performance is therefore, unknown.

This review highlights a number of areas warranting future research. Because of the limited studies on the clinical assessment methods for classifying GJH, more high quality studies, and especially those evaluating aspects of validity are required (concurrent, predictive, measurement error, responsiveness, and interpretability). Additional clinical test assessment methods may further be considered in order to support and endorse the presence of GJH in the diagnostic procedure of heritable connective tissue disorders. Also of importance is that consensus is warranted regarding selection of specific test and questionnaire assessment methods for classifying GJH, the test performance, and the cut-points by which age, gender, and ethnicity may be taken into account.

Limitations of the study are the small amount of studies, for which reason it was decided only to rate reliability (intra- and inter-rater) and validity (hypothesis testing or criterion validity). Use of COSMIN is recommended to be the best evaluation method until now, as has also been used previously to evaluate clinical test assessment methods [Kroman et al., 2014; Larsen et al., 2014]. However, since the COSMIN originally was designed for the evaluation of patient-reported outcomes, there are some adjustments that need to be considered when using COSMIN for clinical test assessment methods. For example, although rating of the number of measurements taken may be useful in settings with continuous scales as in performance-based methods, rating scales in many clinical assessment methods (test or questionnaire) are dichotomous (positive/negative). To adjust for this shortcoming, the present review adjusted the evaluation of methodological quality, corresponding to when "only one measurement" was rated poor in reliability, the study was upgraded from poor to fair, meaning that the study thereby could be included in the best evidence synthesis. Furthermore, the sample size in clinical studies is often much smaller than in questionnaire studies, and therefore, it may be suggested that minor sample sizes should not be rated that strictly as in questionnaire assessment methods, when studying clinical test assessment methods. For validity studies, one poor rating including "no information on the measurement properties of the comparator instrument" or "subject eligibility criteria inadequately described/lacking," allowed upgrading to fair, and the study could thereby be included in the best evidence synthesis.

Strengths of this review are the systematic and rigid use of recommended strategies for systematic reviews of clinical assessment methods, the evaluation of their clinimetric properties and rating of the best evidence synthesis.

CONCLUSION

In the current review, four test and two questionnaire assessment methods for classifying GJH were found with measurement properties of varying methodological strength and results of varying weight. Most of the studies used the BS. The inter-rater reliability of this method seems acceptable to be used in clinical practice, provided that uniformity of testing procedures are included in the testing procedures, in addition to historical information, especially in adults. However, shortcomings were found in studies on the validity of BS, while the three other test assessment methods (CW, RQ, HdM) lack satisfactory information on both reliability and validity. Regarding questionnaire assessment methods, 5PQ is the most frequently method used, however, only in adult population studies. In conclusion provided uniformity of testing procedures, the recommendation for clinical use in adults is BS with cut-point of 5 of 9 including historical information, while in children it is BS with cut-point of at least 6 of 9. However, more studies are needed to conclude, especially on the validity properties of these assessment methods, and before evidence-based recommendations can be made for clinical use on the "best" assessment method for classifying GJH.

In the current review, four test and two questionnaire assessment methods for classifying GJH were found with measurement properties of varying methodological strength and results of varying weight. Most of the studies used the BS.

AUTHORS' CONTRIBUTIONS

BJK contributed to conception and design of the study, including analysis and interpretation of data, writing of the article, critical revision of the article for important intellectual content, and final approval of the article. KS contributed to the collection and assembly of data, analysis and interpretation of data, and critical revision of the article for important intellectual content and final approval of the article. RE and HL contributed to conception and design of the study including analysis and interpretation of data, critical revision of the article for important intellectual content, and final approval of the article. LR contributed to interpretation of data, critically revision of the article for important intellectual content, and final approval of the article. First and last authors take responsibility for the integrity of the work as a whole, from inception to finished article.

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RESEARCH REVIEW

The Ehlers–Danlos Syndromes, Rare Types

ANGELA F. BRADY, SERWET DEMIRDAS, SYLVIE FOURNEL-GIGLEUX, NEETI GHALI, CECILIA GIUNTA, INES KAPFERER-SEEBACHER, TOMOKI KOSHO, ROBERTO MENDOZA-LONDONO, MICHAEL F. POPE, MARIANNE ROHRBACH, TIM VAN DAMME, ANTHONY VANDERSTEEN, CAROLINE VAN MOURIK, NICOL VOERMANS, JOHANNES ZSCHOCKE, AND FRANSISKA MALFAIT*

Dr. Angela F. Brady, F.R.C.P., Ph.D., is a Consultant Clinical Geneticist at the North West Thames Regional Genetics Service, London and she has a specialist interest in Ehlers–Danlos Syndrome. She was involved in setting up the UK National EDS Diagnostic Service which was established in 2009 and she has been working in the London part of the service since 2015.

Dr. Serwet Demirdas, M.D., Ph.D., is a clinical geneticist in training at the Erasmus Medical Center (Erasmus University in Rotterdam, the Netherlands), where she is involved in the clinical service and research into the TNX deficient type of EDS.

Prof. Sylvie Fournel-Gigleux, Pharm.D., Ph.D., is a basic researcher in biochemistry/pharmacology, Research Director at INSERM (Institut National de la Santé et de la Recherche Médicale) and co-head of the MolCelTEG Research Team at UMR 7561 CNRS-Université de Lorraine. Her group is dedicated to the pathobiology of connective tissue disorders, in particular the Ehlers–Danlos syndromes, and specializes on the molecular and structural basis of glycosaminoglycan synthesis enzyme defects.

Dr. Neeti Ghali, M.R.C.P.C.H., M.D., is a Consultant Clinical Geneticist at the North West Thames Regional Genetics Service, London and she has a specialist interest in Ehlers–Danlos Syndrome. She has been working in the London part of the UK National EDS Diagnostic Service since 2011.

Dr. Cecilia Giunta, Ph.D., is a molecular geneticist and established scientist working in the field of Ehlers–Danlos Syndrome and other heritable connective tissue disorders (CTD) since 1995. Together with Dr. Marianne Rohrbach she runs the diagnostic and research activities of the Connective Tissue Unit as part of the Division of Metabolism at the University Children's Hospital, Zurich since September 2008. Her research focuses on the understanding of the Molecular Basis and Pathology of Connective Tissue Disorders, in particular the rare forms of EDS and osteogenesis imperfecta. She is currently a member of the medical and scientific board of the Ehlers–Danlos Society.

Dr. Ines Kapferer-Seebacher, D.M.D., is a periodontist with a clinical and research focus on dental and periodontal manifestations of rare diseases. She is an Associate Professor at the Department of Restorative and Operative Dentistry, Medical University Innsbruck, Austria.

Dr. Tomoki Kosho, M.D., Ph.D., is a pediatrician and clinical geneticist. He is an Associate Professor at the Center for Medical Genetics at Shinshu University Hospital, where he directs clinical service for heritable connective tissue disorders and research especially on D4ST1-deficient EDS.

Dr. Roberto Mendoza-Londono, M.D., is the Director of the EDS clinic at the Hospital for Sick Children (HSC) and University Health Network (UHN) in Toronto and the interim head of the Division of Clinical of Metabolic Genetics at HSC/University of Toronto. He is a clinical geneticist with expertise in skeletal dysplasia's and connective tissue disorders who has an interest in gene discovery and studies of natural history of disease. He has participated in several collaborative projects that led to the identification and characterization of genes that regulate the formation and maintenance of bone and connective tissue.

Prof. Michael F. Pope, M.B.B.Ch., F.R.C.P., M.D., is Consultant in Charge of the new NHS National Commissioning Group Complex EDS Service at the Kennedy Galton Center, Northwick Park Hospital. He is especially interested in the classification, genetics, and diagnosis of Ehlers–Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, cutis laxa, Stickler syndrome, the Marfan syndrome, many of which overlap with the benign hypermobility syndrome (BHS). His expertise lies in the differentiation, separation, and testing of these disorders from BHS.

Dr. Marianne Rohrbach, M.D., Ph.D. in molecular genetics, is a trained pediatrician and clinical geneticist. Together with Dr. Giunta, she leads the diagnostic and research activities of the Connective Tissue Unit at University Children's Hospital in Zurich, Switzerland. Dr. Rohrbach established a multidisciplinary Connective tissue clinic including clinical, biochemical, and molecular diagnosis, as well as patient management and counseling. Her research focus includes long-term follow up and natural history of all connective tissues diseases and the understanding of the Molecular Basis and Pathology of Connective Tissue Disorders, in particular the rare forms of EDS and osteogenesis imperfecta.

Dr. Tim Van Damme is an M.D., Ph.D. student at the Center for Medical Genetics Ghent, Belgium, whose research involves the study of clinical, genetic and pathogenetic aspects of the Ehlers–Danlos syndromes and related disorders.

Dr. Anthony Vandersteen, M.A., Ph.D., M.D., is a medical geneticist, assistant professor at IWK Health Center and Dalhousie University, Nova Scotia, Canada. He has a special interest in EDS and previously worked in the UK National EDS Diagnostic Service.

Caroline van Mourik, B.Ed., M.Sc., Ph.D. (Biology and Geology), has been active in the Swedish patient-organization, previously as Chair but later mainly as the scientific editor. She even presented a paper at the first international symposium on EDS in Ghent, 2012 and frequently lectures about EDS, both for the medical field as well as laymen.

Nicol Voermans, M.D., Ph.D., is a neurologist specialized in neuromuscular disorders at the Radboud University Medical Center (Nijmegen, the Netherlands). She directs the clinical service for neurological and neuromuscular features of various types of EDS, and has a large experience with the TNX-deficient type EDS.

Prof. Johannes Zschocke, M.D., Ph.D., is Professor and Chair of Human Genetics at the Medical University Innsbruck, Austria, where he is also Acting Director of the Department of Medical Genetics, Molecular and Clinical Pharmacology. As Head of the Center for Medical Genetics Innsbruck, he is responsible for the provision of genetic services for the Western Austria and beyond. His clinical and research focus is on inherited metabolic diseases, and he has been involved in the genetic characterization of several Ehlers–Danlos Syndrome subtypes.

Prof. Fransiska Malfait, M.D., Ph.D., is a rheumatologist and clinical geneticist. She is an Associate Professor at the Center for Medical Genetics at the Ghent University Hospital, where she directs the research, clinical service, and laboratory facility for diagnosis and genetic testing for the Ehlers–Danlos syndrome and other heritable disorders of connective tissue. She is the current Chair of the medical and scientific board of the Ehlers–Danlos Society.

*Correspondence to: Fransiska Malfait, M.D., Ph.D., Center for Medical Genetics, Ghent University Hospital, De Pintelaan 185, Gent 9000, Belgium. E-mail: fransiska.malfait@ugent.be

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The Ehlers–Danlos syndromes comprise a clinically and genetically heterogeneous group of heritable connective tissue disorders, which are characterized by joint hypermobility, skin hyperextensibility, and tissue friability. In the Villefranche Nosology, six subtypes were recognized: The classical, hypermobile, vascular, kyphoscoliotic, arthrochalasis, and dermatosparaxis subtypes of EDS. Except for the hypermobile subtype, defects had been identified in fibrillar collagens or in collagen-modifying enzymes. Since 1997, a whole spectrum of novel, clinically overlapping, rare EDS-variants have been delineated and genetic defects have been identified in an array of other extracellular matrix genes. Advances in molecular testing have made it possible to now identify the causative mutation for many patients presenting these phenotypes. The aim of this literature review is to summarize the current knowledge on the rare EDS subtypes and highlight areas for future research.

KEY WORDS: Ehlers–Danlos syndromes; heritable connective tissue disorders; collagen

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INTRODUCTORY STATEMENT

For each genetic EDS subtype, a subcommittee of authors performed a comprehensive literature search. All articles were reviewed for relevance and additional articles were identified from the literature. The articles were summarized and divided into themes: (1) the history of the EDS subtype, (2) mechanisms of disease, (3) allelic heterogeneity, (4) clinical description, (5) genotype–phenotype correlations and penetrance, (6) management, and (7) differential diagnosis. The summary of these themes was critically reviewed by all authors.

Subcommittees:

- Classical EDS due to *COL1A1* p.(Arg312Cys) (cEDS-*COL1A1*): Fransiska Malfait
- Classical-like EDS due to Tenascin-X deficiency (clEDS): Serwet Demirdas, Nicol Voermans
- Cardiac-valvular EDS (cvEDS): Fransiska Malfait
- Arthrochalasia EDS (aEDS): Tomoki Kosho, Cecilia Giunta, Marianne Rohrbach, Fransiska Malfait
- Dermatosparaxis EDS (dEDS): Tim Van Damme, Fransiska Malfait
- Kyphoscoliotic EDS (kEDS-*PLOD1*): Angela Brady, Neeti Ghali, Cecila Giunta, Marianne Rohrbach, Tim Van Damme, Anthony Vandersteen
- Kyphoscoliotic EDS (kEDS-*FKBP14*): Cecila Giunta, Marianne Rohrbach, Tim Van Damme, Fransiska Malfait
- Brittle cornea syndrome (BCS): Marianne Rohrbach, Tim Van Damme
- Spondylodysplastic EDS (spEDS-*B4GALT7* and spEDS-*B3GALT6*): Sylvie Fournel-Gigleux, Tim Van Damme, Fransiska Malfait
- Spondylodysplastic EDS (spEDS-*SLC39A13*): Cecilia Giunta
- Musculocontractural (mcEDS): Tomoki Kosho, Fransiska Malfait
- Myopathic EDS (mEDS): Roberto Mendoza-Londono, Fransiska Malfait
- Periodontal EDS (pEDS): Ines Kapferer-Seebacher, Michael Pope, Anthony Vandersteen, Johannes Zschocke

CLASSICAL EDS DUE TO *COL1A1* p.(Arg312Cys) (*COL1A1*-cEDS)

Synonyms: Classic-like Ehlers–Danlos syndrome with propensity to arterial rupture, Vascular-like EDS

The History of Classical EDS due to *COL1A1* p.(Arg312Cys) (*COL1A1*-cEDS)

Nuytinck et al. [2000] reported two children with a classical EDS phenotype, including skin hyperextensibility, easy bruising, atrophic scarring, and joint hypermobility, with a c.934C>T, p.(Arg312Cys) mutation. Malfait et al. [2007] identified the same mutation in an adult who suffered from a rupture of medium-sized arteries, reminiscent of vascular EDS. In addition, two other arginine-to-cysteine (Arg-to-Cys) substitutions in the proα1(I) chain of type I collagen, c.1720C>T, p.(Arg574Cys) and c.3277C>T, p.(Arg1093Cys°), were identified in two other adults with vascular rupture, but without EDS-signs [Malfait et al., 2007]. The p.(Arg312Cys) mutation has subsequently been identified in two other individuals with EDS and complications of vascular fragility [Ritelli et al., 2013; Gaines et al., 2015]. In view of the major clinical overlap of the p.(Arg312Cys)-associated phenotype with classical EDS due to *COL5A1* or *COL5A2* mutations, both conditions are grouped within the same clinical entity ("Classical EDS") in the new EDS classification. Patients with the p.(Arg312Cys) mutation are particularly at risk for vascular events, highlighting the benefit of molecular confirmation in classical EDS patients for management purposes.

In view of the major clinical overlap of the p.(Arg312Cys)-associated phenotype with classical EDS due to COL5A1 or COL5A2 mutations, both conditions are grouped within the same clinical entity ("Classical EDS") in the new EDS classification.

The prevalence of this condition is unknown.

Mechanism of Disease

The pathogenetic basis for the phenotype resulting from these specific Arg-to-Cys substitutions is currently not well understood. Ultrastructural studies of dermal collagen fibrils have shown fibrils with variable diameters, and slightly irregular contour, and, in case of the p.(Arg312Cys), flower-like abnormalities [Malfait et al., 2007].

Several mechanisms have been suggested to be involved in the pathogenesis [Malfait et al., 2007], including local destabilization of the triple helix due to loss of the stabilizing arginine residue; introduction of a cysteine residue, which can lead to disulfide-bonding with other collagenous or non-collagenous proteins, either intracellularly or in the extracellular matrix (ECM), thereby disturbing normal physiological interactions; interference with pericellular processing of the amino-propeptide of procollagen type I, and/or local unwinding of the region surrounding the mutations, thereby disturbing specific interactions with type I collagen ligands [Malfait et al., 2007].

Allelic Heterogeneity

Three different heterozygous *COL1A1* mutations, leading to a Arg-to-Cys substitution have been reported in association with vascular fragility: c.934C>T, p.(Arg312Cys); c.1720C>T, p.(Arg574Cys); and c.3277C>T, p.(Arg1093Cys).

Clinical Description

To date, six patients from five families have been reported with the p.(Arg312Cys) (Table S1). These include two females (respectively 5 and 43 years old) and five males (respectively 7, 16, 39, and 53 years old). [Nuytinck et al., 2000; Malfait et al., 2007; Ritelli et al., 2013; Gaines et al., 2015].

The hallmark of this condition is the "vascular fragility," leading to spontaneous dissection or rupture of medium-sized arteries, in combination with other EDS signs. It is a rare, but important differential diagnosis of vascular EDS.

Reported clinical features for the p.(Arg312Cys) substitution

- Reproductive, including pregnancy
  Premature preterm rupture of the fetal membranes (PPROM) was reported in one patient. One patient was reported to have neonatal hypotonia. No pregnancy-related complications were reported (one known pregnancy in an affected female).
- Craniofacial features
  None of the patients had characteristic features of vascular EDS. One patient was reported to have redundant skin folds on the eyelids and soft earlobes, reminiscent of classical EDS. One patient had blue sclerae, high palate, and hypoplastic uvula.
- Musculoskeletal system
  Generalized joint hypermobility was reported in four patients. One patient had congenital bilateral hip dislocation and a traumatic shoulder dislocation. Another patient was also reported to have sporadic joint dislocations. Pectus excavatum was reported twice. Two patients complained from chronic joint pain. None of the patients had a history of fractures; DEXA Z-score was normal in two patients.
- Skin and integument
  Skin involvement included skin hyperextensibility (n = 4); soft, doughy skin (n = 2); thin or translucent skin (n = 3); friable skin/skin splitting (n = 2); atrophic scars (n = 4); delayed wound healing (n = 1); unusual tenderness upon touch (hyperalgesia) (n = 1); piezogenic papules (n = 1); molluscoid pseudotumors (n = 1); varicose veins (n = 1). Easy bruising was reported in all patients (n = 6). Finally one patient had hiatal and abdominal and inguinal hernias.
- Ocular involvement
  Blue sclerae were observed on one patient. One patient was operated for strabismus.
- Cardiovascular system
  All three adults had severe cardiovascular complications. The patient reported by Malfait et al. [2007] had a spontaneous dissection of the right iliac artery at 43 years. Her affected 16-year-old son did not have complications of vascular fragility, except for unusual bruising. The patient, reported by Gaines et al. [2015] suffered from a spontaneous rupture of the common iliac artery at 39 years. The patient, reported by Ritelli et al. [2013] had mild mitral and aortic valve regurgitation, left ventricular wall thickening, aortic root dilatation, vertebral artery tortuosity, and a hepatic hemangioma at 53 years. The two children reported by Nuytinck et al. [2000] did not show signs of vascular fragility at the time of report. Clinical follow-up is not available for these patients.

Other Arg-to-Cys substitutions that lead to vascular fragility

EDS-like signs have only been observed in association with the p.(Arg312Cys) mutation. One patient harboring a p.(Arg574Cys) (male, 42 years) suffered from a dissection of the left femoral artery and an aortic aneurysm. One patient harboring a p.(Arg1093Cys) (male, 40 years) had a left kidney infarction at age 34 years, and a dissection of the infrarenal aorta and left iliac artery, with aneurysm of the left renal artery at age 39 years. He also had mitral valve bulging [Malfait et al., 2007].

Genotype–Phenotype Correlation and Penetrance

The Arg-to-Cys substitutions in the α1 (I) collagen chain seem to be associated with specific phenotypes: Classical EDS with vascular fragility for p.(Arg312Cys) and isolated vascular fragility for p.(Arg574Cys) and p.(Arg1093Cys). In addition, three other Arg-to-Cys substitutions have been reported for this gene: c.3040C>T,p.(Arg1014Cys) is associated with autosomal dominant Caffey disease [Gensure et al., 2005], whereas c.3106C>T,p.(Arg1036Cys) and c.3196C>T,p.(Arg1066Cys) are reported in patients with an OI/EDS overlap phenotype without signs of vascular fragility [Cabral et al., 2007;

Lund et al., 2008]. The pathogenic basis for theses specific clinical consequences is unknown.

Penetrance is unknown.

Management

Key management guidelines focus on the cardiovascular system.

Specific management guidelines include:

- Measurement of aortic root size and assessment of heart valves by echocardiogram at the time of diagnosis or by age 5 years
- Echocardiogram at 5-year intervals, even if the initial echocardiogram is normal
- Vigilant observation and control of blood pressure can reduce the risk of arterial rupture
- Further vascular surveillance ought to be considered
- Consider bone densitometry evaluation

Guidelines for management of musculoskeletal problems, skin involvement, ophthalmologic and dental follow-up, and pregnancy should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Differential Diagnosis

- Vascular EDS
- Classical EDS due to *COL5A1* or *COL5A2* mutations
- OI

CLASSICAL-LIKE EDS DUE TO TENASCIN-X DEFICIENCY (clEDS)

The History of the Classical-Like EDS

This type of EDS was first described by Burch et al. [1997]. The authors described a 26-year-old male patient with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency as well as hyperextensible skin, hypermobile joints, easy bruising, and poor wound healing. Skin biopsy of this patient showed small collagen fibers of normal shape and a complete absence of tenascin XB (TNX). Cultured dermal fibroblasts also lacked TNX. PCR of the patients DNA revealed a 30 kb deletion in chromosome 6 overlapping both the *CYP21B* gene and the *TNXB* gene. Subsequently, Schalkwijk et al. [2001] measured TNX in the serum of 151 EDS patients (classical and vascular type), 168 diseased controls (psoriasis and rheumatoid arthritis), and 21 healthy controls. They detected a complete TNX deficiency in five EDS patients and three affected siblings (one of which with the contiguous gene syndrome). Mutation analyses revealed mostly homozygous mutations in the *TNXB* gene for these patients. The authors concluded that the TNX-deficient type is very similar to the classical type of EDS with two major differences: (1) No atrophic scarring was apparent, and (2) the inheritance pattern was autosomal recessive.

The prevalence of this condition is unknown.

Mechanism of Disease

TNX is one of the three known large matricellular proteins of the tenascin family [Mao and Bristow, 2001; Valcourt et al., 2015]. Although the precise function of TNX is unknown, it is known to play a role in the ECM as it is highly expressed in connective tissue of muscle, around tendons, ligaments, and in skin [Mao and Bristow, 2001]. The glycoprotein is encoded by the *TNXB* gene in humans. Classical-like EDS is caused by a complete lack of TNX due to homozygous or compound heterozygous *TNXB* mutations, that lead to nonsense-mediated mRNA decay (NMD), or biallelic deletion of *TNXB*. As a result, the TNX protein is completely absent [Mao and Bristow, 2001].

Allelic Heterogeneity

A total of 24 patients with a complete TNX-deficiency without involvement of the *CYP21B* gene have been reported. In 19 of these patients (15 families), the molecular diagnosis is known. Homozygous and compound heterozygous mutations have been identified. Mutations have been identified throughout the *TNXB* gene, and include missense, frameshift, and nonsense mutations.

There is a registry of reported *TNXB* gene variants [Dalgleish, 1998].

In five out of the 24 reported patients, no genetic confirmation of the clinical diagnosis after TNX serum measurement was performed.

Clinical Description

The clinical phenotype of the 24 patients with a complete TNX-deficiency without involvement of the *CYP21B* gene was reviewed (Table S1) [Schalkwijk et al., 2001; Peeters et al., 2004; Lindor and Bristow, 2005; Voermans et al., 2007, 2009b; O'Connell et al., 2010; Hendriks et al., 2012, Pénisson-Besnier et al., 2013; Sakiyama et al., 2015; Demirdas et al., 2016].

The absence of TNX throughout the body leads to a phenotype resembling the classical type of EDS. The hallmarks of the disorders are GJH, hyperextensible, soft and/or velvety skin, without the typical atrophic scarring seen in classical EDS, easy bruising, and an autosomal recessive inheritance pattern.

- Reproductive, including pregnancy
  Egging et al. [2008] retrospectively investigated genitourinary and obstetric complications in seven women with classical-like EDS, aged 38–57 years (six from the cohort of Schalkwijk et al. [2001] and Patient 1 from the series of Lindor and Bristow [2005]). These women have had a total of 13 pregnancies and 12 deliveries. Two women (one with CAH due to 21-hydroxylase deficiency as a contiguous gene syndrome; one with additional spina bifida who decided to have no biological

children) did not have any pregnancies. One out of 13 pregnancies ended in intrauterine death of the fetus, and one out of 12 deliveries was complicated with post-partum hemorrhage. No premature births or neonatal complications were reported. No urinary incontinence was seen. Vaginal (n = 1), uterine (n = 2), and rectal (n = 1) prolapse were present. One undefined prolapse was mentioned. Three out of five women had partus-related complications (vaginal uterine extirpation after uterine prolapse, post-partum hemorrhage, intra-uterine death at 24 weeks with post-partum hemorrhage, and precipitous second stage during at term deliveries). The authors concluded that pregnancy is without major complications in TNX-deficient patients, apart from one incident of postpartum hemorrhage. However, uterine and vaginal prolapse regularly occurs in TNX-deficient women, even at a young age, suggesting laxity of the genitourinary tissues. Furthermore, no premature births have been observed in the offspring; however, some patients had been born prematurely themselves.

Demirdas et al. [2016] described the gynecologic and obstetric history of seven women in their cohort. Three of these women had previously been included in the study by Egging et al. [2008]. The other four women reported a total of 10 pregnancies, two of which ended in intrauterine demise of the fetus. Furthermore, four out of 10 deliveries were complicated with post-partum hemorrhage, two women had perineal rupture, and one pregnancy was complicated by PPROM. In this cohort, another woman was reported to have pelvic instability without ever having been pregnant [Egging et al., 2008].

Obviously, some caution must be taken in making conclusions and extrapolating data from such a small group of TNX-deficient patients (n = 11) [Egging et al., 2008].

- Age of onset
  Symptoms of patients with the TNX-deficiency have been described as starting as early as 5 years of age in a girl by Hendriks et al. [2012] and 7 years of age by O'Connell et al. [2010]. Furthermore, in some adult cases, a childhood onset of hypermobility and dermatological symptoms was reported. Demirdas et al. [2016] reported that all patients (n = 17) had a clinical onset in childhood, ranging from the neonatal age to puberty. The most encountered initial symptoms in this group were (sub)luxations, hypermobility, and velvety/hyperextensible skin. Based on the data we found, we conclude that patients already experience symptoms such as skin hyperextensibility, a velvety skin, easy bruising/spontaneous ecchymosis, subluxations, and joint hypermobility in childhood. Piezogenic papules of the feet and pes planus are also apparent at the pediatric age.
- Craniofacial features
  Craniofacial features reported in the patients included a slight asymmetry of the face (n = 1), lax skin of the cheeks (n = 1), and a narrow and/or high arched palate (n = 4).
- Musculoskeletal system
  Frequently described musculoskeletal features included joint and/or muscular pains. Furthermore, one paper reported frequently observed deformities of the hands and feet. Twelve out of 17 included patients had pes planus and four patients had short/broad feet with brachydactyly of the toes. Four of the patients had deformities of the fingers and acrogeric hands [Demirdas et al., 2016].
- Skin and integument
  It is noted that all reported patients had hyperextensible skin, frequently described to be soft and velvety of structure. The atrophic scars typical for classical EDS were not observed. Bilateral inguinal hernia was described in a male patient and unilaterally in a female patient. An umbilical hernia was described in a 6-year-old male.
- Ocular involvement
  Ocular involvement was infrequently reported in patients with TNX-deficient classical-like EDS. One patient was described to have esotropia/amblyopia [Lindor and Bristow, 2005], another to have astigmatism, and a third patient was described to have bilateral conjunctivochalasis. Five out of 17 patients from the cohort of Demirdas et al. [2016] were described to have frequent subconjunctival hemorrhage.
- Dental involvement
  Recurrent periodontitis was reported in one, and another patient was described to have dental crowding due to a narrow palate.
- Cardiovascular system
  Peeters et al. [2004] investigated the cardiac features in seven TNX-deficient patients (all from the cohort of Schalkwijk et al. [2001]). They found a systolic murmur at the apex in one patient. Three of the seven patients were found to have mitral valve abnormalities (billowing of the mitral valve in two patients of the same family and a severe mitral valve prolapse (MVP) in another patient). Although the number of patients was small and such abnormalities are not infrequent in the general population, the authors recommended echocardiography at baseline and if a cardiac murmur appears [Peeters et al., 2004]. Subsequently, Lindor and Bristow [2005] also described a patient who had mitral valve surgery due to a MVP. Demirdas et al. [2016] also described cardiologic features of their patients. Four out of 17 of the patients had hypertension and two patients (4/17 patients were previously included by Peeters et al. [2004]) had mitral valve abnormalities. One patient developed a post-partum cardiomyopathy [Demirdas et al., 2016].
- Gastrointestinal system
  Two patients reported by Lindor and Bristow [2005] suffered from bleeding of gastrointestinal structures, namely the sigmoid and duodenum, secondary to diverticulitis and as complications of spontaneous ileus. Hendriks et al. [2012] reported a gastric hemorrhage due to ulcers in a male patient initially reported by Schalkwijk et al. [2001]. He died at the age of 57 years due to a septic shock following elective mitral valve replacement surgery, which was complicated by a sinuspiriformis perforation by a transesophageal ultrasound probe [Hendriks et al., 2012; Knuijt et al., 2014]. Sakiyama et al. [2015] also presented a patient who had recurrent gastrointestinal perforation due to tissue fragility (diverticulitis, spontaneous ileus

and a subsequent perforation of the duodenum). Demirdas et al. [2016] did not observe severe gastrointestinal problems in their patients. However, one patient had a gastric ulcer at age 16 and a bowel perforation due to diverticulitis at age 48 years [Demirdas et al., 2016].

- Neuromuscular features and motor development

  A total of six articles describe research concerning muscular function in patients with TNX-deficiency or their muscle tissue [Voermans et al., 2007, 2009b; Ottenheijm et al., 2012; Gerrits et al., 2013; Pénisson-Besnier et al., 2013; Sakiyama et al., 2015]. All papers conclude that there is some degree of muscle weakness in patients with TNX-deficiency. Voermans et al. [2007] studied a cohort of 40 EDS patients, among which 10 with TNX-deficiency (six of the cohort of Schalkwijk et al. [2001], and four additional patients). Muscle weakness, myalgia, and easy fatigability were reported by the majority of patients, whereas all patients were able to walk independently without aids. Mild-to-moderate muscle weakness (80%) and reduction of vibration sense (60%) were common. Other findings were axonal polyneuropathy (40%) on nerve conduction studies and mild myopathic features on muscle biopsy (20%). Patients with hypermobile EDS (hEDS) caused by TNXB haploinsufficiency were less affected [Voermans et al., 2009b]. This was confirmed in a quantitative study on isometric function of the thigh muscles in seven patients (four of the cohort of Schalkwijk et al. [2001] and three of the other patients in the study of Voermans et al. [2009b] and Gerrits et al. [2013]). The results showed that muscle weakness in this type of EDS is most likely due to increased compliance of the series-elastic component of muscle tissue and failure of maximal voluntary muscle activation. Further proof of this concept was obtained in single fiber study of muscle tissue of four of these patients (one of the cohort of Schalkwijk et al. [2001] and three of the other patients in the study of Voermans et al. [2009b] showing that in response to the increased compliance of the extracellular matrix in muscle of TNX-deficient EDS patients, a marked intracellular stiffening of the sarcomere protein titin occurs. The stiffening of titin most likely compensates for the muscle weakness [Ottenheijm et al., 2012]. The report by Pénisson-Besnier et al. [2013] presented a 42-year-old male patient with proximal limb muscle weakness, subclinical heart involvement, minimal skin hyperextensibility, no joint abnormalities, and a history of easy bruising. He had been asymptomatic until age 30 but mentioned low performances at upper bodybuilding exercises. Since then, he experienced gradually worsening lower limb weakness, leading to inability to run from age 40, frequent falls, and the recent need of a banister for stairs. He was initially diagnosed as having a primary myopathy and only later diagnosed with EDS [Pénisson-Besnier et al., 2013].

  Motor development was not studied in the included papers. We detected no comments on delayed motor development other than mild to moderate muscle weakness.
- Neurological features and neuromotor development

  Cognitive development was not studied in the included papers. Intellectual disability was not reported.
- Other

  Severe edema of the ankles and/or feet was described in four patients.
- Family history

  Demirdas et al. [2016] asked their patients about family history and found that 4/11 mothers and 5/11 fathers complained of (sub)luxations (n = 4), pes planus (n = 2), easy bruising (n = 1), artralgia (n = 4), hyperextensible skin (n = 3), hypermobility (n = 1), and inguinal hernia (n = 1). Of the 17 patient's siblings, 11 out of 26 were tested and proven heterozygous carriers. Three of these 11 carrier siblings reported hypermobile joints [Demirdas et al., 2016].

Genotype–Phenotype Correlations and Penetrance

No genotype–phenotype correlations are reported within the group. We assume that penetrance is high, but the research to support this assumption is lacking. Family members with a haploinsufficient mutation in the *TNXB* gene have been described to have symptoms of joint hypermobility in 60% of the cases, but more research is needed to confirm this [Zweers et al., 2003].

Management

No specific guidelines for management of patients with classical-like EDS are available. Guidelines for management of musculoskeletal problems, skin involvement, cardiovascular involvement, and pregnancy should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Specific management guidelines may include:

- Musculoskeletal

  In case of operations, special attention for the effect of general anesthesia and of adequate positioning and support is important to prevent pressure or stretch neuropathies [Voermans et al., 2006]. Furthermore, intubation and endoscopic studies should be performed carefully in order to prevent rupture of trachea or esophagus [Besselink-Lobanova et al., 2010; Hendriks et al., 2012]
- Pregnancy

  Gynecological follow-up throughout pregnancy is not warranted based on the retrospective study in five patients [Egging et al., 2008]. However, the severe complications that have been reported during insertion of a trachea tube and a transesophageal ultrasound probe call for a very careful handling of patients, especially in emergency

situations. Therefore, we advise a clinical delivery for all patients

Differential Diagnosis

- Classical EDS
- Congenital myopathies, including collagen VI- and collagen XII-related disorders

THE CONTIGUOUS GENE SYNDROME WITH CONGENITAL ADRENAL HYPERPLASIA AND TNX-DEFICIENCY

Burch et al. [1997] first described the TNX-deficient pheno- and genotype in a male patient (26 years old) with hyperextensible skin, hypermobile joints, easy bruising and 21-hydroxylase deficiency. A heterozygous 30 kb deletion was found on chromosome 6 involving both the *CYP21B* gene and the *TNX* gene as a causative explanation for all symptoms. They also reported that TNX in serum, skin and muscle was measured and absent. The authors concluded that a small deletion or missense mutation had probably remained undetected on the maternal allele [Burch et al., 1997].

The second patient with this Continuous gene syndrome was included in the initial series of Schalkwijk et al. [2001] (Patient 3) and subsequent cohorts [Egging et al., 2008; Voermans et al., 2009b; Gerrits et al., 2013]. She was homozygous for the 30-kb deletion detected in the index case reported by Bristow. Both her parents and two siblings were heterozygous for the deletion and were clinically normal, providing evidence of recessive inheritance in this family. This 32-year female patient was described to have recurrent (sub) luxations, hypermobile joints, hyperextensible, and velvety skin that easily bruises, musculoskeletal pain, and CAH. Besselink-Lobanova et al. [2010] presented the follow-up of this case in order to draw attention to the severe complications encountered during intubation. During elective surgery at the age of 41 years (because of a luxation of the left knee joint) a tracheal rupture developed, despite the initially uneventful intubation. The authors acknowledge that the patient had other anatomic risk factors for a tracheal rupture (obesity and short stature for example). However, the authors also state that TNX alters the characteristics of the ECM and therefore advise caution when intubating patients with TNX-deficiency, or even to refrain from intubating entirely [Besselink-Lobanova et al., 2010].

TNXB Haploinsufficiency

Zweers et al. [2003] studied the 20 heterozygous family members of the index cases in Schalkwijk et al. [2001] regardless of clinical symptoms. In all of these individuals, significantly reduced serum TNX levels were detected, and in 17 of them, they confirmed heterozygosity for a truncating *TNXB* mutation. Clinical examination in these family members showed generalized joint hypermobility (GJH) in nine family members (45%; all female). Skin hyperextensibility and easy bruising, frequently seen in the individuals with complete TNX deficiency, were absent. Subsequently, they measured serum TNX levels (by ELISA) in an unselected cohort of 80 patients with hEDS. Six of these patients (7.5%; all female) had serum TNX levels more than 2.5 SD below the mean for unaffected individuals. Clinically, patients with reduced TNX levels showed hypermobile joints, often associated with joint subluxations and chronic musculoskeletal pain. The authors concluded that *TNXB* haploinsufficiency is associated with hEDS [Zweers et al., 2003].

Merke et al. [2013] investigated the prevalence of a Continuous gene syndrome in a cohort of 192 consecutive unrelated CAH patients. *TNXB* haploinsufficiency, here termed CAH-X syndrome, was present in 13 patients (and two sibs). Twelve of 91 patients carrying a *CYP21A2* deletion (13%) carried a contiguous deletion that extended into *TNXB*. One patient carried a *TNXB* premature stop codon. Twelve of 13 patients with CAH-X had EDS clinical features. Patients with CAH-X were more likely than age-matched controls to have joint hypermobility ($P < 0.001$), chronic joint pain ($P = 0.003$), multiple joint dislocations ($P = 0.004$), a structural cardiac valve abnormality by echocardiography ($P = 0.02$), and reduced TNX expression by Western blot and immunostaining. Piezogenic papules on the feet were also observed. A subset of parents was investigated (five mothers, two fathers), of which three had GJH with a Beighton score of 5 or more [Merke et al., 2013].

Morissette et al. [2015] investigated the genetic background of this cohort in the same natural history study ($n = 246$). Seven families (10 patients) harbored a novel *TNXB* missense variant c.12174C>G,p.(Cys4058Trp) and had a clinical phenotype consistent with hEDS. Fourteen CAH probands carried previously described *TNXA/TNXB* chimeras, resulting in a CAH-X prevalence of 8.5%. This highly conserved pseudogene-derived variant in the *TNX* fibrinogen-like domain is predicted to be deleterious and disulfide-bonded, resulting in reduced dermal elastin and fibrillin-1 staining and altered TGF-1 binding, and represents a novel *TNXA/TNXB* chimera. TNX protein expression was normal in dermal fibroblasts, suggesting a dominant-negative effect. They concluded that the CAH-X syndrome is commonly found in CAH due to 21-hydroxylase deficiency and may result from various etiological mechanisms [Morissette et al., 2015]. Patients in this cohort were considered to be heterozygous for the *TNXB* deletion, and had reduced but not absent TNX levels in serum. Therefore, this phenotype is likely be more in line with what is reported by Zweers et al. [2003] in patients with reduced serum levels of TNX, and with the reported features in some of the sibs who are obligate carriers of the mutation in their affected family member.

CARDIAC-VALVULAR EDS (cvEDS)

History of Cardiac-Valvular EDS

In 1987 and 1988, Sasaki et al. [1987], Kojima et al. [1988], and Hata et al. [1988] reported two Japanese patients with complete absence of the proα2(I) collagen chains, both presenting EDS-like features, including joint hypermobility, skin hyperextensibility, abnormal wound healing, but also cardiac-valvular problems. Nicholls et al. [2001] reported a total absence of α2(I) collagen chains in a 9-year-old girl with phenotypic manifestations of both OI and EDS, but without cardiovascular anomalies. A homozygous splice site mutation led to the introduction of a premature termination codon (PTC). Schwarze et al. [2004] reported four patients from three independent families (including the patient reported by Kojima et al. [1988]) with a rare, recessively inherited form of EDS, characterized by joint hypermobility, skin hyperextensibility, and severe cardiac-valvular defects, resulting from biallelic *COL1A2* mutations, leading to complete absence of proα2(I)-chains. Because of the severe cardiac valve problems in most of the adult patients, this phenotype was called "cardiac-valvular EDS" [Schwarze et al., 2004]. One additional child with this condition was subsequently reported by Malfait et al. [2006].

The exact prevalence of this rare condition is unknown.

Mechanism of Disease

The biallelic *COL1A2* mutations result in the complete absence of proα2(I)-chains. Cells from affected individuals produce type I collagen molecules that contain only proα1(I) chains. The mRNA from the mutant alleles is unstable and degraded so that no protein is produced. Nicholls et al. [1984] reported a 5-year-old boy with severe, progressively deforming OI (OI type III). No cardiac abnormalities were reported in this patient [Nicholls et al., 1984]. A homozygous 4-nucleotide frame shift deletion within the carboxy (C)-terminal propeptide of pro-α2(I) collagen was identified. This mutation escapes nonsense-mediated mRNA decay (NMD) and the mRNA is stable, but the proα2(I) chains fail to fold normally and are degraded, which eventually also results in the production of pro-α1(I) homotrimers [Pihlajaniemi et al., 1984]. Given that proα(I) homotrimer formation alone does not lead to OI, the OI phenotype in the latter patient suggests that the intracellular accumulation of mutant proα2(I) chains and the cellular alterations, resulting from a high rate of degradation of these chains, contributes to the skeletal phenotype. In contrast, the EDS phenotype that results from unstable mRNA and no proα2(I) chains reflects what appears to be a more limited response in the ECM.

Allelic Heterogeneity

Seven different mutations have been reported in five independent cardiac-valvular EDS patients. These include one homozygous nonsense mutation (c.213dupC,p.(Arg99*)), and six splice site mutations (two homozygous (c.3105+2T>C and c.3601G>T)) and two compound heterozygous (c.70+717A>G; c.1404+1G>A and c.540+5G>A; c.1404G>C). The patient reported by Sasaki et al. [1987] was only analyzed at the biochemical level and no molecular data were reported.

Clinical Description

To date, six patients from five independent families have been reported (Table S1). Their age at diagnosis ranged from 6 to 65 years [Hata et al., 1988; Kojima et al., 1988; Nicholls et al., 2001; Schwarze et al., 2004; Malfait et al., 2006].

The hallmark of the condition is the severe cardiac-valvular disease, necessitating valve replacement surgery at adult age, in conjunction with variable skin hyperextensibility, atrophic scarring and joint hypermobility, and autosomal recessive inheritance.

- Muscoloskeletal system
  Three patients were reported to have GJH, whereas in the other three the hypermobility was restricted to the small joints. One patient had shoulder dislocations, pectus excavatum, and muscle and tendon tears. One patient had recurrent patellar dislocations. Foot deformities were reported in three patients: A 6-year-old boy displayed pes planus with valgus heels, hallux valgus, and subluxations of the toes; a 9-year-old girl had pedes palonvalgi with secondary shortening of Achilles tendon; and in an adult man pes planus and calcaneovalgus were reported. One patient had increased bone fragility.
- Skin and integument
  Reported skin abnormalities included: Skin hyperextensibility (n = 4) (ranging from mild to severe), soft skin (n = 2), atrophic scar formation (classical EDS-like) (n = 2), easy bruising (n = 2) delayed wound healing (n = 1), thin skin (n = 1), striae (n = 1). Inguinal hernia was reported in two males, including congenital bilateral inguinal hernia in one.
- Ocular involvement
  Myopia and astigmatism was reported in one patient; one patient was reported to have blue sclerae.
- Cardiovascular system
  All four reported adults had severe cardiac-valvular problems, resulting in valve replacement surgery. A 45-year-old male had severe mitral valve regurgitation due to MVP, resulting in left atrium and ventricle dilatation and mild ventricular hypertrophy. He also had aortic valve insufficiency, eventually necessitating mitral and aortic valve replacement. Post-surgery, there was dehiscence of the mitral annulus from the ventricle, and of the aortic valve from the atrioventricular groove. Finally, there was massive leakage through the left ventricular myocardium with disintegration of the entire left ventricle, from which the patient died. A 65-year-old woman had mitral valve insufficiency with uncomplicated replacement surgery. A 30-year-old male had a secundum-type atrial septum defect (ASD), MVP with regurgitation, and aortic valve regurgitation. He underwent mitral and aortic valve replacement with no complications. His 25-year-old brother had aortic valve replacement because of aortic insufficiency [Schwarze et al., 2004].

The two reported children had no severe cardiovascular features, although mitral valve bulging was noted in one [Nicholls et al., 2001; Malfait et al., 2006].

Genotype–Phenotype Correlations and Penetrance

All mutations result in complete absence of the proα2(I) chains. There are no reported genotype–phenotype correlations. Obligate carriers displayed no overt symptoms. Penetrance is presumably complete.

Management

Key management guidelines focus on the cardiovascular system.

Specific management guidelines include:

- Measurement of aortic root size and assessment of heart valves by echocardiogram at the time of diagnosis or by age 5 years
- Yearly echocardiogram, even if the initial echocardiogram is normal
- Cardiac valve replacement surgery
- Consider bone densitometry evaluation

Management guidelines for musculoskeletal problems, skin, ophthalmologic and dental follow-up, and pregnancy should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Differential Diagnosis

- Classical EDS
- Hypermobile EDS

ARTHROCHALASIA EDS (aEDS)

Synonyms: Ehlers–Danlos syndrome, type VII (VIIA, VIIB); Arthrochalasis multiplex congenita

The History of EDS Arthrochalasia Type

Hass and Hass [1958] proposed presence of a distinct entity of congenital flaccidity of the joints, which they called "arthrochalasis multiplex congenita" and which may or may not involve skin changes. In 1973, three patients with the condition "EDS VII" were reported with accumulation of procollagen in their skin and tendon [Lichtenstein et al., 1973a]. The disorder was therefore supposed to be caused by a defect in the conversion of procollagen to collagen, resembling dermatosparaxis in cattle, and the activity of the converting proteinase in the cultured fibroblasts from these patients was found to be reduced to between 10 and 40% of normal [Lichtenstein et al., 1973b]. However, Steinmann et al. [1980] demonstrated, through reinvestigation of the fibroblasts from one of the patients, the presence of mutant pNα2(I) collagen chains (precursor procollagen chains in which the (C)- but not the N-propeptide is cleaved off) in collagen extracted from skin or produced by fibroblasts and the normal activity of procollagen N-proteinase in cell extracts. They concluded the condition to be caused by a structural abnormality in the portion of the pro-α2(I) chain that is normally cleaved by N-proteinase (and other proteinases) [Steinmann et al., 1980]. Subsequently, Cole et al. [1987] found mutant pNα1(I) in a patient with similar features. EDS VII was, therefore, subdivided into types VIIA and type VIIB, depending on whether the α1(I) or the α2(I) chain is affected, respectively [Beighton et al., 1998].

Prevalence of this condition is unknown.

Mechanism of Disease

Arthrochalasia EDS is caused by heterozygous mutations in either *COL1A1* (previously EDS type VIIA) or *COL1A2* (previously EDS type VIIB). Heterozygous mutations that lead to entire or partial loss of exon 6 of either *COL1A1* or *COL1A2* determines lack of the N-telopeptide linking the N-propeptide to the major triple helical domain of the α1(I) or the α2(I) chain. Deletion of the respective 24 and 18 amino acid residues in the pro-α1(I) and the pro-α2(I) chain results in loss of the small globular region of the N-propeptide (present only in the pro-α1(I) chain), the procollagen N-proteinase cleavage site (Pro-Gln and Ala-Gln at positions 4–5, respectively), the cross-linking lysine residue at position 13 and 9, respectively, of the N-telopeptide and the first triplet of the main helical Gly-X-Y domain [Giunta et al., 1999].

Allelic Heterogeneity

Most of the mutations are splice site mutations leading to skipping of exon 6 in *COL1A1* (intron 5−2A>G/T; intron 5−1G>A/C/T; exon 6−1G>A/C) or *COL1A2* (intron 5−2A>G; intron 5−1G>A/C; exon 6−1G>A; intron 6+1G>A/T/C; intron 6+2T>C/G) [Steinmann et al., 2002]. Genomic deletions of exon 6 [Byers et al., 1997] and exon 5+6 [Nicholls et al., 2000] were also reported.

There is a registry of reported *COLI* gene variants [Dalgleish, 1998].

Clinical Description

At present, 49 patients from 36 families have been published (Table S1). The ages at the publication ranged from 2.5 months to 46 years (n = 35; Median age, 7.5 years of age) [Steinmann et al., 1980; Eyre et al., 1985; Cole et al., 1986; Viljoen et al., 1987; D'Alessio et al., 1991; Nicholls et al., 1991; Vasan et al., 1991; Chiodo et al., 1992; Pope et al., 1992; Carr et al., 1994; Ho et al., 1994; Lehmann et al., 1994; Byers et al., 1997; Giunta et al., 1999; Hudgins et al., 1999; Nicholls et al., 2000; Whitaker et al., 2009; Giovannucci Uzielli et al., 2011; Klaassens et al., 2012; Giunta and Steinmann, 2014; Hatamochi et al., 2014].

The hallmarks of the disorder are severe generalized joint hypermobility, congenital bilateral hip dislocation, and recurrent subluxations and dislocations of both small and large joint [Steinmann et al., 2002] (Representative picture of the phenotype are given in Fig. 1).

- Reproductive, including pregnancy
  At least four affected women were reported to be pregnant, and to deliver a total of 11 children, including seven affected ones. Pregnancy or delivery-related complications included breech presentation (n = 4), PPROM (n = 2), polyhydramnios (n = 2), and decreased fetal movement (n = 2).

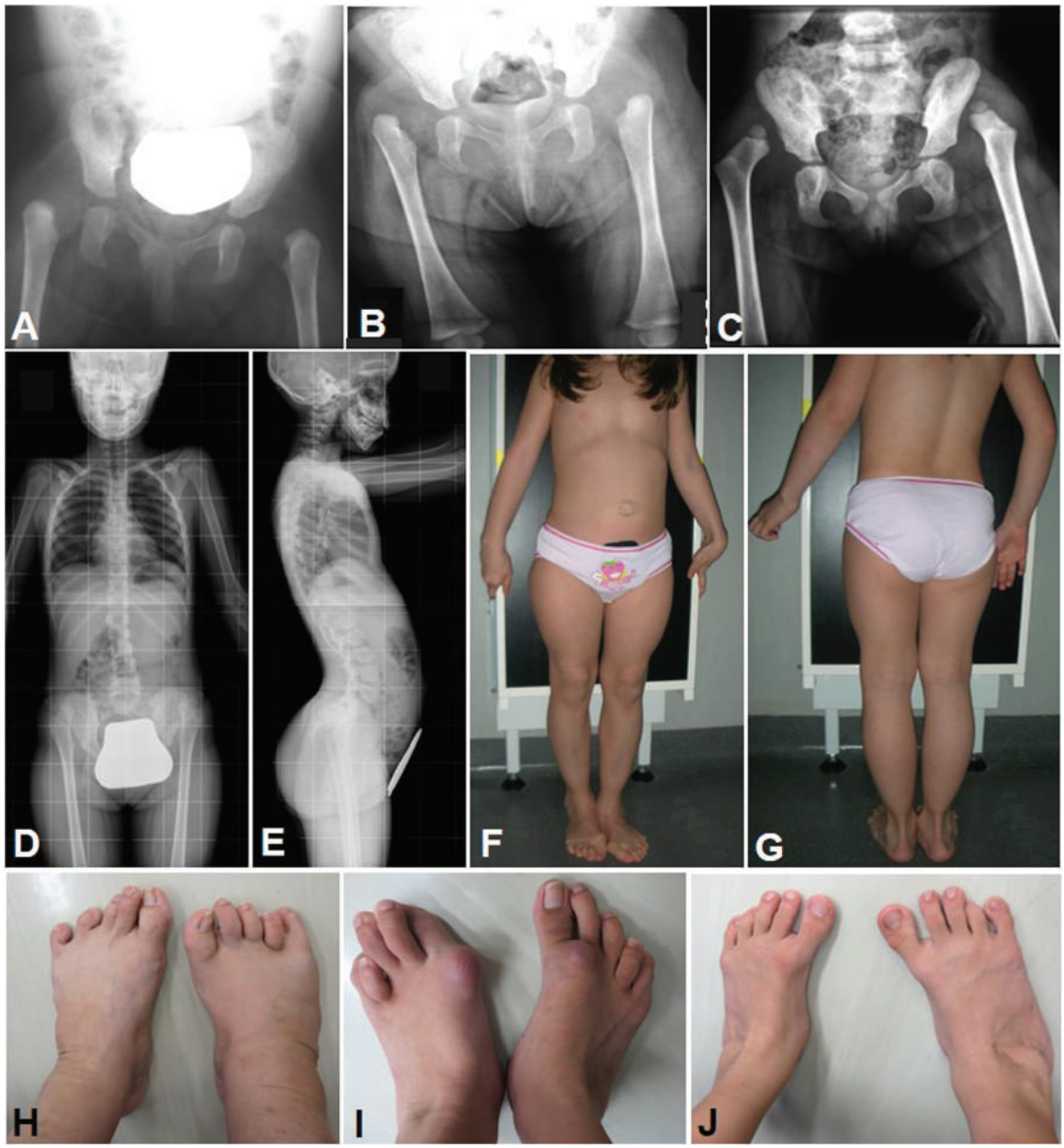

Figure 1. Clinical photographs and radiological images of patients with aEDS. A girl (**A**–**G**) with a c.279+1G> mutation in *COL1A2* and a mother and her two sons (**H**–**J**) with a c.279+2T>C in *COL1A2*. (**A**) X-rays of the hip at age 7 days showing congenital bilateral hip dislocation and femoral and acetabular deformities. (**B** and **C**) Status of the hip dislocation at age 5 months and 3 years, respectively. (**D**) An anterioposterior total body radiograph at age 11 years showing unsuccessful treatment of the hip dislocation with harness and bracing. (**E**) A left lateral total body radiograph at age 11 years showing lumbar lordosis. (**F** and **G**) The patient at age 9 years with umbilical hernia, lordotic posture of the spine, and foot deformities. Foot deformities of an affected mother at age 38 years (**H**), her first son at age 14 years (**I**), and her second son at age 5 years (**J**) (Images **A**–**G** kindly provided by Prof. Maria Luisa Giovannucci-Uzielli, with permission).

- Craniofacial characteristics
  Characteristic craniofacial features include large fontanelle (n = 6), frontal bossing (n = 9), hypertelorism (n = 4), blue sclerae (n = 3), epicanthal folds (n = 3), depressed nasal bridge (n = 6), midfacial hypoplasia (n = 3), and micrognathia (n = 6).
- Musculoskeletal features
  Congenital bilateral hip dislocation was described in all reported patients (n = 41). One unreported patient is known to have had a unilateral congenital hip dislocation (Byers et al, personal communication). Joint hypermobility (n = 29) and recurrent dislocations or subluxations affecting both large and small joints (n = 26) were frequent. Foot deformities (n = 15), including pes equinovarus (n = 8), pes planus (n = 7), pes valgus (n = 2) and hallux valgus (n = 6) (Fig. 1), and spinal deformities (n = 13), including scoliosis (n = 9), kyphoscoliosis (n = 2), and lordosis (n = 3), were also frequent. Swan neck deformity of hands was described in several adults (n = 3). Pectus excavatum was observed in some (n = 3). Fractures (n = 9) and Wormian bones on cranial radiographs (n = 5) suggested bone fragility, similar to patients to mild OI.
- Skin and integument
  The skin was often described to be hyperextensible; hyperelastic or redundant (n = 26); soft, doughy, or velvety (n = 17); and/or fragile (n = 9). Easy bruising (n = 12), atrophic scarring (n = 10), abnormal wound healing (n = 3), and crisscross patterning of palms/soles (n = 4) were also noted. Umbilical hernia was sometimes described (n = 8).
- Ocular involvement
  Blue sclerae (n = 3) and ectopia lentis (n = 1) were recorded.
- Dental involvement
  Dentinogenesis imperfecta was recorded in a few patients (n = 3).
- Neuromuscular features and motor development
  Motor developmental delay was recorded in 16 patients, six of whom were not ambulatory at the time of publication because of hypotonia and/or foot deformity.
- Neurological features and neurodevelopment
  Mild learning disability was recorded in a patient with leptomeningocele and intracranial hemorrhage, presenting with seizures, the 3rd cranial nerve palsy, left hemiparesis, and left homonymous hemianopsia.

Genotype–Phenotype Correlations and Penetrance

Interfamilial and intrafamilial variability seems to be slight [Steinmann et al., 2002]. Type I collagen consists of two α1 (I) and one α2(I) chains, thus three quarters of the collagen I molecules in aEDS due to *COL1A1* mutations contain one or two mutant pNα1(I) chains, whereas only half of the collagen I molecules in aEDS due to *COL1A2* mutations are affected [Steinmann et al., 2002; Giunta et al., 2008a]. This difference in the stoichiometry suggests that *COL1A1*-associated aEDS might be more severe than *COL1A2*-assiated aEDS. Because the number of patients with a *COL1A1* mutation is small, it is uncertain whether this correlation holds true [Giunta et al., 2008a]. Severe phenotypes in patients with a *COL1A1* mutation have been described: A patient with a *COL1A1* "intron 5−1G>A" leading to complete loss of exon 6 presented with dermatosparaxis EDS-like features [Nicholls et al., 2000] and a patient with a *COL1A1* mutation "intron 5−2A>T" had multiple congenital dislocations and dermatosparaxis EDS-like skin features (doughty, redundant) [Giunta et al., 2008a].

Penetrance is complete.

Management

Key management guidelines focus on the musculoskeletal system and the skin.

- The advice to management of the musculoskeletal system is:
  - At diagnosis a whole body skeletal survey is recommended
  - Management of orthopedic problems is the center of care for patients with the disorder. Stable reductions of congenital hips dislocations were not achieved frequently through closed reductions with orthoses or hip spica. Anterolateral open reductions with capsular plication were also ineffective. In contrast, open reductions with an iliac osteotomy, with or without femoral osteotomy, were favorable in some patients. Appropriate surgical intervention is therefore difficult to plan but is crucial for reducing the risk of recurrence of hip dislocations, avascular necrosis, and premature osteoarthritis [Giunta et al., 1999; Steinmann et al., 2002; Giunta and Steinmann, 2014]
  - Recurrent and/or persistent dislocations and hypermobility of upper limb joints are also disabling, but operative intervention is rarely considered because limited effectiveness of operative procedures is predicted [Giunta et al., 1999; Steinmann et al., 2002; Giunta and Steinmann, 2014]
  - Orthotic management and early intervention, including physical and occupational therapy are recommended to assist standing, walking, and activities of daily living [Giunta et al., 1999; Steinmann et al., 2002; Giunta and Steinmann, 2014]
  - Contact sports should be avoided to prevent dislocations
  - Consider bone mineral density studies
- The advice to management of the skin, cardiovascular, and ophthalmological features is similar to that for patients with classical EDS (see "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue)
- Pregnancy management
  - Follow-up throughout pregnancy is warranted
  - Delivery should be performed in a medical center where intensive treatment could be given to an affected pregnant woman and an affected neonate
  - Breech presentation is frequent if the fetus is affected. Though not described previously, affected pregnant women might be predisposed to tearing of the perineal skin and to have postpartum extension of

episiotomy incisions as well as prolapse of the uterus and/or bladder, as described in cEDS

Differential Diagnosis

- Larsen syndrome
- Classical EDS
- Dermatosparaxis EDS
- Kyphoscoliotic EDS
- Musculocontractural EDS
- Loeys–Dietz syndrome
- PYCR1-related autosomal recessive cutis laxa

DERMATOSPARAXIS EDS (dEDS)

Synonyms: Dermatosparaxis; Ehlers–Danlos dermatosparaxis type; EDS-VIIC; EDS7C

The History of Dermatosparaxis EDS

Dermatosparaxis was first reported in cattle [Lenaers et al., 1971; Hanset and Lapiere, 1974] and subsequently in sheep [Fjolstad and Helle, 1974], cats [Counts et al., 1980; Holbrook and Byers, 1982] and dogs [Holbrook and Byers, 1982]. Affected animals display a loose and extremely fragile skin (dermatosparaxis means "tearing of the skin"), resulting in large skin lacerations during delivery or early in life, with subsequent infections and premature death. Early ultrastructural studies showed alterations in the dermis of these animals, with loosely packed, thin, and twisted ribbon-like collagen fibrils that displayed a typical "hieroglyphic aspect" on cross sections, pointing toward impaired collagen biosynthesis and fibrillogenesis. Subsequent biochemical studies performed on dermatosparactic cattle revealed that these abnormal collagen molecules were composed of incompletely processed type I procollagen precursor molecules, in which the N-propeptide was insufficiently cleaved [Lenaers et al., 1971]. Deficient activity of the endopeptidase that excises the N-propeptide of procollagen chains was eventually demonstrated [Smith et al., 1992]. Although animal dermatosparaxis was the first recognized collagen disorder, it took more than 20 years to confirm the existence of a human counterpart for the disorder. In 1992, three independent infants were reported with clinical signs resembling dermatosparaxis [Nusgens et al., 1992; Smith et al., 1992]. Ultrastructural studies of the dermis demonstrated the same "hieroglyphic" pattern of the collagen fibrils as those observed in dermatosparactic animals, and biochemical studies on cultured human fibroblasts confirmed deficient cleavage of the proα1(I) and proα2(I) N-propeptides. Seven additional patients were identified subsequently, all of them displaying a severe phenotype with an extremely fragile and lax skin, severe bruising, and a characteristic dysmorphic face, leading to a diagnosis usually within the first few months of life. It lasted until 1999 to identify the first biallelic mutations in *ADAMTS2*, the gene encoding the procollagen I N-proteinase ADAMTS-2 (a disintegrin and metalloproteinase with thrombospondin motifs 2), in several patients with the dermatosparaxis type of EDS as well as in a strain of dermatosparactic cattle [Colige et al., 1999].

The exact prevalence of this rare condition is unknown.

Mechanism of Disease

Dermatosparaxis EDS (dEDS) is caused by homozygous or compound heterozygous mutations in *ADAMTS2*, the gene that encodes ADAMTS-2. ADAMTS-2 is a metalloproteinase containing properdin repeats and a cysteine-rich domain with similarities to the disintegrin domain of reprolysin. This enzyme is the main procollagen I N-proteinase, but it can also cleave the N-propeptides of type II and type III procollagens [Colige et al., 2005]. The mutations result in decreased activity of ADAMTS-2, which leads to defects in processing of type I procollagen to mature type I collagen [Colige et al., 1999; Colige et al., 2004; Van Damme et al., 2016]. There is an accumulation of pN-collagen type I, resulting in polymerization of abnormal collagen fibers that appear thin, irregular, branched and "hieroglyphic" in cross-section.

Allelic Heterogeneity

Up till now eight biallelic mutations have been reported in 15 patients (14 independent families), including a recurrent homozygous nonsense mutation p.(Gln225*) in six patients, a unique homozygous nonsense mutation p.(Trp795*), a homozygous in-frame skip of exons three to five a homozygous in-frame skip of exon 17 and compound heterozygosity for an out-of-frame exon-skip of exon 3 and an in-frame skip of exons 14–16, three homozygous loss-of-function mutations (c.2927_2928delCT, p.(Pro976Argfs*42); c.669-670dupG, p.(Pro224Argfs*41); c.2751-2A>T) and one compound heterozygous mutation (c.2T>C, p.? and c.888-891delTGAA, p.(Met295Thrfs25*)). All mutations result in deficient activity of ADAMTS-2.

There is a registry of reported *ADAMTS2* gene variants [Dalgleish, 1998]

Clinical Description

To date 15 patients from 14 independent families have been reported. Three patients were born to known consanguineous parents (Table S1). Age at diagnosis ranged from birth to 13 years. [Nusgens et al., 1992, Smith et al., 1992; Wertelecki et al., 1992; Reardon et al., 1995; Fujimoto et al., 1997; De Coster et al., 2003; Malfait et al., 2004; Bar-Yosef et al., 2008; Solomons et al., 2013; Van Damme et al., 2016]. Clinical follow-up into puberty and early adulthood is reported for only two patients.

The hallmark of the disorder is the extreme skin fragility with redundant, almost lax skin, and the severe susceptibility of bruising.

- Reproductive, including pregnancy
  Preterm birth was reported in nine patients, and was preceded by PPROM in six. Mean gestational age was 34 weeks and 4 days (n = 14, range: 28–41 weeks). The umbilical cord was noted to be friable in two infants; one of them

also had a short umbilical cord that ruptured after clamping. Perinatal complications were reported in several patients. One patient died shortly after birth (39 weeks gestation) due to severe hemorrhage and shock. A boy with a gestational age of 33 weeks was born with multiple skull fractures and an extensive subgaleal hemorrhage. A dural tear at the site of the skull fracture led to the development of a large cerebrospinal fluid collection, and he died due to secondary infection at 145 days of age. Three other prematurely born infants were admitted to a neonatal intensive care unit for several weeks for a range of complications, including cerebral hemorrhage (n = 2); pneumothorax and respiratory distress (n = 1); hydronephrosis (n = 1); and hypoglycemia, hypocalcemia, and hypothyroidism (n = 1).
No pregnancies have been reported in affected individuals.

- Craniofacial involvement
  Most patients were born with a severe and recognizable facial gestalt, including prominent and protuberant eyes with puffy, edematous eyelids and excessive periorbital skin, large fontanels and/or wide cranial sutures, a hypoplastic chin and bluish or greyish discoloration of the sclerae (n = 12). Less frequent findings included gingival hyperplasia (n = 6), dental lamina cysts (n = 2), and generalized hypertrichosis (n = 6). These patients also presented extreme skin fragility with tearing of the skin, either at birth (n = 2) or within the first few years of life (n = 10). In addition, they had a lax and sagging skin with redundant skin folds, especially in the neck, and around wrists and ankles (n = 10). Together, these findings led to an early diagnosis in these patients. A number of patients displayed a strikingly milder phenotype, with absence of obvious congenital facial dysmorphic features, skin fragility or redundancy. Mild dysmorphic features, skin fragility, and features of generalized connective tissue fragility however gradually became more apparent during childhood and adolescence.
- Musculoskeletal system
  Whereas height, weight, and orofacial circumference were usually within normal limits at birth, postnatal growth retardation was reported in all patients, except for those that died shortly after birth (n = 13). Eleven patients presented with non-rhizomelic shortening of the limbs and short, plump hands and feet with stubby fingers and toes. Joint hypermobility was a consistent finding (n = 11), but often mild at birth. Follow-up data in older patients demonstrated that the joint hypermobility becomes more pronounced later on. Four patients had a history of fractures, including (congenital) skull fractures in three. Several other skeletal abnormalities were reported, including delayed ossification of the cranial vault (n = 3), Wormian bones (n = 2), delayed bone age (n = 2), and persistence of woven bone in the ribs of one patient 15. Osteopenia was reported in only two patients.
- Skin and integument
  Frequently occurring skin features, apart from the severe skin fragility (n = 14) and loose, lax, or hyperextensible skin (n = 15), included a soft and doughy skin texture (n = 12), increased palmar wrinkling (n = 6), and atrophic scarring (n = 5). One of the most consistent clinical findings was an umbilical hernia at birth (n = 14).
- Ocular involvement
  One patient had severe, congenital myopia, whereas several others presented with early onset and progressive myopia (n = 5). Three others had astigmatism, and one patient developed severe glaucoma at very young age.
- Dental involvement
  In addition to gingival hyperplasia and dental lamina cysts, several other dental abnormalities have been reported. These include microdontia (n = 6) or even agenesis of several permanent teeth (n = 3), and tooth discoloration (n = 3). Abnormal morphology of the molars (n = 2) and severe enamel attrition of the deciduous teeth (n = 2) have been reported in a limited number of patients [De Coster et al., 2003; Malfait et al., 2004].
- Cardiovascular system
  Easy bruising was frequent (n = 11) and often very severe with the formation of large subcutaneous hematomas. Bleeding problems were encountered in seven patients, ranging from severe epistaxis and gum bleeds to internal and (congenital) cerebral hemorrhages. Arterial rupture or aortic dilatation has not been reported so far.
- Neuromuscular features and motor development
  A mild delay in gross motor development was reported in about half of the patients (n = 8).
- Visceral complications
  A 9-year-old girl ruptured her diaphragm due to postoperative vomiting. She subsequently developed a paraesopagheal hernia with incarceration of the stomach that was further complicated by the occurrence of a large abdominal hematoma after reduction. Two patients had bladder diverticula, complicated by spontaneous bladder rupture, and two other patients developed rectal prolapse with profuse anal bleeding in puberty.

Genotype–Phenotype Correlations and Penetrance

The patients harboring the c.2927_2928delCT and the c.2751-2A>T mutations have a relatively milder phenotype compared to the others. These mutations lead to introduction of a PTC. The milder phenotype could be due to the fact that NMD might be only partially efficient for these alleles and some transcripts can escape NMD. As such, these alleles could produce truncated ADAMTS-2 enzymes lacking either the last thrombospondin 1 (TSP1) domain and the PLAC (protease and lacunin) domain (c.2927_2928delCT), or the two most C-terminal TSP1 domains and the PLAC domain (c.2751-2A>T) [Van Damme et al., 2016]. Interestingly, investigation of the N-endopeptidase activity of various forms of recombinant ADAMTS-2 has previously shown that removal of one or two of the most C-terminal TSP1 and the PLAC domain results in an enzyme which is still significantly active [Colige et al., 2005]. In addition, two other members of the ADAMTS family, ADAMTS-3 and ADAMTS-14, have been shown to possess procollagen

N-endopeptidase activity, and could compensate for the reduced activity of ADAMTS-2 [Fernandes et al., 2001; Colige et al., 2002; Le Goff et al., 2006].

Penetrance is presumably complete.

Management

No specific guidelines for management of patients with dEDS are available. Management guidelines should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Differential Diagnosis

- Classical EDS
- Cutis laxa syndromes
- OI
- Arthrochalasia EDS
- RIN2 syndrome
- Achondroplasia

KYPHOSCOLIOTIC EDS (kEDS) DUE TO LYSYL HYDROXYLASE 1 DEFICIENCY (kEDS-*PLOD1*)

Synonyms: Kyphoscoliotic EDS; EDS Type 6; EDS Type VIA; Ocular-scoliotic EDS; Nevo syndrome; Cutis hyperelastica; Lysyl hydroxylase-deficient EDS

The History of Kyphoscoliotic EDS

Kyphoscoliotic EDS was the first inborn error of human collagen metabolism to be defined at the biochemical level, as early as 1972. Based on a family study in which two sisters had marked muscular hypotonia, severe progressive scoliosis from birth, marked joint hypermobility, and recurrent joint dislocations [Krane et al., 1972; Pinnell et al., 1972], the authors found lysyl-hydroxylase deficiency in fibroblasts from the two siblings that produced hydroxylysine-deficient collagen. Because the sisters also presented microcornea, fragility of ocular tissues, and a distinct biochemical defect, it was suggested that they be classified as a new subtype, EDS VI, the ocular type or the ocular-scoliotic type [McKusick, 1972]. Later, it was recognized that the ocular signs, though dramatic, were far less frequent than initially reported, prompting the Villefranche Nosology to reclassify the disorder as the kyphoscoliotic type of EDS [Beighton et al., 1998]. At that time it was recognized that in the majority of cases, the condition was caused by the lysyl hydroxylase 1 enzyme deficiency and specified as the kyphoscoliotic form of EDS (EDS VIA), whereas a rarer, clinically similar condition with normal lysyl hydroxylase activity was designated EDS VIB [Steinmann et al., 2002; Walker et al., 2004b]. Thereafter, it was recognized that the Nevo Syndrome, first reported in 1974, was an allelic condition to kEDS [Giunta et al., 2005a].

Recently, a number of rare autosomal recessive entities with distinct molecular and biochemical abnormalities that clinically overlap with kEDS have been described, and are discussed below: kEDS due to *FKBP14* mutations, the Brittle cornea syndrome (BCS) (*ZNF469* and *PRDM5*), the spondylodysplastic form of EDS caused by *SLC39A13* mutations (previously called spondylocheirodysplastic EDS), and musculocontractural EDS (*CHST14* and *DSE*).

The exact prevalence of kEDS due to lysylhydoxylase 1 deficiency is unknown.

Mechanism of Disease

kEDS-*PLOD1* is caused by deficiency of the collagen-modifying enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1 or LH1 [lysylhydroxylase1]) due to homozygosity or compound heterozygosity for mutated *PLOD1* alleles. Lysylhydroxylase 1 (LH1) plays an important role as a post-translational modifying enzyme in collagen biosynthesis through (1) hydroxylation of helical lysyl residues in Xaa-Lys-Gly collagen sequences to hydroxylysyl residues which serve as sites of attachment for carbohydrate units (either galactose or glucosyl-galactose), and (2) in the formation of intra- and intermolecular collagen cross-links. LH1 deficiency results in underhydroxylation of lysyl residues and underglycosylation of hydroxylysyl residues in collagens and, hence, impaired cross-link formation with consequent mechanical instability of the affected tissues [Rohrbach et al., 2011].

Allelic Heterogeneity

A total of 139 mutations in *PLOD1* have been identified in the 84 confirmed cases, of these there are 39 different mutations. The 8.9 kb duplication of 7 exons (exons 10–16; c.1067_1846 dup) is the most common and has been reported in 42/139 (30%) mutations (20 individuals homozygotes; 2 patients compound heterozygotes). Nine patients from six families are homozygous for the nonsense mutation p.Arg319*, all of Arab descent. The nonsense mutation p.Tyr511* has been identified in five patients, two of whom are homozygous.

There is a registry of reported *PLOD1* gene variants [Dalgleish, 1998].

Clinical Description

At present, 84 patients from 73 families with confirmed kEDS-*PLOD1* (either by demonstration of biallelic *PLOD1* mutations or by urinary analysis) have been identified [Beighton, 1970b; Krieg et al., 1979; Ihme et al., 1983; Dembure et al., 1984; Chamson et al., 1987; Wenstrup et al., 1989; Hyland et al., 1992; Hautala et al., 1993; Ha et al., 1994; Al-Gazali et al., 1997; Yeowell and Walker, 1997; Brinckmann et al., 1998; Heikkinen et al., 1999; Walker et al., 1999, 2004a, 2005; Yeowell et al., 2000a, b, 2005; Brunk et al., 2004; Giunta et al., 2005b; Yis et al., 2008; Esaka et al., 2009; Voermans et al., 2009a; Kariminejad et al., 2010; Rohrbach et al., 2011; Gok et al., 2012; Busch et al., 2014; Tosun et al., 2014; Abdalla et al., 2015]. The ages at publication ranged from 5 months to 54 years. Clinical features were adequately reported in 74 patients with kEDS-*PLOD1* (either by demonstration of biallelic *PLOD1* mutations or by urinary analysis) (Table S1).

The hallmarks of the disorder include (congenital) kyphoscoliosis, muscle hypotonia, and joint hypermobility (Representative pictures of the phenotype are given in Fig. 2).

- Reproductive, including pregnancy
  Pregnancy of an affected fetus is usually uneventful although reduced fetal movements have been reported (n = 7). PPROM was reported in three cases, four patients were known breech presentation and there were three reports of oligohydramnios.
  Affected pregnant women may be at increased risk for spontaneous abortions, premature rupture of membranes, and rupture of arteries. The patient reported by Esaka et al. [2009] experienced minor trauma at 29 weeks gestation resulting in a stillbirth and maternal death. Post mortem autopsy showed a spontaneous rupture of the right iliac artery [Esaka et al., 2009]. Two affected women had a total of seven pregnancies resulting in three miscarriages and four healthy children, three of whom were born vaginally at term and one of whom was born at 24 weeks; there were no maternal complications [Steinmann, unpublished].
- Craniofacial features
  A number of dysmorphic features have been reported. However, individual case series often report the same feature in a number of patients. As a result, the occurrence of certain features may be over-represented. The most frequently observed features are high palate, epicanthal folds, down-slanting palpebral fissures, synophrys and low-set ears.
- Musculoskeletal system
  Kyphoscoliosis is present and usually severe and progressive. In most patients, this is congenital (n = 55) but postnatal kyphoscoliosis (n = 12) or scoliosis alone (n = 1) have been reported. Almost all patients have joint hypermobility (n = 69). Joint dislocations/subluxations are common. Congenital hip dislocations has been reported in 15 patients and post-natal hip dislocation in an additional three patients. Besides hip, shoulder (n = 12), knee (n = 5), and wrist (n = 2) were the most commonly noted dislocations/subluxations. Generally, recurrent dislocations were noted in 18 patients. Hand deformities were noted in 13 patients. Foot deformities were also noted in 17, which included four cases of talipes equinovarus. Pes planus was reported in 11 patients.

  A marfanoid habitus has been reported in 19/74 patients. Arachnodactyly was reported in eight separate patients. High palate was recorded in 11 patients, and in association with arachnodactyly in five, or with marfanoid habitus in three patients. A pectus deformity was observed, with pectus excavatum being more common (n = 12) than pectus carinatum (n = 2). Osteopenia (n = 17) or osteoporosis (n = 2) was sometimes seen on X-ray; however, fractures were not reported in any patients.
- Skin and integument
  Skin abnormalities are almost universally described. Skin hyperextensibility (n = 48) and soft, doughy, or velvety skin (n = 43) were most frequently observed. Fragility was reported (n = 26) with easy bruising (n = 26); thin, translucent skin (n = 8); and abnormal wound healing (n = 17). Atrophic scarring was reported in 35 patients. Criss-cross patterning of the palms was only reported in one patient. Hernia was reported in 12 patients including six umbilical and five inguinal.

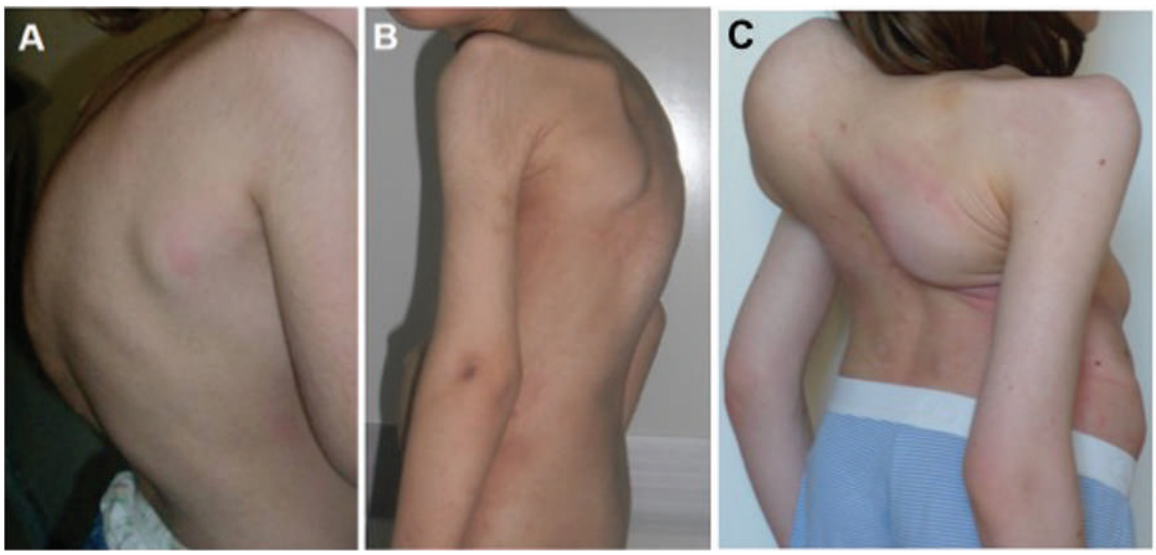

Figure 2. Clinical findings in patients with kEDS: (**A** and **B**) Kyphoscoliosis in two unrelated patients homozygous for causative mutations in *PLOD1*. (**C**) Severe kyphoscoliosis in a patient homozygous for a causative mutation in *FKBP14* (Images kindly provided by Prof. Ebtesam Abdalla and Dr. Matthias Baumann, with permission).

- Ocular involvement
  Ophthalmic features are variable and include bluish sclerae (n = 18), microcornea (n = 16), and myopia (n = 16). Rupture of the eye globe, following minimal trauma has been reported in five individuals including one patient with both eyes affected [Beighton, 1970a; Pinnell et al., 1972; Ihme et al., 1983; Kariminejad et al., 2010].
- Cardiovascular system
  Medium-sized vessel rupture has been reported in several individual case reports. These events appear to be more prevalent from teenage years and into adulthood; however, there have been six cases of antenatal/neonatal brain haemorrhage [Wenstrup et al., 1989; Yeowell and Walker, 1997; Yeowell et al., 2000a; Giunta et al., 2005b; Rohrbach et al., 2011; Tosun et al., 2014]. Arterial rupture has been reported in various locations and during pregnancy as mentioned above [Esaka et al., 2009].

  In one of the first reported siblings [Beighton, 1970b], the sister died from a dissecting aortic aneurysm at the age of 50 and the brother had a cerebral bleed in the distribution of the right middle cerebral artery at the age of 19. Dembure et al. [1984] reported a patient, who was then followed up by Ha et al. [1994] who had a spontaneous arterial rupture into his upper thigh at the age of 15. In Wenstrup et al. [1989], one patient had a rupture of a vertebral artery and another patient had multiple ruptures of the femoral artery and two episodes of spontaneous intrathoracic arterial rupture. Brinckmann et al. [1998] reported two patients with vascular complications; one suffered a stroke at the age of 15 years and subsequently at age 30 years, he had spontaneous bleeding of minor pancreatic arteries; and at age 32 years, he had spontaneous bleeding from branches of the right profundal femoral artery [Brinckmann et al., 1998; Busch et al., 2014]; another patient had an aneurysm of the mesenteric artery age 12 years.

  The patient reported by Yeowell et al. [2000a] had an intracranial haemorrhage and brachial plexus injuries at birth; he had dextrocardia and mild aortic root dilatation with mild aortic insufficiency due to a biscuspid aortic valve and he died from arterial rupture age 14 years. Voermans et al. [2009a] followed-up patient 7 from Giunta et al. [2005b] who had a ruptured aneurysm of the left popliteal artery at the age of 15 years. Rohrbach et al. [2011] reported a 27-year-old man with chest symptoms who during coronary angiography had a spontaneous dissection of the ramus interventricularis anterior (RIVA) and main coronary artery causing acute cardiac failure. A Turkish boy presented with a left brachial artery pseudo-aneurysm at the age of 12 [Gok et al., 2012]. There has been one report of aortic stenosis [Ihme et al., 1983]. Another three patients were reported to have MVP [Pinnell et al., 1972; Rohrbach et al., 2011].
- Neuromuscular features and motor development
  One of the key features of the condition is congenital muscular hypotonia (n = 56), with associated feeding problems (n = 17). Gross motor delay is common (n = 54) with varying severity, but with only one non-ambulatory case.
- Neurological features and neurodevelopment
  Intelligence is usually normal but learning disabilities have been reported in eight patients (two of these patients were reported to have antenatal or perinatal intracranial bleeds) [Wenstrup et al., 1989; Rohrbach et al., 2011].

Genotype–Phenotype Correlation and Penetrance

A range of clinical severity is observed in individuals with kEDS-*PLOD1* for each of the systems discussed as detailed in the above section [Steinmann et al., 2002; Rohrbach et al., 2011]. No specific work has been carried out looking at genotype–phenotype correlations. There are two siblings with the same mutations reported by Hyland et al. [1992]. The younger sibling appears be much less severely affected. Intrafamilial variation has been observed.

Penetrance is complete.

Management

Key management guidelines focus on the musculoskeletal system, skin, and the cardiovascular system.

- The advice to management of the musculoskeletal system is:
  - According to that for patients with classical EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue)
  - Photographic and radiologic documentation of the spine is recommended in view of the progressive kyphoscoliosis. Regular follow-up by an orthopedic surgeon for management of kyphoscoliosis is appropriate
  - Any surgery should be carried out with caution due to the risk of vascular complications
  - Consider bone densitometry evaluation
  - Consider sleep study to assess for nocturnal hypoxemia, and nighttime ventilation in case of severe muscle hypotonia
- The advice to management of the skin is:
  - According to that for patients with classical EDS (see "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue)
  - Routine examination for hernia and surgical referral as necessary
- The advice for management of the cardiovascular system is:
  - Measurement of aortic root size and assessment of heart valves by echocardiogram at the time of diagnosis or by age 5 years
  - Echocardiogram at 5-year intervals, even if the initial echocardiogram is normal
  - Vigilant observation and control of blood pressure can reduce the risk of arterial rupture

  - Further vascular surveillance ought to be considered
- The advice for management of the ophthalmologic system is:
  - Formal ophthalmologic evaluation at diagnosis for myopia, astigmatism, and potential for retinal detachment
  - Routine ophthalmologic examination for management of myopia and early detection of ophthalmic complications
  - Myopia and/or astigmatism may be corrected by glasses or contact lenses
  - Laser treatment of the retina is indicated in case of imminent detachment
- Pregnancy management
  - Follow-up throughout pregnancy and delivery should be performed in a specialized fetal medicine center
  - Measurement and monitoring of aortic root size by echocardiogram during pregnancy

Differential Diagnosis

- Kyphoscoliotic EDS-*FKBP14*
- Brittle cornea syndrome
- Spondylodysplastic EDS
- Musculocontractural EDS
- Classical EDS
- Congenital myopathies, including collagen VI and collagen XII-associated myopathies (myopathic EDS)
- Metabolic disorders
- Vascular EDS
- Marfan syndrome
- Loeys–Dietz syndrome

KYPHOSCOLIOTIC EDS (kEDS) DUE TO FKBP22-DEFICIENCY (kEDS-*FKBP14*)

Synonyms: *FKBP14*-related EDS, FKBP22-deficient EDS

The History of Kyphoscoliotic EDS (kEDS) due to FKBP22-Deficiency (kEDS-*FKBP14*)

Baumann et al. [2012] reported five families with an autosomal recessive variant of EDS, characterized by severe congenital muscle hypotonia, joint hypermobility, skin hyperextensibility, progressive kyphoscoliosis, and sensorineural hearing loss. The condition was shown to be caused by biallelic mutations in *FKBP14* [Baumann et al., 2012]. In view of the major clinical overlap of this phenotype with kEDS-*PLOD1*, both conditions are grouped within the same clinical entity ("Kyphoscoliotic EDS" in the new EDS classification).

Baumann et al. [2012] reported five families with an autosomal recessive variant of EDS, characterized by severe congenital muscle hypotonia, joint hypermobility, skin hyperextensibility, progressive kyphoscoliosis, and sensorineural hearing loss. The condition was shown to be caused by biallelic mutations in FKBP14.

The prevalence of kEDS-*FKB14* is unknown.

The Mechanisms of Disease

FKBP14 encodes FKBP22, a member of the F506-binding family of peptidyl-prolyl cis–trans isomerases found in the lumen of the endoplasmic reticulum (ER), where it is thought to catalyze cis–trans-isomerization of peptidyl-prolyl peptide bonds and to accelerate protein folding, particularly of procollagens [Galat, 2003]. FKBP22 interacts with types III, VI, and X collagen, but does not show direct binding to other types of collagen, such as type I or V collagen [Ishikawa and Bachinger, 2014]. Deficiency of FKBP22 was shown to result in enlarged ER cisterns in dermal fibroblasts, and an altered assembly of the ECM [Baumann et al., 2012].

Allelic Heterogeneity

Four different *FKBP14* mutations have been identified to date [Baumann et al., 2012; Aldeeri et al., 2014; Murray et al., 2014; Dordoni et al., 2016]. The c.362dup, p.(Glu122Argfs*7) has been identified in homozygous state in five independent families. Furthermore, this mutation was twice identified in compound heterozygosity with another mutation: One with a nonsense mutation (c.42_60del, p.(Thr15*)) and once with a 3-bp deletion (c.573_576del, p.(Gly191del)). A homozygous deletion of four amino acids was recently reported: c.197+5_197+8delGTAA [Alazami et al., 2016].

Clinical Description

To date, 10 patients with kEDS-*FKBP14* from nine independent families have been described: Five pediatric (<12 years), three adolescents (16 years), and two adults (42- and 48-year-old) (Table S1) [Baumann et al., 2012, Aldeeri et al., 2014, Murray et al., 2014, Alazami et al., 2016, Dordoni et al., 2016]. Sufficient clinical data are available for nine patients.

The hallmarks of the disorder include kyphoscoliosis (either progressive or non-progressive), severe congenital muscle hypotonia with muscle atrophy, joint hypermobility, and congenital hearing loss (sensorineural, conductive, or mixed) (Representative pictures of the phenotype are given in Fig. 2).

- Craniofacial features
  Facial dysmorphisms are not always described and a facial "gestalt" is not recognizable. Some patients had epicanthal folds (n = 3), micrognathia (n = 3), hypotelorism (n = 1), square nasal root (n = 1), or long-narrow face (n = 1).
- Musculoskeletal
  Kyphoscoliosis was noted at a mean age of 12 months (range 2–18 months) and was either non-progressive (n = 3) or progressive (n = 7). Orthotic treatment seemed successful in case of non-progressive kyphoscoliosis, progressive kyphoscoliosis required a

surgical approach. Atlantoaxial instability was reported in one patient, the other patients presented uncomplicated joint hypermobility without recurrent dislocations/sprains or chronic pain (mean value of Beighton score 7/9). Height was generally within the normal range, but at lower level (10th–25th centile in 4 of 8), two patients had short stature (lower than third centile).

- Skin and integument
  The most distinctive cutaneous features in kEDS-*FKBP14* are soft skin (n = 8), hyperextensible skin (n = 7) and hyperkeratosis follicularis (n = 5). Other skin features include atrophic scarring, umbilical skin redundancy, and multiple merging comedones in a few patients. Four patients had a hernia, including umbilical hernia in three and inguinal hernia in one.
- Ocular features
  Opthalmologic features include myopia, hypermetropia, and blue sclerae.
- Hearing
  Hearing impairment was noted in most patients. It varied from sensorineural (n = 6), to conductive (n = 2), or mixed. In one patient, because of the mixed origin of this sign, hearing improved after transtympanic drains.
- Cardiovascular system
  Vascular complications were described in an adult patient, who presented a celiac artery pseudoaneurysm rupture at the age of 41 years, and in the older likely affected sister of a patient, likely affected but without molecular confirmation, who died due to unspecified aortic rupture at age 12 years. Celiac artery pseudoaneurysm rupture was observed in a child at age 6 years.
- Neuromuscular features and motor development
  Myopathic signs include muscle hypotonia and atrophy, poor head control in infancy, and delayed motor development. Muscular weakness seemed to regress with age and all of the subjects-but one-became able to walk at the mean age of 33 months. The outcome was very variable and the final ability to walk ranged from myopathic gait, impossibility of walking without aids, to a motor self-sufficiency from 200 m to 1 km. Muscle biopsy showed pathological results in six patients, with myopathic changes and/or fiber atrophy; creatine kinase was generally within the normal range or slightly elevated and electromyographic patterns were usually normal at very young age, but sometimes myopathic later on [Baumann et al., 2012].
- Visceral complications
  Large bladder diverticula (n = 3) or rectal prolapse (n = 1) were reported.

Genotype–Phenotype Correlation and Penetrance

No genotype–phenotype correlations have been described. Penetrance is presumably complete.

Management

Key management guidelines focus on the musculoskeletal, cardiovascular, and auditory systems. No specific guidelines for management of patients with kEDS-*FKBP14* are available. Guidelines for management of musculoskeletal problems, skin involvement, cardiovascular involvement, ophthalmologic and dental follow-up, and pregnancy should follow those formulated for kEDS-*PLOD1*.

Specific management guidelines should also include hearing evaluation at initial diagnosis and annual hearing evaluation.

Differential Diagnosis

- Kyphoscoliotic EDS-*PLOD1*
- Musculocontractural EDS
- Spondylodysplastic EDS
- Congenital myopathies, including collagen VI and collagen XII-associated myopathies (myopathic EDS)
- Vascular EDS
- Classical EDS
- Marfan syndrome
- Loeys–Dietz syndrome

BRITTLE CORNEA SYNDROME (BCS)

Synonyms: EDSVIB

History of Brittle Cornea Syndrome

Brittle cornea syndrome is a rare autosomal recessive generalized HCTD, hallmarked by a thin and fragile cornea that tends to perforate spontaneously or after minor trauma. It was originally described as a constellation of brittle cornea, blue sclerae, and red hair [Ticho et al., 1980; Cameron, 1993]. On the basis of overlapping clinical features, BCS and EDS kyphoscoliosis type were previously considered to represent the same disorder [Cameron, 1993]. Because of subtle clinical differences, this claim was later questioned and proven wrong on the basis of biochemical studies. In kEDS-*PLOD1* there is deficient activity of LH1 whereas in BCS the LH1-activity is normal [Royce et al., 1990; Al-Hussain et al., 2004].

Abu et al. [2008] first mapped the BCS gene to a 4.7 Mb region on chromosome 16q24 and later identified recessive mutations in *ZNF469* (MIM 612078). The single exon gene *ZNF469* encodes a C2H2 zinc finger protein of which the function is yet to fully be understood. Because not all BCS patients harbored *ZNF469* mutations, a second locus for BCS was suspected. This was confirmed by the discovery of mutations in *PRDM5* (MIM 614161) [Burkitt Wright et al., 2011]. *PRDM5* encodes a C2H2 zinc finger protein of the PR/SET family of proteins. *PRDM5* was first characterized as a potential tumor suppressor gene in the development of several types of cancer [Watanabe et al., 2007, 2009; Cheng et al., 2010], but has now been shown to regulate transcription of collagen and several other ECM genes in a mouse osteoblast cell line (MC3T3) [Galli et al., 2012]. In addition, expression profiling studies suggest that both *PRDM5* and *ZNF469* might be part of a common pathway regulating the

expression of ECM genes such as fibrillary collagens, and several studies have suggested a role for *ZNF469* normal corneal development [Lu et al., 2010; Vitart et al., 2010; Vithana et al., 2011; Rohrbach et al., 2013].

The report of a single BCS family with mutations in neither *PRDM5* or *ZNF469* suggests the existence of a third genetics locus, but the large majority of cases is probably attributable to mutations in *ZNF469* or *PRDM5* [Rohrbach et al., 2013].

The exact prevalence of BCS is unknown.

Mechanism of Disease

ZNF469 encodes ZNF469, a zinc finger protein of unknown function, but limited homology (~30%) with a number of collagens suggests that ZNF469 could be involved in collagen transcription and fibrillogenesis. Genome-wide association studies have consistently associated single nucleotide polymorphisms (SNPs) in the vicinity of the *ZNF469* locus with central corneal thickness (CTT) [Lu et al., 2010; Vitart et al., 2010; Vithana et al., 2011; Hoehn et al., 2012; Ulmer et al., 2012], and pathogenic *ZNF469* alleles have been identified as the single most significant genetic risk factor in the development of keratoconus (relative risk of 12) [Lechner et al., 2014].

PRDM5 encodes a protein of the PR/SET protein family that lacks the intrinsic histon methyltransferase activity of other PR-domain containing proteins, but suppresses or activates the transcription of its target genes by recruiting the histone methyltransferase G9a and class I histone deacetylases [Duan et al., 2007]. In line with its role in BCS, PRDM5 was shown to regulate transcription of ECM genes, including several collagen genes and small leucine-rich proteoglycans (SLRP) in pre-osteoblastic mouse cells. More specifically, it regulates collagen transcription and fibrillogenesis by binding collagen genes and maintaining RNA polymerase II occupancy [Galli et al., 2012].The role of PRDM5 does not appear to be limited to ECM development. Early studies focused on hypermethylation of the *PRDM5* promotor in several types of cancer and its tumor suppressor activity by modulating the Wnt signaling pathway and expression of oncogenes [Watanabe et al., 2007, 2009; Meani et al., 2009; Cheng et al., 2010]. Its involvement in vertebrate development has been addressed in zebrafish studies; prdm5 was shown to be essential for convergent extension movements through regulation of Wnt signaling [Meani et al., 2009].

Allelic Heterogeneity

The following *ZNF469* mutations have been reported: 13 frameshift mutations: c.9611del, p. (Gln3206Argfs*23); c.9483 delG, p.(His3162Thrfs*20); c.8901_89 14dup, p.(Glu2972Glyfs*50); c.6647 delA, p.(Gln2216Argfs*19); c.6444 delG, p.(Gln2149Serfs*51); c.6638del, p.(Leu2210Trpfs*27); c.6027delA, p. (Gly2011Alafs*16); c.5787ins, p.(Gln1 902Profs*13); c.5787delG, p.(Gln190 2Argfs*6); c.3476del, p.(Gly1159Ala fs*15); c.2234del, p.(Phe717Serfs*15); c.2150delT, p.(Phe717Serfs*15); and c.350dupC, p.(Gln118Thrfs*32), five missense mutations: c.10106G>C, p. (Arg3369Pro); c.10100G>A, p.(Cys 3339Tyr); c.7508C>A, p.(Arg2478 Glu); c.7424C>A, p.(Arg2478Glu); and c.5686C>G, p.(Pro1896Ala), and four nonsense mutations: c.5353C>T, p. (Gln1785*); c.4258G>T, p.(Glu1420*); c.3304G>T, p.(Glu1109*); and c.2029G>T, p.(Gly677*).

The following *PRDM5* mutations have been reported: Three frameshift mutations: c.1517_1527del11, p. (Val506Glufs*5); c.974delG, p.(Cys325Leufs*2); and c.711_714delTGTT, p.(Val238Alafs*35), one nonsense mutation (c.1768C>T, p.(Arg590*)), two missense mutations (c.320A>G, p.(Tyr107Cys) and c.17T>G, p. (Val6Gly)), one splice site mutation (c.93+1G>A), and one multiple-exon deletion (exons 9–14) [Burkitt Wright et al., 2011; Avgitidou et al., 2015a].

Clinical Description

To provide a comprehensive overview of the clinical phenotype of BCS, we reviewed the data on 51 patients (*ZNF469*: n = 32; PRDM5: n = 19) (Table S1) [Al-Hussain et al., 2004; Abu et al., 2008; Christensen et al., 2010; Khan et al., 2010; Burkitt Wright et al., 2011; Al-Owain et al., 2012; Aldahmesh et al., 2012; Rohrbach et al., 2013; Ramappa et al., 2014; Avgitidou et al., 2015b; Porter et al., 2015]. Only those patients with individual clinical and molecular data were included in the review. Their age ranged between 6 months and 48 years.

The hallmarks of the condition in the thin, fragile cornea, with an increased risk for spontaneous corneal rupture (Representative pictures of the phenotype are given in Fig. 3).

- Craniofacial involvement
  In the experience of the authors, patients with BCS present with a somewhat recognizable facial gestalt, including frontal bossing, high palate, depressed nasal bridge, and/or prominent chin. These features may however be mild.
- Musculoskeletal system
  Joint hypermobility was a frequent finding (n = 40), and was sometimes complicated by joint dislocations (n = 6), but appeared mostly limited to small joints. Other frequent features include developmental dysplasia of the hip (DDH, n = 16), kyphoscoliosis (n = 22), foot deformities (n = 22) including pedes planovalgi and hallux valgus, and arachnodactyly (n = 6). Fractures (n = 5) and osteopenia/osteoporosis (n = 2) have been reported in a limited number of patients.
- Skin and integument
  Patients with BCS have a mild skin phenotype with soft, velvety (n = 16), and transparent (n = 11) skin. A hyperextensible skin was noted in a minority of patients (n = 3), and is often mild. Wound healing and easy bruising was sometimes delayed (n = 4), but atrophic scarring was absent.
  Soft connective tissue herniations were reported in five patients.
- Ocular
  BCS is associated with a severe ocular phenotype. Its most striking feature is a high risk of corneal perforation (n = 36), either spontaneously or after minor trauma, due to extreme corneal thinning (central corneal thickness or CCT: 220–450 μm, normal range 520–560 μm), and often leading to

Figure 3. Clinical findings of a 13 year old female BCS patient homozygous for a causative mutation in *PRDM5*: (**A**) Marfanoid habitus with heigth on P75 and weigth on P3; velvety skin, hematomas lower leg and hallux valgus bilaterally, pectus excavatum. Shoulder symmetrical, spine straight. Facial: depressed nasal bridge and/ prominent chin. (**B**) Blue sclerae. (**C**) Current protective spectacles after bilateral successful cornea-crosslinking (Images kindly provided by Dr. Marianne Rohrbach, with permission).

irreversible blindness. Ocular rupture frequently occurred at young age, but several adults without ocular rupture have been described. Prior to rupture, visual acuity in BCS patients was often affected by keratoconus and/or keratoglobus (n = 27) and high myopia (n = 17). The most consistent ophthalmic feature was blue sclerae (n = 49). Secondary glaucoma was reported in several patients (n = 5), particularly those with extensive corneal damage following rupture. Retinal detachment and neovascularization were both reported once. Of note and in contrast to kEDS-*PLOD1*, microcornea was never observed. Megalocornea, on the other hand, was reported in three cases. BCS usually presents as a generalized connective tissue disorder with multi-tissue involvement, but one adult case with isolated ocular findings has been described [Khan et al., 2012]. This suggests that recessive mutations in *ZNF469* and *PRDM5* could be a rare cause of isolated keratoconus or corneal rupture. It should be noted however that the majority of BCS cases has been reported in ophthalmological journals, and that extraocular findings might be underestimated.

- Hearing
  Hearing loss has been recognized as a predominant feature, but has not yet been comprehensively studied. Approximately, one third was affected with hearing loss (n = 19). The most frequent type was mixed conductive/sensorineural hearing loss (n = 11) with a predominance of conductive hearing loss in childhood. Both inter- and intrafamilial variability with respect to age of onset and progression of deafness were observed. The combined hearing loss and decreased visual acuity often led to severe sensorineural disability.
- Cardiovascular
  Cardiovascular defects were uncommon, but mitral valve insufficiency has been described (n = 3). Notably and in contrast to kEDS, vascular and visceral fragility has not been described in the context of BCS.

Genotype–Phenotype Correlation and Prevalence

There is currently no evidence of a clear genotype–phenotype correlation: All types of mutations scattered across both genes appear to cause indistinguishable clinical phenotypes.

Penetrance is presumably complete. Individuals heterozygous for BCS-associated mutations have been reported to have blue sclerae and small joint hypermobility. These are not always present, and in particular may not be striking in adult carriers. Heterozygous carriers may have very mild corneal thinning (e.g., CCT around 500 μm). Keratoconus has also been diagnosed in a young adult, heterozygous for a *PRDM5* mutation [Burkitt Wright et al., 2011].

Management

Early diagnosis (prior to ocular rupture) is possible and desirable to make anticipatory management as effective as possible. The distinctive syndromic features of BCS, such as DDH, kyphoscoliosis, blue sclerae, soft and/or translucent skin, and hypercompliant tympanic membranes, serve as important diagnostic clues in the early recognition of patients with this condition, particularly where they are the only affected individual in their family.

Key management guidelines focus on the ocular system, with primary prevention of corneal rupture by provision of protective polycarbonate eyeglasses and careful screening of vision, but also hearing. An overview of clinical management strategies for BCS patient is given in Burkitt Wright et al. [2013].

Guidelines for management of musculoskeletal problems, skin involvement, cardiovascular problems, and pregnancy should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Differential Diagnosis

- Kyphoscoliotic EDS
- Spondylodysplastic EDS
- Musculocontractural EDS
- OI

SPONDYLODYSPLASTIC EDS DUE TO B4GALT7-DEFICIENCY (spEDS-*B4GALT7*)

Synonyms: EDS progeroid type, EDS progeroid type 1, EDS with short stature and limb anomalies

The History of Spondylodysplastic EDS due to β4GalT7-Deficiency (spEDS-*B4GALT7*)

Hernandez et al. [1979, 1981, 1986] reported five patients with EDS-features and features of early aging, including wrinkled facies, significant growth failure, fine/curly hair, periodontitis, bilateral cryptorchidism, apparent intellectual deficit. Kresse et al. [1987] reported a patient with a similar phenotype, and showed its skin fibroblasts converted only half of the core protein of the small dermatan sulfate proteoglycan decorin to a mature glycosaminoglycan (GAG) bearing proteoglycan. This defective proteoglycan biosynthesis was shown to result from biallelic mutations in *B4GALT7*, encoding galactosyltransferase I [Quentin et al., 1990; Okajima et al., 1999]. Cartault et al. [2015] detected a homozygous missense mutation (c.808C>T, p.(Arg270Cys)) in *B4GALT7* in a series of 22 patients with Larsen of Reunion Island syndrome (LRS), a skeletal dysplasia with clinically overlaps with spEDS-*B4GALT7*.

In view of the major clinical overlap of EDS caused by *B4GALT7* mutations with the phenotypes caused by *B3GALT6* and by *SLC39A13* mutations, these three conditions are now grouped within the same clinical entity ("Spondylodysplastic EDS") in the new EDS classification.

In view of the major clinical overlap of EDS caused by B4GALT7 mutations with the phenotypes caused by B3GALT6 and by SLC39A13 mutations, these three conditions are now grouped within the same clinical entity ("Spondylodysplastic EDS") in the new EDS classification.

The prevalence of spEDS-*B4GALT7* is unknown.

Mechanism of Disease

B4GALT7 encodes galactosyltransferase I (β1,4-galactosyltransferase 7 or β4GALT7), a Golgi-resident enzyme, that is involved in synthesizing the GAG linker region of proteoglycans. GAGs are long, unbranched polysaccharides composed of repeating disaccharide units, which consist of alternating uronic acids and amino sugars. Most GAGs are covalently attached to specific serine residues of core proteins via a defined linker region of xylose, two galactoses and one glucuronic acid, thus assembling to proteoglycans (PG). Alternative addition of N-acetylglucosamine or N-galactosylglucosamine to the terminal glucuronic acid of the linker region leads to the formation of heparan sulfate (HS) or chondroitin/dermatan sulfate (CS/DS), respectively (Fig. 4). Cosynthetic modifications such as epimerization and sulfation result in the formation of diverse motifs in the GAG chains, that allow binding of a variety of ligands, thus regulating growth factor signaling, cell adhesion, proliferation, differentiation, and motility. The β1,4-galactosyltransferase 7 is a glycosyltransferase catalyzing the transfer of the first galactose onto the xylose residue of the PG core protein-GAG linker region.

Seidler et al. [2006] studied fibroblasts of a patient harboring the homozygous p.(Arg270Cys) substitution and showed reduced β1,4-galactosyltransferase 7 activity, reduced glycanation of decorin and biglycan, and reduced epimerization of the decorin GAG chain. In addition, morphological alterations and intracellular accumulation of degradative vacuoles were seen in the patient's fibroblasts. Analysis of the collagen fibrils showed that the β4GalT7-deficient cells had an altered suprastructure, no banded collagen fibrils and an altered ratio of α1–α2 collagen chains. Finally the β4GalT7-deficient cells showed reduced proliferation rates compared to controls. Gotte et al. [2008] analyzed structural alterations in HS and their functional consequences in fibroblasts harboring this mutation. They showed a reduced sulfation degree of HS, delayed in vitro wound repair, and increased fibronectin adhesion, impaired actin stress fiber formation, delayed collagen gel extraction with reduced formation of pseudopodia and filopodia, and finally diminished formation of collagen suprastructures.

Bui et al. [2010] studied the ability of mutant β4GalT7 harboring either the homozygous p.(Arg186Asp), p.(Leu206Pro), and p.(Arg270Cys) substitution to prime GAG biosynthesis in recombinant cells. Whereas the p.(Arg185Asp) did not affect GAG biosynthesis severely, the p.(Leu206Pro) mutation led to complete inhibition and the p.(Arg270Cys) to significant reduction of GAG biosynthesis. Molecular modeling predicted that the p.(Leu206-Pro) mutation located in a conserved secondary structure affected the overall structure of the protein, whereas p.(Arg186Asp) is located in a less structural critical domain and the p.(Arg270Cys) in the vicinity of the substrate active site.

Allelic Heterogeneity

In total, seven missense and two frameshift mutations have been reported for *B4GALT7*. The c.808C>T, p.(Arg270Cys) is most frequent. It has once been reported in homozygous state, once in compound heterozygosity with c.122T>C, p.(Leu41Pro), and once in compound heterozygous state with c.421C>T, p.(Arg141Trp). Furthermore, the c.557C>A, p.(Ala186Asp) mutation was identified in compound heterozygosity with the c.617T>G, p.(Leu206Pro) mutation, the c.641G>A, p.(Cys214Tyr) with c.277dup, p.(His93Profs*73) and finally a homozygous c.970T>A, p.(Cys324Ser) was reported. All mutations are localized in the luminal catalytic domain, except for the p.(Leu41Pro), which is localized in the transmembrane domain.

Clinical Description

At present seven patients from six families with molecularly confirmed

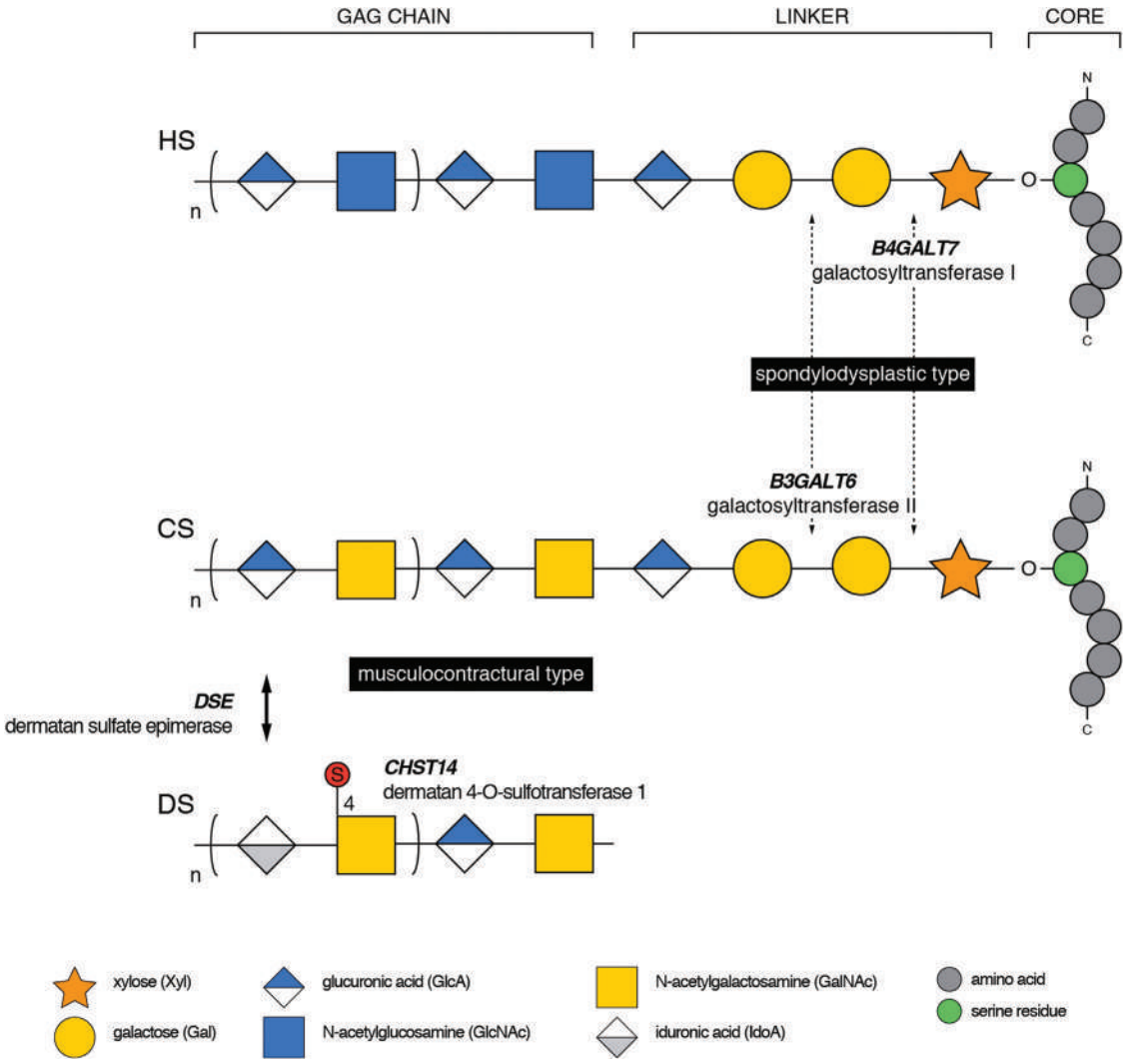

Figure 4. Biosynthesis of the HS and CS/DS GAG chains is initiated by the attachment of a common tetrasaccharide linker region to a specific serine residue of the core protein. This linker region is synthesized by the stepwise action of specific enzymes: Xylosyltransferase I/II (encoded by *XYLT1* and *XYLT2*, respectively), galactosyltransferase I (β4GalT7, encoded by *B4GALT7*) and II (β3GalT6, encoded by *B3GALT6*), and glucuronyltransferase I (encoded by *B3GAT3*). Following completion of the linker region, the addition of the next residue determines whether HS or CS/DS is synthesized. CS is formed by the alternating addition of N-acetylgalactosamine (GalNAc) and glucuronic acid (GlcA) residues, which are subsequently modified by several sulfotransferases. The formation of DS requires the epimerisation of GlcA residues to iduronic acid (IdoA), an event catalyzed by dermatan sulfate epimerases I and II (DS-epi1 encoded by *DSE* and DS-epi2 encoded by *DSEL*, respectively), and subsequent 4-O-sulfation of the adjacent GalNAc residue by dermatan 4-O-sulfotransferase-1 (D4ST1, encoded by *CHST14*). Defects in the initiation and modification of the GAG chains are associated with different EDS subtypes (indicated in black boxes). Defects in linker enzymes *B4GALT7* and *B3GALT6* lead to spEDS and affect the formation of both HS and CS/DS whereas alterations in *DSE* and *CHST14* result in mcEDS and compromise the formation of DS.

spEDS-*B4GALT7* have been identified (Table S1). The ages at publication ranged from 2 years to 33 years [Kresse et al., 1987, Faiyaz-Ul-Haque et al., 2004, Guo et al., 2013, Arunrut et al., 2016, Salter et al., 2016]. The clinical features reported in the patients with LRS are not included in this review.

The hallmarks of the disorder include short stature, muscle hypotonia, radio-ulnar synostosis, and intellectual disability.

- Reproductive, including pregnancy
  Antenatal ultrasonography showed asymmetrical ventriculomegaly in one patient and severe intrauterine growth retardation in another patient. No pregnancies have been reported in affected individuals.

- Craniofacial features
  The most consistent craniofacial features include triangular face (n = 7), wide-spaced eyes (n = 6), proptosis (n = 6), narrow mouth (n = 5), low-set ears (n = 5), sparse scalp hair (n = 4), abnormal dentition (n = 4), flat face (n = 4), wide forehead (n = 4), blue sclerae (n = 3), cleft palate/bidif uvula (n = 2), high palate (n = 1), small jaw

(n = 1). Of note, none of the patients was described to have progeroid features.

- Musculoskeletal features
  The most consistent musculoskeletal features include severe growth retardation (n = 7), present at birth but progressing later on, generalized joint hypermobility (n = 7), which was noted to be quite severe in several patients, bowing of limbs (n = 5), and foot deformities (pes planus (n = 4), pes equinovarus (n = 1)). Other reported symptoms include dislocations/subluxations (n = 3), bilateral elbow contractures or limited elbow movement (n = 3), syndactyly (n = 2), pectus carinatum (n = 2), scoliosis (n = 1), long fingers (n = 4), thin fingers with bulbous tips and broad thumbs (n = 1). One patient with low-impact rib and vertebral fractures in infancy received bisphosphonate treatment, with improvement of bone pain and muscle function [Salter et al., 2016].
- Skeletal X-ray imaging
  Reported abnormalities include: Radio-ulnar synostosis (n = 6), metaphyseal flaring (n = 4), osteopenia (n = 4), radial head subluxation or dislocation (n = 3), short clavicles with broad medial ends (n = 3), anterior splaying of ribs (n = 2), swedish key feature of the femur (n = 1), bulbous appearance of distal phalangeal tufts (n = 1), coxa valga (n = 1), reduced height of vertebral bodies (n = 1).
- Skin and integument
  Hyperextensible (n = 6), single transverse palmar crease (n = 5), loose skin (n = 3), atrophic scarring (n = 3), soft and doughy skin (n = 2), reduced subcutaneous fat (n = 1), prominent scalp veins (n = 1), prominent venous pattern on chest (n = 1).
- Ocular features
  Hypermetropia at very young age was reported in 5/7 patients. In most of them, it was severe. One patient was operated at age 3 months for unilateral ptosis. He also had astigmatism and intermittent exotropia. Small optic nerves (n = 1), and strabismus (n = 1) were reported. Arunrut et al. [2016] reported a patient with congenital cloudy cornea, bilateral high hypermetropia, pendular nystagmus, coloboma of iris and optic nerves, and posterior subcapsular cataracts.
- Dental features
  Yellowish teeth with defective enamel was reported in one patient.
- Hearing
  Mild conductive hearing loss was reported in one patient, likely related to cleft palate.
- Neuromuscular features and motor development
  Muscle hypotonia was reported in all patients but ranged from mild to very severe. Three patients were reported to be "floppy" at birth, one had mild congenital hypotonia, and the other three were reported to be mildly hypotonic later in childhood. Delayed motor development was reported in 6/7 patients, but none of them remained non-ambulatory. In none of the reported patients, a muscle biopsy was taken.
- Neurological features and neurodevelopment
  Five patients were reported to have mild intellectual deficit. This included speech delay in three patients, mild learning difficulties in one, and a somewhat more severe delay in one patient.

Genotype–Phenotype Correlation and Penetrance

Although marked differences in ability to prime GAG biosynthesis have been described for different missense substitutions (see "Mechanism of Disease" section), no genotype–phenotype correlations have emerged to date. It remains also unclear why the p.(Arg270Cys) is associated with either an EDS phenotype or with LRS. Cartault et al. [2015] hypothesized this could be due to the high levels of homozygosity among the LRS population and modification by interaction with other variants in close linkage disequilibrium to *B4GALT7*.

Penetrance is presumably complete. Obligate carriers display no overt clinical symptoms.

Management

No specific guidelines for management of patients with spEDS-*B4GALT7* are available. Management guidelines should be tailored to the individual's specific problems and should follow those formulated for other forms of EDS.

Specific management guidelines may include:

- Musculoskeletal:
  - At diagnosis a whole body skeletal survey and bone densitometry studies are recommended
  - In patients with recurrent fractures, bisphosphonate therapy should be considered, with treatment protocols following those formulated for patients with OI

Differential Diagnosis

- Spondylodysplastic EDS-*B3GALT6*
- Spondylodysplastic EDS-*SLC39A13*
- Musculocontractural EDS
- kEDS (*PLOD1* and *FKBP14*)
- Chondrodysplasia

SPONDYLODYSPLASTIC EDS DUE TO B3GALT6-DEFICIENCY (spEDS-*B3GALT6*)

Synonyms: EDS progeroid type 2

The History of β3GalT6-Deficient EDS

In 2013, two independent research studies identified biallelic mutations in *B3GALT6*, encoding β3GalT6 (galactosyltransferase II or β1,3-galactosyltransferase 6), in two different conditions. Nakajima et al. [2013] identified *B3GALT6* mutations in seven Japanese families with spondyloepimetaphyseal dysplasia with joint laxity type 1 (SEMD-JL1 or SEMD-JL Beighton type) by whole exome sequencing. In three other families with a phenotype resembling β4GalT7-deficient EDS,

targeted *B3GALT6* sequencing subsequently identified causal mutations in all of them. Coincidently, Malfait et al. [2013] identified *B3GALT6* mutations in three unrelated families with a pleiotropic EDS-like connective tissue disorder, characterized by severe kyphoscoliosis, joint hypermobility and contractures, multiple early-onset fractures, SEMD, skin fragility, and intellectual disability. Following the identification of *B3GALT6* as the causal gene for SEMD-JL1, Vorster et al. [2015] identified the same mutations and a novel p.(Thr79Ala) mutations, all located in or in the vicinity of the stem region, in eight prototype South African families. A few additional patients with an EDS/SEMDJL1 overlap phenotype have also been reported [Sellars et al., 2014; Ritelli et al., 2015; Alazami et al., 2016].

In view of the major clinical overlap of EDS caused *B3GALT6* mutations, with the phenotypes caused by *B4GALT7* and by *SLC39A13* mutations, these three conditions are grouped within the same clinical entity ("Spondylodysplastic EDS") in the new EDS classification.

The exact prevalence of spEDS-*B3GALT6* is unknown.

Mechanisms of Disease

B3GALT6 encodes galactosyltransferase II (β1,3-galactosyltransferase 6 or β3GalT6), a membrane Golgi-resident enzyme, that catalyzes the addition of the third galactose onto the second galactose of the GAG linker region (for introduction, see also "Mechanism of Disease for spEDS-*B4GALT7*" section). Malfait et al. [2013] showed, using cultured dermal fibroblasts, that GAG synthesis and activity was strongly reduced by the homozygous or compound p.(Asp207His) mutation found in two patients, as well as by the homozygous p.(Gly217Ser) mutation present in one of the patients. Expression of both HS and CS GAG chains was affected in these patients. This study also showed that the GAG defects were associated with abnormal collagen structure and delayed migration in a wound healing assay, emphasizing the role of GAG in collagen fibril formation, as well as in various physiological functions of connective tissue, such as cicatrisation. Nakajima et al. [2013] showed that a recombinant mutant, lacking the initiation codon (p.Met1) produced a truncated protein that was mislocalized to the cytoplasm and nucleus, presumably inactive. Also using recombinant proteins, they reported that both enzyme mutants (p.(Ser65Gly), p.(Pro67Leu)) were inactive, emphasizing the role of the conserved N-terminal end of the catalytic domain in the functional activity of the enzyme. Other mutants studied, harboring mutations in the central or C-terminal part of the catalytic domain, that is, p.(Asp156Asn) and p.(Cys300Ser), also exhibited severely impaired enzyme activity except for p.(Glu174Asp) (50% loss in activity). Importantly, in the lymphoid cells of three SEMD-JL1 patients, the amount of HS was reduced whereas CS/DS was increased (2–5-fold). The molecular basis of these observations remains to be established. In two patients harboring a compound deletion and catalytic domain mutation [Ritelli et al., 2015] showed by micro-array transcriptome and immunofluorescence analyses a reduced expression of cartilage oligomeric matrix protein (*COMP*) and osteopontin (*SPP1*). Interestingly, these authors reported reduced expression and disassembly of HS GAG chains and of the HS-matrix PG perlecan.

Allelic Heterogeneity

In total, 22 missense mutations, eight frameshift mutations, two in-frame deletions, two start codon mutations, one splice site, and one in-frame duplication have been reported for *B3GALT6*.

The most frequent mutation is the p.(Pro67Leu) substitution, which is frequent among South Africaner patients, but which was also reported in a Vietnamese patient, followed by the p.(Thr79Ala) mutation, identified seven times among South Africaner patients. Other recurrent substitutions include p.(Arg232Cys) (n = 4 families), p.(Asp207His) (n = 3 families), p.(Phe186Leu) (n = 3 families), p.(Arg6Trp) (n = 2 families), p.(Glu265Asp) (n = 2 families), p.(Ser309Thr) (n = 2 families), and p.(Glu174Alafs*266) (n = 2 families). The p.(Met1?) was reported in five families.

Other reported missense mutations include: p.(Val61Leu), p.(Ser65Gly), p.(Asp144Asn), p.(Asp156Asn), p.(Ser158Tyr), p.Tyr182Cys, p.(Pro211Ser), p.(Gly217Ser), p.(Arg256Trp), p.(Arg261His), p.(Cys300Ser), p.(Tyr310Cys), and p.(Pro318Leu).

Other reported frameshift mutations are: p.(Ile76Thrfs*202), p.(Ala108Glyfs*163), p.(Asp118Alafs*160), p.(Met 139Ala141del), p.(Phe180Serfs*118), and p.(Arg197Alafs*81). Finally, p.(Arg179_Arg180dup), and p.(Ala66_Arg84del) were each reported once.

Out of 36 families, 25 were compound heterozygous and 11 were homozygous. Except for the homozygous p.(Arg179_Arg180dup), compound heterozygosity always included a missense mutation on one of the two alleles.

Four highly deleterious mutations are found outside the catalytic domain, one mutant lacking the initiation Met codon (p.(Met1?), one mutant in the cytoplasmic tail (p.(Arg6Trp)), and two in the stem region (p.(Ser65Gly) and p.(Pro67Leu)). Other mutations are located in the luminal catalytic domain.

Clinical Description

At present, 47 patients from 36 families with molecularly confirmed spEDS-*B3GALT6* have been identified (Table S1). The ages at publication ranged from birth to 33 years [Malfait et al., 2013; Nakajima et al., 2013; Sellars et al., 2014; Ritelli et al., 2015; Alazami et al., 2016; Honey, 2016, Van Damme et al., unpublished]. Detailed clinical data are available for 36 patients. This overview includes the SEMD-JL1 patients reported by Nakajima et al. [2013], but not those reported by Vorster et al. [2015], since detailed clinical data of the latter patients were not available.

The hallmarks of the disorder include: (1) Characteristic craniofacial features, (2) kyphoscoliosis, (3) joint hypermobility, mostly of distal joint,

(4) joint contractures, (5) short stature, (6) muscle hypotonia, (7) osteoporosis with multiple fractures, (8) radiographic skeletal abnormalities compatible with SEMD, and (9) intellectual disability (Representative pictures of the phenotype are given in Fig. 5).

- Reproductive, including pregnancy
  Antenatal ultrasound abnormalities were reported in eight pregnancies. Reported abnormalities included prenatal kyphoscoliosis (n = 2), shortening of tubular bones (n = 2), contractures of wrists and clubfeet (n = 1), oligohydramnios (n = 1); polyhydramnios (n = 1), decreased fetal movements (n = 1), and small cerebellum (n = 1). For two siblings, the pregnancy was terminated around 22 weeks of gestation because of "severe skeletal dysplasia."
  Reported perinatal complications include breech presentation (n = 3), congenital kyphoscoliosis (n = 3), congenital bilateral hip dislocation (n = 1), bilateral clubfeet (n = 3), congenital fractures (n = 1), cloudy cornea (n = 1), unilateral unilateral agnesis of the kidney (n = 1), open foramen ovale (n = 1), cleft palate (n = 3), Pierre–Robin sequence (n = 1), severe congenital muscle hypotonia or floppy infant (n = 2), and a cerebral hemorrhage following vaginal delivery (n = 1)
- Craniofacial features
  Characteristic craniofacial features include blue sclerae (n = 24), frontal bossing (n = 21), midfacial hypoplasia (n = 20), downslanting palpebral fissures (n = 4), low-set, sometimes posteriorly rotated, ears (n = 19), prominent eyes/proptosis (n = 15), long philtrum (n = 15), micrognathia (n = 11), depressed nasal bridge (n = 9), small nose (n = 6), tooth discoloration (n = 5), hypoplastic teeth (n = 4), sparse hair (n = 4), high arched palate (n = 3), prominent chin (n = 2), cleft palate (n = 3), Pierre–Robin sequence (n = 1), asymmetrical skull (n = 2), large anterior fontanel (n = 1), short neck with low hairline (n = 1)
- Musculoskeletal system
  Kyphoscoliosis is very frequent (n = 32), and may be congenital or develop during the first 24 months of age, and is usually progressive. Severe short stature was frequently reported (n = 26). While stature may be short at birth, growth restriction usually evolved postnatally. Patients present joint hypermobility (n = 27), either generalized or restricted to distal joints, and sometimes complicated by dislocations of large and small joints (n = 14). Joint contractures were frequent (n = 21); they were either congenital, such as talipes equinovarus (n = 21), and/or evolved postnatally, and mostly affected fingers (e.g., adducted thumbs, camptodactyly), wrists, elbows, feet, and knees. Pectus deformities, either carinatum or excavatum, were reported in 8 patients. A total of 13 patients had a history of multiple spontaneous bone fractures and 12 had documented generalized osteoporosis or osteopenia. Finger shapes were characteristically described as "slender," "arachnodactyly," or "tapering," with "spatulate or broad distal phalanges" (n = 13).
- Skeletal X-ray imaging
  Reported abnormalities include: Short ilia (n = 17), platyspondyly (n = 16) (described as becoming less conspicuous over time by Nakajima et al. [2013]), ovoid vertebra (n = 1), metaphyseal flaring (n = 13), osteopenia (n = 12), anterior beak of vertebral body (n = 12), prominent lesser trochanter (n = 11), elbow malalignment (n = 10), epihyseal dysplasia femoral head (n = 10), metacarpal shortening (n = 7), overtubulation (n = 6), radial head dislocation (n = 5), advanced carpal ossification (n = 5), bowing of long bones (n = 3), narrowing of long bones (n = 3), acetabular dysplasia (n = 2), vertebral listhesis (n = 2), radioulnar synostosis (n = 1), craniosynostosis (n = 1), coxa valga (n = 1), coxa valga (n = 1), wedged vertebral bodies (n = 1), bony fusion of proximal ends of ulna and radius (n = 1), carpal fusion (n = 1). One patient had a severe torticollis at 12 months due to a posterior displacement of the vertebral column, with atlanto-occipital and atlanto-axial dislocation. Two patients had an invagination of the atlas into the foramen magnum and anterior atlanto-axial subluxation. In two patients, the cervical instability was associated with hydrocephalus [Van Damme et al., unpublished].
- Skin and integument
  The skin was usually described as hyperextensible or loose (n = 19), soft and doughy (n = 18), and/or thin or translucent (n = 8). In 10 patients, increased palmar wrinkling of the hands was reported. Atrophic scarring (n = 5) and easy bruising (n = 3) were rarely reported. Other reported skin features include wrinkling of the skin on the dorsum of the hands (n = 1), and loose, redundant skin folds on wrists and ankles (n = 1). Bilateral inguinal hernia was described in one patient.
- Ocular involvement
  Refractive errors were reported in five patients. Other ocular problems include microcornea (n = 1); intermittent glaucoma (n = 1); congenital corneal clouding with sclerocornea (n = 1), and repetitive retinal detachment (n = 1). One patient had optic nerve atrophy.
- Dental involvement
  Dental involvement was reported in a number of patients and includes tooth discoloration (n = 5), hypoplastic teeth (n = 4), and early decay of teeth (n = 1).
- Hearing
  Hearing impairment with a conductive component was described in one patient.
- Cardiovascular system
  Two patients had a dilation of the ascending aorta in infancy, two patients had a mitral valve prolapse, two patients had an atrial septum defect, one patient had a patent ductus arteriosus, and one patient had a patent foramen ovale. Two patients suffered from a cerebral hemorrhage. One patient was reported with severe bruising, spontaneous scalp hematomas, and multiple hemorrhagic blisters.
- Gastro-intestinal system
  Constipation was described in one patient, and gastro-oesophageal reflux in another.
- Urogenital system
  Hydronephrosis was detected in one patient, unilateral renal agenesis in one, dilatation of renal pelvis ureterocoele in one and bladder atonia in one. One patient developed a Wilms tumor.

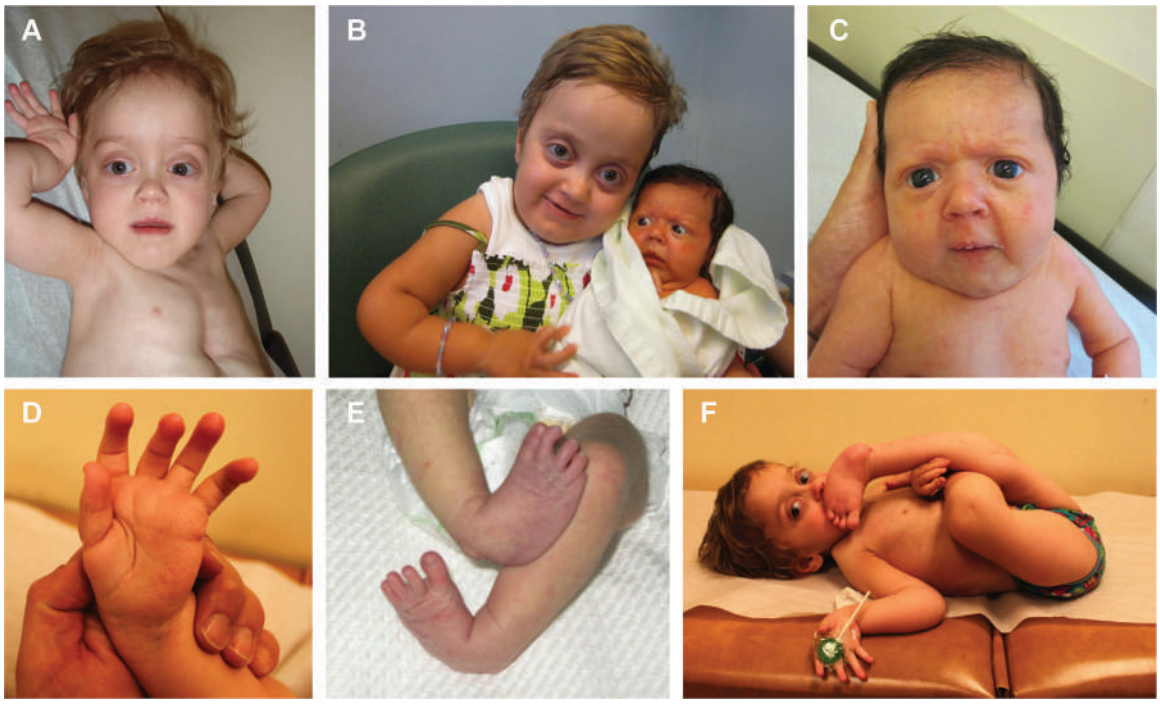

Figure 5. Clinical characteristics of patients with spEDS-*B3GALT6*. Facial characteristics at 2 years of age (**A**), 6 years of age (**B**) and 2 months of age (younger sister in panel **C**) include long face with mild micrognatia in infancy, proptotic eyes with shallow orbits and blue tint to the sclerae. The palpebral fissures are downslanting. The nasal bridge is broad and there is a low nasal ridge. Chest shows moderate pectus excavatum. The limbs show significant hyperextensibility, reduced movement of distal joints that leads to absent creases of the distal interphalangeal joints (**D**), increased creases of the skin of the palms (**D**) and club feet (**E**). There is muscle hypotonia, which is compounded by the hyperextensibility of the joints and makes anti-gravitational movements difficult (**F**) (Images kindly provided by Dr. Roberto Mendoza-Londono, with permission).

- Pulmonary involvement
  Several pulmonary problems were reported: Three patients were reported with restrictive lung disease; in one of them this was due to lung hypoplasia and a diaphragmatic hernia. Respiratory distress due to lung hypoplasia was reported in another patient. Other reports included mild respiratory deficiency (n = 1), sleep apneu (n = 1), chronic aspiration and pneumonia (n = 1), and asthma (n = 1).
- Neuromuscular features and motor development
  Muscle hypotonia was reported in 16 patients, and four of them had documented muscle hypoplasia. Gross motor developmental delay, with a delay in sitting and walking, was described in seven patients mainly because of muscle hypotonia. The age at which unassisted walking occurred in patients who accomplished ranged between 2 and 7 years. Three patients remained non-ambulatory during childhood. In three patients, feeding problems, due to muscle hypotonia, were reported.
- Neurological features and neurodevelopment
  Two patients were reported with brain atrophy, and two patients had hydrocephalus.
  Mild to moderate cognitive delay was suggested in 11 patients.

Genotype–Phenotype Correlation and Penetrance

No genotype–phenotype correlations have been described.

Penetrance is complete. Obligate carriers display no overt clinical symptoms.

Management

No specific guidelines for management of patients with spEDS-*B3GALT6* are available. Management guidelines should be tailored to the individual's specific problems and should follow those formulated for other forms of EDS.

Specific management guidelines may include:

- Musculoskeletal:
  - At diagnosis a whole body skeletal survey and bone densitometry studies are recommended
  - In patients with recurrent fractures, bisphosphonate therapy should be considered, with treatment protocols following those formulated for patients with OI
  - Physical therapy for the contractures and muscle hypotonia, and monitoring for any signs of feeding or respiratory difficulties, in particular nocturnal hypoventilation. If the latter is present then assisted non-interventional ventilation at night may be indicated

- Cardiovascular system:
  - Measurement of aortic root size and assessment of heart valves by echocardiogram at the time of diagnosis or by age 5 years.
  - Echocardiogram at 5-year intervals, even if the initial echocardiogram is normal
  - Further vascular surveillance ought to be considered

Differential Diagnosis

- Spondylodysplastic EDS-*B4GALT7*
- Spondylodysplastic EDS-*SLC39A13*
- Kyphoscoliotic EDS (*PLOD1* and *FKBP14*)
- Musculocontractural EDS
- OI
- Cutis laxa syndromes
- Chondrodysplasia
- Congenital myopathies

SPONDYLODYSPLASTIC EDS DUE TO SLC39A13 MUTATIONS (spEDS-*SLC39A13*)

Synonyms: spondylocheirodysplastic EDS (SCD-EDS)

History of Spondylodysplastic EDS due to *SLC39A13* Mutations (spEDS-*SLC39A13*)

Giunta et al. [2008b] reported a "new" clinical entity caused by a mutation in the zinc transporter gene *SLC39A13*. The clinical features of six patients from two unrelated consanguineous families were similar to those of kEDS-*PLOD1*, but lack (kypho)scoliosis and in addition presented distinct phenotypic components, including platyspondyly, osteopenia, short stature and widened metaphyses, tapered fingers, and a tendency to develop contractures of small joints. Because of features affecting mainly the spine (spondylo) and the hands (cheiro) this variant was termed the Spondylocheirodysplastic form of EDS (SCD-EDS) [Giunta et al., 2008b]. The six patients presented with EDS-like features, short stature, finger contractures, distinct radiological features, elevated ratios of lysyl pyridinoline to hydroxylysyl pyridinoline (LP/HP) (but to a lesser degree then in EDS type VIA), and underhydroxylated collagens in culture despite normal in vitro activities of lysyl hydroxylase and prolyl 4-hydroxylase, respectively. The underhydroxylation was a generalized process which occurs along the entire molecule, and is not confined to specific residues as shown by tandem mass spectrometry of the α1(I)- and α2(I)-chain derived peptides of collagen type I and involves at least collagen types I and II [Giunta et al., 2008a]. Subsequently, Fukada et al. [2008] reported a third family with two affected siblings presenting with similar clinical findings who were homozygous for a missense mutation in *SCL39A13* [Fukada et al., 2008]. The authors furthermore generated a Slc39a13−/− knockout mouse that recapitulated defects observed in the patients, thereby demonstrating that mutations in *SLC39A13* cause Spondylocheiro-dysplastic EDS [Fukada et al., 2008].

In view of the clinical overlap of EDS caused by *SLC39A13* mutations, with the phenotypes caused by *B3GALT6* and by *B4GALT7* mutations, these three conditions are grouped within the same clinical entity ("Spondylodysplastic EDS") in the new EDS classification.

The exact prevalence of spEDS-*SLC39A13* is unknown.

Mechanisms of Disease

SpEDS-*SLC39A13* is caused by homozygous loss-of-function mutations in the zinc transporter gene *SLC39A13*. This gene encodes the homodimeric transmembrane Zrt/irt-like protein 13 (ZIP13) protein, a member of the SLC39A/ZIP family that regulates the influx of zinc (Zn^{++}) into the cytosol [Bin et al., 2011]. This protein is a member of the LIV-1 subfamily of ZIP zinc Transporters (LZT), a highly conserved group of eight transmembrane domain proteins known to transport zinc and/or other metal ions from the extracellular space or from the organellar lumen into the cytoplasm [Eide, 2006]. Mutant ZIP13 proteins are easily degraded, and disturb the intracellular Zn^{++} homeostasis [Bin et al., 2014a,b]. It has been shown that ZIP13 loss-of-function leads to a generalized disturbed hydroxylation of lysyl and prolyl residues in collagen α chains [Giunta et al., 2008b]. Since Zn^{++} was found to be an effective competitive inhibitor with respect to iron (Fe^{++}) for prolyl 4-hydroxylase and for lysyl hydroxylase, it was initially suggested that the generalized underhydroxylation of collagen was likely due to Zn^{++} overload in the ER. Zn^{++} competes with Fe^{++} for binding to lysyl hydroxylase, prolyl 4-hydroxylase, and prolyl 3-hydroxylase, thus impairing hydroxylation of lysyl and prolyl residues [Giunta et al., 2008b]. Further studies however have disputed this hypothesis. One study proposed that trapping of Zn^{++} in vesicular stores reduces the availability of Zn in the ER and other cellular components and induces ER stress [Jeong et al., 2012]. Another study showed that ZIP13 is required for full activation of BMP/TGF-β signaling via regulation of the intracellular localization of Smad proteins in connective tissue forming cells; this study put forward the hypothesis that incomplete activation of BMP/TGF-β signaling is responsible for the observed phenotype [Fukada et al., 2013].

Allelic Heterogeneity

Three mutations have been identified so far in a total of eight patients from three independent families.

A homozygous 9-bp in-frame deletion in exon 4, c.483_491del9 was found in two unrelated consanguineous families originating from North-Western Iraq and the Southeastern part of Turkey, respectively. At the protein level, the c.483_491del9 mutation leads to the deletion of the highly conserved amino acid residues Phe-Leu-Ala from the third transmembrane domain of

ZIP13 [Giunta et al., 2008b]. The second mutation, a homozygous missense variant c.221G>A, p.(Gly64Asp) [Bin et al., 2011] has been identified in two siblings from Portugal [Fukada et al., 2008]. It is localized in the second transmembrane domain of *SLC39A13* and is conserved through all vertebrate species down to fish.

Clinical Description

To date, eight patients with spEDS-*SLC39A13* from three independent families have been described: Three pediatric (<12 years), two adolescents (12.5 and 14.5 years), and three adults (>20 years) (Table S1) [Fukada et al., 2008, Giunta et al., 2008b].

The hallmarks of the disorder include: (1) Moderate short stature; (2) hyperelastic, velvety, thin skin with an easily visible venous pattern, and bruisability which leads to atrophic scars; (3) slender, tapering fingers, wrinkled palms, and considerable thenar (and hypothenar) atrophy; (4) distal joint hypermobility which later results in contractures; (5) characteristic radiographic abnormalities; and (6) a ratio of urinary pyridinolines, LP/HP, of ~1.0 [Giunta et al., 2008b] (Representative pictures of the phenotype are given in Fig. 6).

- Reproductive, including pregnancy
  All affected individuals were born at term from uncomplicated pregnancies. No pregnancies have been reported in the affected individuals.
- Craniofacial features
  Protuberant eyes and down-slanting palpebral fissures were described in the majority of affected from the three families.
- Musculoskeletal system
  Short stature with height at the third centile or below was reported for all patients but one, whose height was at the 10th centile at age 8.5 years. The adult patients presented with mildly shortened truck. Slender tapering fingers were also reported in the majority of the affected.
- Skeletal X-ray imaging
  Reported features include: platyspondyly, osteopenia of the axial skeleton, widening of the ends with relative narrowing of the diaphyses and flat epiphyses of metacarpals and phalanges, small ileum, mildly flat proximal epiphyses, and short and wide femoral necks.
- Skin and integument
  The most distinctive cutaneous features were thin, velvety and fragile, easy bruisable skin with atrophic, cigarette paper-like scars. The skin of the palm of the hands was wrinkled in all affected individuals. In some individuals the skin was translucent particularly on legs and feet with easily visible veins.
- Ocular features
  Opthalmologic features included myopia, hyperopia, astigmatism, and blue sclerae.
- Dental features
  Hypodontia of one or few teeth in permanent dentition or abnormally shaped teeth were described in all affected individuals, but one.
- Cardiovascular system
  Vascular complications were described in the male patient from Portugal who suffered from a cerebral hemorrhage posteriorly to the left putamen at age 21 years, from which he recovered completely. The adult patients had venous varicosities on their feet and legs in adulthood.
- Neuromuscular features and motor development
  The most distinctive muscular feature was atrophy of the thenar and the hypothenar and muscle weakness of the fingers. This feature was not reported in the two adult siblings described by Fukada et al. [2008].
  Motor development was normal.

Genotype–Phenotype Correlation and Penetrance

No genotype–phenotype correlations have been described. Penetrance is presumably complete. Obligate carriers have no overt phenotype.

Management

No specific management guidelines have been reported. Guidelines for management of musculoskeletal problems, skin involvement, cardiovascular problems, and pregnancy should follow those formulated for other forms of EDS (for reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

MUSCULOCONTRACTURAL EDS (mcEDS)

Synonyms: Adducted thumb, clubfoot, and progressive joint and skin laxity syndrome; Adducted thumb-club foot syndrome (ATCS); Dündar syndrome; EDS Kosho type (EDS-KT); EDS musculocontractural type 1 (EDS-MC); EDS type VIB, EDS6B; Distal arthrogtyposis with peculiar facies and hydronephrosis

The History of Musculocontractural EDS

EDS caused by D4ST1 deficiency has initially been reported as three independent conditions: A rare type of arthrogryposis syndrome, "adducted thumb-clubfoot syndrome (ATCS)"; a specific type of EDS, "EDS, Kosho Type (EDSKT)"; and a subset of kEDS without lysyl hydroxylase deficiency, "musculocontractural EDS (MCEDS)," all of which are now concluded to be a single clinical entity [Kosho et al., 2005, Malfait et al., 2010, Janecke et al., 2011, Kosho et al., 2011, Shimizu et al., 2011].

EDS caused by D4ST1 deficiency has initially been reported as three independent conditions: A rare type of arthrogryposis syndrome, "adducted thumb-clubfoot syndrome (ATCS)"; a specific type of EDS, "EDS, Kosho Type (EDSKT)"; and a subset of kEDS without lysyl hydroxylase deficiency, "musculocontractural EDS

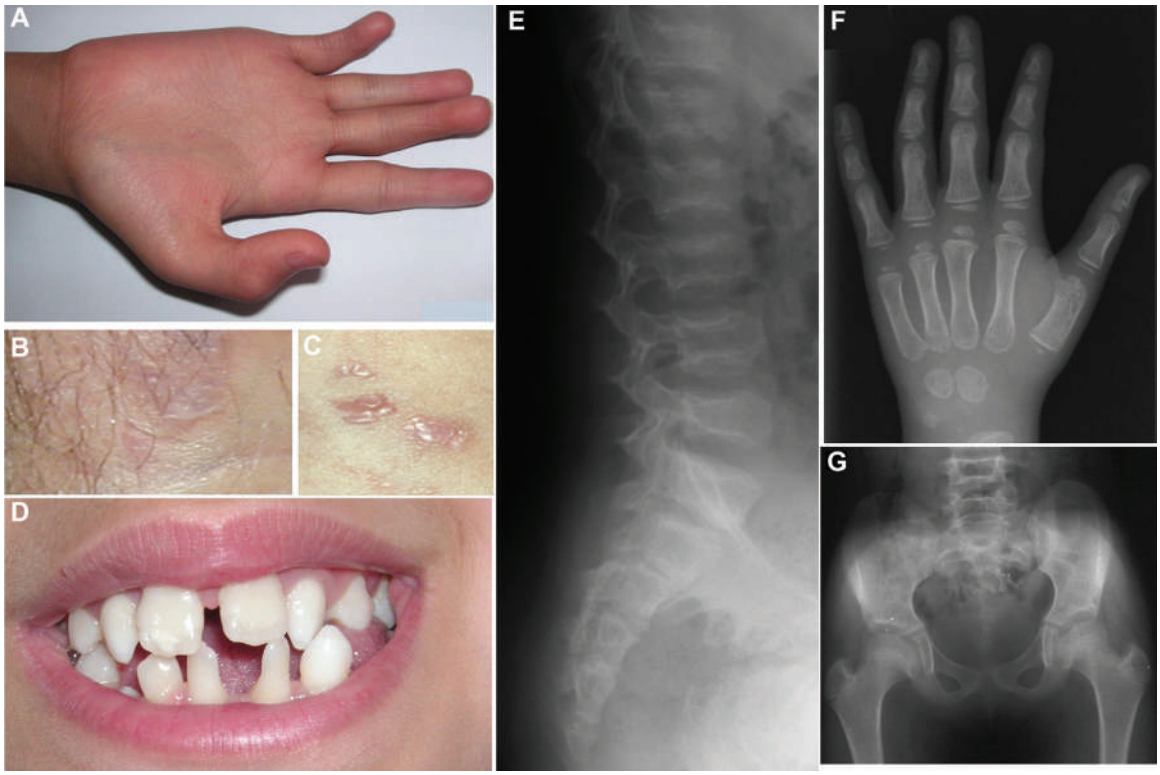

Figure 6. Clinical and radiological findings in patients with spEDS-*SLC39A13*. (**A**) Appearance of the hand in a 10.1 years old patient. Excessively wrinkled palm, thenar and hypothenar atrophy, tapering fingers, and contracted thumb. (**B** and **C**) Abnormal scar formation in two patients. (**D**) Abnormal dentition and hypodontia. (**E**) Radiograph of the low thoracic and lumbar spine in a patient aged 11.5 year with flattening, irregular endplates, and osteopenia of the vertebral bodies. (**F**) Radiograph of the hand of a 3.5 years old patient showing alterations of shape and flat epiphyses of the short tubular bones. (**G**) Radiograph of the pelvis of a 10 years old patient showing small ilia, mild flattening of the proximal epiphyses, short and wide femoral necks (Images kindly provided by Prof. Beate Albrecht and Prof. Nursel Elçioglu, with permission).

(mcEDS)," all of which are now concluded to be a single clinical entity.

The prevalence is unknown.

- Adducted thumb-clubfoot syndrome
  Dündar et al. [1997] originally reported on two cousins from consanguineous Turkish family, both having developmental delay, ocular abnormalities, characteristic facial features, generalized joint laxity, arachnodactyly, camptodactyly, and distal arthrogryposis with adducted thumbs and clubfeet. The authors named this condition adducted thumb-clubfoot syndrome (ATCS) [Dündar et al., 1997]. They subsequently reported a similar patient from another consanguineous Turkish family with three other similarly affected siblings who died of an unknown etiology in early infancy [Dündar et al., 2001]. The authors suggested that two brothers from a Japanese consanguineous family, manifesting multiple distal arthrogryposis, characteristic facial features, cleft palate, short stature, hydronephrosis, cryptorchidism, and normal intelligence, also had the syndrome [Sonoda and Kouno, 2000]. Janecke et al. [2001] described two affected brothers from another consanguineous Austrian family, and concluded that the syndrome would represent a new type of arthrogryposis with central nervous system involvement, congenital heart defects, urogenital defects, myopathy, connective tissue involvement (GJH), and normal or subnormal intellectual development [Janecke et al., 2001]. Dündar et al. [2009] reported that loss-of-function mutations in *CHST14* was causal for the syndrome, through homozygosity mapping using samples from previously described consanguineous families. They also described follow-up clinical findings of previously reported patients, including GJH, delayed wound healing, ecchymoses, hematomas, and osteopenia/osteoporosis, from which the authors categorized the syndrome into a generalized connective tissue disorder.
- EDS, Kosho Type
  In 2000, Kosho and colleagues encountered the first patient with a specific type of EDS, and the second unrelated patient with parental consanguinity in 2003. Both patients were Japanese girls with characteristic craniofacial features, skeletal features (multiple congenital contractures, marfanoid habitus, pectus excavatum, GJH recurrent dislocations, progressive talipes, and spinal deformity), cutaneous features (hyperextensibility, bruisability, and fragility with

atrophic scars), recurrent large subcutaneous hematomas, and hypotonia with mild motor developmental delay [Kosho et al., 2005] which were strikingly similar manifestations observed in Pakistani siblings classified as having a rare variant of kEDS with normal lysyl hydroxylase activity ("EDS type VIB") [Steinmann et al., 1975]. Kosho et al. [2005] proposed that these patients represented a clinically recognizable subgroup of EDS, tentatively classified as EDS type VIB. Kosho et al. [2010] described four additional unrelated Japanese patients with similar features, including a patient with parental consanguinity and a patient reported by Yasui et al. [2003]. They concluded that these patients represented a new clinically recognized form of EDS with distinct craniofacial features, multiple congenital contractures, and multisystem fragility-related manifestations [Kosho et al., 2010]. The syndrome was registered as "EDS, Kosho type" in the London Dysmorphology Database (http://www.lmdatabases.com/index.html) and also in POSSUM (http://www.possum.net.au/). Miyake et al. [2010] identified *CHST14* as the causal gene for this condition through homozygosity mapping using the two consanguineous families.

- Musculocontractural EDS
  Malfait et al. [2010] found mutations in *CHST14* through homozygosity mapping in two Turkish sisters and an Indian girl, both with parental consanguinity. The patients shared characteristic craniofacial features, joint contractures, and wrinkled palms in addition to common features of kEDS, including kyphoscoliosis; joint hypermobility; muscular hypotonia; hyperextensible, thin, and bruisable skin with atrophic scarring; and ocular complications. The authors concluded that these patients and those diagnosed with ATCS or EDS, Kosho type had a single clinical condition, which they termed "Musculocontractural EDS (MCEDS)" [Malfait et al., 2010].
- EDS caused by DSE deficiency
  Janecke and colleagues identified a homozygous loss-of-function *DSE* mutation, through positional candidate gene approach, in a boy from a consanguineous Indian family, who had characteristic facial features, congenital contractures of the thumbs and the feet, joint hypermobility, muscle weakness, and atrophic scars and was diagnosed with MCEDS [Müller et al., 2013]. Malfait and colleagues found a missense *DSE* mutation in two affected sisters from a Spanish family, who shared hyperextensible and fragile skin, recurrent large hematomas, long slender fingers, and clubfeet, but no adducted thumbs [Syx et al., 2015]. In OMIM, the syndrome is termed as EDS, musculocontractural type 2 (EDSMC2) to be distinguished from EDS caused by D4ST1-deficiency termed as EDS, musculocontractural type 1 (EDSMC1).

Mechanisms of Disease

- D4ST1 deficient EDS
  EDS caused by D4ST1-deficiency results from recessive mutations in the carbohydrate sulfotransferase 14 gene (*CHST14*), localized at 15q14. *CHST14* is a single-exon gene encoding carbohydrate sulfotransferase 14 or dermatan 4-O-sulfotransferase 1 [Evers et al., 2001]. D4ST1 is a Golgi-resident enzyme which is involved in the biosynthesis of the GAG dermatan sulfate, where it catalyzes 4-O-sulfation of N-acetylgalactosamine (GalNAc) in the sequence "L-iduronic acid (IdoA)-GalNAc," immediately after epimerization of D-glucuronic acid (GlcA) to IdoA by dermatan sulfate epimerase (DSE) [Evers et al., 2001].

  The sulfotransferase activity of cos-7 cells transfected with *CHST14* containing p.(LysK69*), p.(Pro281Leu), p.(Cys289Ser), or p.(Tyr293Cys) mutations was decreased at almost the same level, suggesting that loss-of-function mutations in *CHST14* (i.e., D4ST1 deficiency) are the basis of this disorder [Miyake et al., 2010].

  Sulfotransferase activity toward DS in mutant skin fibroblasts was significantly decreased to 6.7% in a patient with the compound heterozygous mutation p.(Pro281Leu)/p.(TyrY293Cys) and to 14.5% in a patient with the homozygous mutation p.(Pro281Leu), compared with each age- and sex-matched control [Miyake et al., 2010]. Disaccharide composition analysis of CS/DS chains isolated from the affected skin fibroblasts in these two patients showed a negligible amount of DS and excess amount of CS, which was suggested to result from impaired 4-O-sulfation lock due to D4ST1 deficiency, followed by back-epimerization from IdoA to GlcA [Dündar et al., 2009; Miyake et al., 2010; Syx et al., 2015]. Decorin, a major DS-PG in the skin, consists of a core protein and a single GAG chain that plays an important role in assembly of collagen fibrils, possibly through an electrostatic interaction between decorin DS chains and adjacent collagen fibrils. GAG chains of decorin from the affected skin fibroblasts contained exclusively CS and no DS disaccharides, while those from the controls contained mainly DS disaccharides (approximately 95%) [Miyake et al., 2010; Syx et al., 2015]. Light microscopy of the affected skin specimens using hematoxylin and eosin staining showed that fine collagen fibers were predominantly present in the reticular to papillary dermis with marked reduction of normally thick collagen bundles [Miyake et al., 2010]. Transmission electron microscopy showed that collagen fibrils in the affected skin specimens were dispersed in the reticular dermis in contrast to the regularly and tightly assembled collagen fibrils observed in the controls and that each collagen fibril in affected skin specimens was smooth and round, not varying in size and shape, similar to that in the controls [Miyake et al., 2010].

  In view of these findings, skin fragility in patients with EDS caused by D4ST1 deficiency is postulated to result from impaired assembly of collagen fibrils caused by the replacement of a DS with a CS chain of decorin through alterations in the electrostatic binding of decorin to collagen fibrils followed by difference in the spatial relationship between collagen fibrils and decorin [Kosho, 2013; Kosho et al., 2014; Kosho, 2016].

- DSE-deficient EDS
  EDS caused by DSE deficiency results from recessive mutations in the dermatan sulfate epimerase gene (*DSE*). DSE is a Golgi-resident enzyme that catalyzes the epimerization of D-glucuronic acid (GlcA) toward iduronic acid (IdoA). This allows D4ST1 to catalyze the 4-O-sulfation of the adjacent GalNAc, which then prevents back-epimerization of the IdoA to GlcA.

  Two homozygous missense mutations (p.(Arg267Gly); p.(Ser268Leu)) have been detected [Müller et al., 2013; Syx et al., 2015]. Heterologous expression of mutant full-length and soluble recombinant DSE proteins harboring the p.(Ser268Leu) substitution showed a loss of activity towards partially desulfated DS, and patient-derived fibroblasts also showed a significant reduction in epimerase activity. The amount of DS disaccharides was markedly decreased in the conditioned medium and cell fraction from cultured patient fibroblasts compared to control. No difference was seen in CS chains from the conditioned media, though the total amount of CS disaccharides in the cell fraction from the patient was increased approximately 1.5-fold, consistent with increased synthesis or reduced conversion of CS chains [Müller et al., 2013].

  Syx et al. [2015] analyzed fibroblasts from a patient harboring the p.(Arg267-Gly) substitution and could show that a minor fraction of decorin DS was present, consisting of IdoA-containing disaccharides, which could be attributed to residual DSE activity, or compensating DSE2 activity. In this patient, no pronounced ultrastructural abnormalities of dermal collagen fibrils were noted, but immunofluorescent stainings of collagen types I, III, and V and fibronectin showed evidence of abnormal ECM assembly [Syx et al., 2015].

Allelic Heterogeneity

- *CHST14*
  Mutations have been detected throughout the *CHST14* gene. These include 11 missense mutations, six frameshift mutations, and two nonsense mutations.

  The p.(Pro281Leu) was most frequent (n = 9), other recurrent mutations include p.(Val49*) (n = 3), p.(Arg213Pro) (n = 2), and p.(Tryr293Cys) (n = 4). All other mutations were reported once: p.(Arg29Gfs*113), p.(Lys69*), p.(Gln113Argfs*14), p.(Arg135Gly), p.(Leu137Gln), p.(Cys152Leufs*10), p.(Phe209Ser), p.(Arg218Ser), p.(Gly228Leufs*13), p.(Glu262Lys), p.(Arg274Pro), p.(Met280-Leu), p.(Cys289Ser), p.(Trp327Cfs*29), and p.(Glu334Glyfs*107).
- *DSE*
  Two homozygous *DSE1* missense mutations (p.(Arg267Gly) and p.(Ser268-Leu)) have been detected.

  A registry with *CHST14* and *DSE* gene variants is available [Dalgleish, 1998].

Clinical Description

At present, 39 patients (18 females, 21 males) from 26 families have been published with recessive *CHST14* mutations (Table S1). The ages of patients with *CHST14* mutations at the latest publication ranged from 0 day to 59 years. [Dündar et al., 1997; Sonoda and Kouno, 2000; Dündar et al., 2001; Janecke et al., 2001; Yasui et al., 2003; Kosho et al., 2005; Kosho et al., 2010; Malfait et al., 2010; Shimizu et al., 2011; Mendoza-Londono et al., 2012; Winters et al., 2012; Voermans et al., 2012; Syx et al., 2015; Janecke et al., 2016; Mochida et al., 2016].

Three patients (one child, two adult women) from two families have been published with recessive *DSE1* mutations [Müller et al., 2013; Syx et al., 2015].

The hallmarks of the disorder include: (1) Characteristic craniofacial features, (2) congenital multiple contractures, including adducted thumbs and talipes equinovarus, (3) characteristic cutaneous features including fine palmar creases, (4) peculiar finger shapes, (5) progressive spinal and foot deformities, (6) large subcutaneous hematomas, and (7) ophtalmological and urogenital involvement (Representative pictures of the phenotype are given in Fig. 7).

- Reproductive, including pregnancy
  Pregnancy-related findings include hand/foot anomalies (n = 3), oligohydramnios (n = 2), and decreased fetal movement (n = 2). No deliveries have been described in female patients with EDS caused by D4ST1 deficiency. Two deliveries were described in a female patient with EDS caused by DSE deficiency, followed by uterine and bladder prolapse [Syx et al., 2015].
- Craniofacial features
  Characteristic craniofacial features include a large fontanelle (n = 24), hypertelorism (n = 36), downslanting palpebral fissures (n = 35), blue sclerae (n = 28), short nose with hypoplastic columella (n = 17), ear deformities (n = 35) including low-set (n = 22) and posteriorly rotated (n = 14) ears, high palate (n = 21), long philtrum and/or thin upper lip vermilion (n = 24), and small mouth and/or micro-retrognathia (n = 16) at birth to early childhood. Slender facial shapes with protruding jaws (n = 11) and facial asymmetry (n = 8) are evident from adolescence.
- Musculoskeletal system
  Mild prenatal growth restriction was suggested: Mean birth length −0.5 SD and median −0.6 SD (n = 9; range, from −1.6 to +1.3 SD); mean birth weight −0.6 SD and median −0.67 SD (n = 11; range, from −2.0 to +0.5 SD); and mean birth occipital frontal circumference −0.2 SD and median −0.5 SD (n = 8; range, from −1.0 to +1.0 SD) [Shimizu et al., 2011]. Mild postnatal growth restriction was suggested with slenderness and relative macrocephaly: Mean height −0.9 SD and median −0.6 SD (14 data points from 12 patients; range, from −3.9 to +1.2 SD); mean weight −1.5 SD and median −1.4 SD (11 data points from 9 patients; range, from −2.4 to −0.4 SD); and mean occipital frontal circumference −0.2 SD and median 0.0 SD (10 data points from 8 patients; range, from −1.2 to >2.0 SD) [Shimizu et al., 2011].

  Multiple congenital contractures were cardinal features and typically included adduction-flexion contractures of the thumbs (n = 32; no adducted

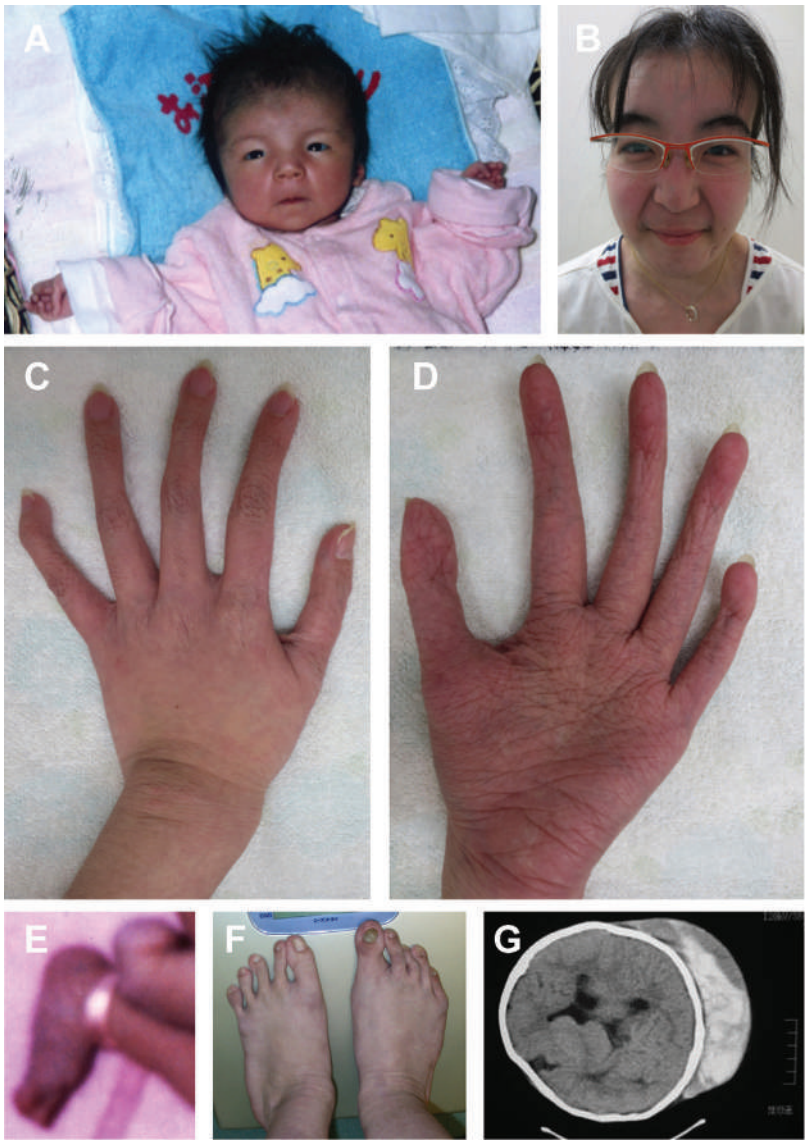

Figure 7. A female patient with mcEDS-*CHST14*. Facial characteristics at age 23 days (**A**) and 24 years (**B**). (**A** and **C**) Congenital contractures of fingers including adducted thumbs (**A**) and cylindrical fingers at age 24 years (**C**). (**D**) Characteristic wrinkling palmar creases. (**E**) Left talipes equinovarus. (**F**) progressive foot deformities at age 15 years. (**G**) A large subcutaneous hematoma at age 6 years (Images kindly provided by Dr. Tomoki Kosho, with permission. **A** and **E**, originally published in Kosho et al. [2010], in American Journal of Medical Genetics; **G**, originally published in Kosho et al. [2005], in American Journal of Medical Genetics).

thumbs in seven and data not available in two) and talipes equinovarus (n = 42). Finger shapes were characteristically described as "arachnodactyly," "tapering," "slender," or "cylindrical" (n = 36). Progressive talipes deformities (planus, valgus, or severer) (n = 27) and spinal deformities (decreased physiological curvature, scoliosis, or kyphoscoliosis) (n = 23) were observed. Marfanoid habitus (n = 13); recurrent, chronic or easy joint dislocations (n = 19), and pectus deformities (flat and thin, excavatum, or carinatum) (n = 18) were also noted.

- Skin and integument
  Skin hyperextensibility (from childhood) and redundancy (from adolescence) (n = 24), bruisability (n = 22), and fragility with atrophic scars (n = 23) were common. Acrogeria-like fine palmar creases or wrinkles were characteristic and became evident with aging (n = 29). Hyperalgesia to pressure was suggested (n = 8) because patients disliked being hugged in infancy or disliked blood pressure measurement in the upper arms. Recurrent subcutaneous infections with fistula formation were also observed (n = 8).
- Ocular involvement
  Refractive errors, typically myopia (n = 12) followed by astigmatism (n = 5) and hyperopia (n = 4), were described in 16 patients; strabismus in 13 patients; microcornea in 13; glaucoma or elevated intraocular pressure in eight; and retinal detachment in seven. Progressive visual field loss was described in a 31-year-old female [Kosho et al., 2010], deterioration in vision of the right eye because of the lacquer crack in Bruch's membrane adjacent to right fovea in a 15-year-old male [Syx et al., 2015], and right-sided blindness because of retinal detachment in a 45-year-old female [Janecke et al., 2016].
- Hearing
  Hearing impairment was described in nine patients (specified for high-pitched sounds in five).
- Cardiovascular system
  Recurrent large subcutaneous hematomas (skull, extremities, or hips) are a serious complication that can, even after minor trauma, progress acutely and massively to hemorrhagic shock requiring intensive treatment (hospital admission, blood transfusion, or surgical drainage) (n = 21). Intranasal administration of 1-desamino-8-D-arginine vasopressin (DDAVP) after trauma effectively prevented large subcutaneous hematomas in three patients [Kosho et al., 2010; Janecke et al., 2016]. Congenital heart defects, typically ASD, were detected in seven patients. Valve abnormalities and/or aortic root dilatation were also detected in seven patients. Infectious endocarditis occurred in two patients: One was successfully treated with surgical resection of the vegetation [Kosho et al., 2010] and the other expired [Janecke et al., 2016].

- Gastro-intestinal system
  Constipation was described in nine patients. Two adults and one adolescent patient had colonic diverticula perforation, corrected surgically [Kosho et al., 2010; Kono et al., 2016]. One adolescent patient had a severe progressive gastric ulcer, treated with partial gastrectomy [Kosho et al., 2010]. Complications associated with gastrointestinal malformations included a common mesentery, spontaneous volvulus of the small intestine associated with absent gastrocolic omentum [Janecke et al., 2001], and duodenal obstruction due to malrotation [Malfait et al., 2010].
- Urogenital system
  Hydronephrosis was detected in eight patients. It was caused by renal ptosis in one patient, who underwent laparoscopic placement of a ureteral stent, complicated by severe hemorrhage due to tissue fragility [Malfait et al., 2010]. Another patient had a pelviureteric junction obstruction requiring nephrostomy in the neonatal period [Syx et al., 2015]. Nephrolithiasis or cystolithiasis was described in six patients, and recurrent urinary tract infection in three. Cryptorchidism was observed in most male patients. One patient who underwent orchidopexy developed hypogonadism in adulthood.
- Pulmonary
  Pneumothorax or pneumohemothorax occurred in three adult patients, who were treated with chest tube drainage [Kosho et al., 2010].
- Neuromuscular features and motor development
  Muscle hypotonia or weakness was described in 17 patients. A myopathic process was suggested as the cause of the muscle weakness in a patient. Electromyographic examination demonstrated muscle action potentials with reduced amplitude but with a normal distal latency time and nerve conduction velocity, and muscle biopsy revealed no histological abnormalities [Dündar et al., 1997]. In another patient, quantitative muscle ultrasonography showed increased echo intensity in the forearm extensors and anterior tibial muscles as well as marked bilateral atrophy of the forearm flexors, forearm extensors, and quadriceps. Nerve conduction studies showed low compound muscle action potential amplitudes in the distal muscles. Needle electromyography showed an abnormal and mixed pattern of short-duration, low-amplitude, polyphasic motor units, as well as polyphasic motor units with a longer duration and higher amplitude, reflecting an increase in fiber size diameter. Muscle biopsy showed fiber type 1 predominance without fiber type grouping, increased variation in the diameter of both type 1 and type 2 fibers, and some type 1 fibers in close proximity to lobulated fibers. These findings were compatible with a myopathy, similar to other EDS types [Voermans et al., 2012]. Elevation of serum CK (creatine kinase) level was described in four patients (277, 698, 1838, 3000 IU/L) [Janecke et al., 2016].
  Gross motor developmental delay was described in 23 patients mainly because of muscle hypotonia. The median age at which unassisted walking occurred in patients who accomplished it was 2 years 4 months (n = 10; range, from 1 year 5 months to 4 years). One adult patient could not walk unassisted because of severe foot deformities and leg muscle weakness [Kosho et al., 2010].
- Neurological features and neurodevelopment
  Ventricular enlargement was described in six patients and asymmetry in three on brain ultrasonography, computed tomography, or magnetic resonance imaging. Additional minor findings were also recorded: Absence of the left septum pellucidum [Janecke et al., 2001], a short corpus callosum with lack of an isthmus and well-defined rostrum, mild prominence of the Sylvian fissures, and a few small gray matter heterotopias along the lateral walls of the temporal horns of the lateral ventricles [Mendoza-Londono et al., 2012], absence of the septum pellucidum, hypoplasia of the inferior vermis with a normally sized posterior fossa (Dandy–Walker variant), hypoplasia of the hippocampi and splenium of the corpus callosum, and hypoplasia of the optic nerves (septo-optic dysplasia) [Winters et al., 2012] and mild cerebellar hypoplasia, hypoplasia of the cerebellar vermis (reminiscent of Dandy–Walker variant), and absence of the septum pellucidum [Syx et al., 2015]. Spinal cord tethering was noted in three patients, two of whom underwent corrective surgery.
  Mild intellectual delay was suggested in three patients; one reportedly had global psychomotor delay in infancy, but his IQ was around 90 at the age of 7 years 2 months [Dündar et al., 1997; Janecke et al., 2011].
- Other
  Poor breast development was noted in seven female patients beyond adolescence.

Genotype–Phenotype Correlation and Penetrance

Penetrance is complete, whereas differences in phenotypic severity among affected siblings have been suggested. No apparent genotype–phenotype correlations have been described among patients with EDS caused by D4ST1 deficiency. Phenotypic features in three patients with EDS caused by DSE deficiency seemed to be milder than those in patients with EDS caused by D4ST1 deficiency, presumably associated with the glycobiological finding that some DS moieties were present in the decorin GAG in the fibroblasts derived from patients with EDS caused by DSE deficiency, whereas DS was completely replaced by CS in the fibroblasts derived from patients with EDS caused by CHST14/D4ST1 deficiency [Syx et al., 2015].

Management

Management should be comprehensive especially focusing on musculoskeletal, cutaneous, cardiovascular, visceral, and ocular complications [Shimizu et al., 2011; Kosho, 2016]. No specific guidelines for management of patients with D4ST1/DSE-deficient EDS are available. Guidelines for management of musculoskeletal problems, skin involvement, cardiovascular involvement, ophthalmologic and dental follow-up, and pregnancy should follow those formulated for other forms of EDS (for

reference: See "management guidelines for the classical Ehlers–Danlos syndrome," by Bowen et al., this issue).

Specific management guidelines may include:

- At diagnosis:
  - Screening for congenital heart defects through a cardiac ultrasonography
  - Screening for ocular malformations through an examination by a pediatric ophthalmologist
  - Screening for malformations in the renal system through a renal ultrasonography
  - Screening for hearing impairment by an automated auditory brainstem response (aABR) as well as an examination of a pediatric otologist
- Musculoskeletal:
  - Orthopedic intervention (e.g., serial plaster casts or surgery) for talipes equinovarus and physical therapy for motor developmental delay as the center of care for patients with the disorder
  - After walking independently, special attention to progressive foot deformities and trauma that could cause skin lacerations, joint dislocations, or large subcutaneous hematomas
  - Assessment of spinal deformities (scoliosis, kyphoscoliosis)
- Skin: A wrist-type sphygmomanometer for patients with hyperalgesia to pressure
- Ophtalmological: Regular check-ups for strabismus, refractive errors, glaucoma
- ORL: Regular check-up for otitis media with effusion, hearing impairment
- Urological: Regular check-up for urination problems, bladder enlargement. Surgical fixation for cryptorchidism in males
- Cardiovascular: Regular check-up for valve abnormalities, aortic root dilation
- Gastro-intestinal: Regular check-up for constipation and evaluation for need of laxatives and/or enemas
- Assessment of secondary sex characteristics (breast development in females and gonadal function in males)
- Emergent treatment for pneumothorax or pneumohemothorax, large subcutaneous hematomas, and diverticular perforation

Differential Diagnosis

- Spndylodysplastic EDS
- Kyphoscoliotic EDS (*PLOD1, FKBP14*)
- Freeman–Sheldon syndrome
- Loeys–Dietz syndrome

MYOPATHIC EDS (mEDS)

Synonyms: EDS/Myopathy overlap syndrome

The History of Myopathic EDS (mEDS)

The spectrum of diseases characterized by muscle weakness, hypotonia, myopathy, and connective tissue symptoms was first associated with mutations in the genes that code for collagen type VI. These conditions have a wide spectrum of severity that ranges from the most severe Ullrich congenital muscular dystrophy to the milder Bethlem myopathy. Zou et al. [2014] and Hicks et al. [2014] investigated groups of patients that had some symptoms of these myopathies but presented with a distinctive phenotype and did not have mutations affecting type VI collagen. Through these studies they identified eight patients in four families that presented with autosomal recessive (two patients, one family) and dominant (six patients, three families) forms of EDS/myopathy. Since then, one additional patient has been described [Punetha et al., 2016]. Prevalence of this condition is unknown.

Mechanism of Disease

Collagen XII is synthesized as a homotrimer made up of three α1 collagen chains coded by *COL12A1*. It is found along the surfaces of the fibers of collagen type I in tissues that express that collagen, and it is presumed to act as a bridge between the collagen I fibers and other extracellular components including decorin, fibromodulin, and TNX [Zou et al., 2014]. Deficiency of this collagen results in lax tissues due to a mechanical problem with the ECM. Because collagen XII is expressed in the muscle ECM, its absence results in disorganized patterning, abnormal force transmission, and other biomechanical alterations resulting in myopathy. Its absence in skin and tendons would explain the overlapping EDS manifestations.

Allelic Heterogeneity

To date, nine patients from five families with myopathic EDS have been reported [Hicks et al., 2014; Zou et al., 2014; Punetha et al., 2016]. The mutations include four heterozygous missense mutations that have an autosomal dominant mode of inheritance: c.7167 T>C, p.(Ile2334Thr), c.C5893T, p.(Arg1965Cys), 8329G>C, p.(Gly2777Arg), and c.G8357A, p.(Gly2786Asp), and one homozygous frameshift mutation, introducing a PTC, associated with autosomal recessive inheritance (c.8006 +1 G>A, p.(2567Asp>Phefs*2).

Clinical Description

At present, nine patients from five families have been reported (Table S1). Their age at publication ranged from birth to 48 years (Table S1) [Hicks et al., 2014; Zou et al., 2014; Punetha et al., 2016]. The severity ranges from a severe autosomal recessive neonatal form that was described in two boys born to a consanguineous couple, to a milder autosomal dominant form that presents in childhood with muscle weakness, large joint contractures, and variable degrees of joint hypermobility and hypertrophic scarring. The phenotype may not be fully understood as there are so few reported cases.

The hallmark of the disorder is muscle weakness that is present in infancy or childhood and is associated with proximal large joint contractures and distal joint hypermobility. Characteristically, the muscle weakness tends to get better with age until young adulthood with some deterioration in the 4th decade.

- Reproductive, including pregnancy
  One patient was born after a selective caesarian section because of oligohydramnios, intrauterine growth restriction, and breech presentation.

- Craniofacial features
  One patient displayed facial asymmetry with skull flattening at birth, and mild dysmorphic facial features, including micrognathia, high palate, short nose, big dysplastic ears. High arched palate was reported in two other patients.
- Musculoskeletal
  Congenital proximal joint contractures in combination with distal joint hypermobility were reported in three patients. One patient was reported to have proximal contractures at birth without mentioning of distal join hypermobility. At age 7 years, contractures had disappeared but she had joint hypermobility in childhood. All patients tended to have congenital kyphosis, in conjunction with torticollis in one, and some developed scoliosis. The patients reported by Hicks et al. [2014] (n = 5) developed long finger flexions (n = 4), rigid spine (n = 2), flexion contractures of knee (n = 2), elbow (n = 1), and wrist (n = 1). Hip dislocation or subluxation was reported in two patients. One patient had a pectus excavatum.
- Skin and integument
  Reported skin features include hypertrophic scars (n = 3), atrophic scars (n = 2), hyperkeratosis pilaris (n = 1).
- Neuromuscular features and motor development
  The siblings reported by Zou et al. [2014] (homozygous mutation) had the most severe phenotype with profound muscle hypotonia at birth, poor feeding and swallowing, and night-time hypoventilation, with need for tube feeding and non-invasive night-time ventilation. They had a severe delay in motor development, and they eventually were able to reach a sitting position, but were never able to stand or walk [Zou et al., 2014]. All other patients had congenital muscle hypotonia, with delayed gross motor development, but symptoms seemed to improve over time. None of these patients remained non-ambulatory. In one adult, muscle strength was reported to deteriorate again in his late 30s.

  Reported abnormalities on muscle biopsy include myopathy with variability in fiber diameter, without overt sins of degeneration or regeneration. In one instance, there was decreased laminin B1. CK was elevated in several, but not all patients (of note: It was normal in the siblings with the most severe, autosomal recessive form).

Genotype–Phenotype Correlation and Penetrance

There appears to be a clear genotype–phenotype correlation. In general, from the five mutations described so far it seems that missense mutations that affect critical residues in the molecule have a dominant-negative effect and result in variable degrees of severity. There are no documented instances of non-penetrance. There is significant variability, within and between families, with individuals carrying the same mutation presenting with different degrees of severity.

The one family with the autosomal recessive condition harbors a homozygous loss of function mutation. The affected siblings have a more severe form of the condition. Reportedly carrier parents walked late (almost at 2 years of age); therefore there appears to be a mild phenotype (dominant) in the carriers and a severe phenotype (recessive) in the individuals that are homozygous [Zou et al., 2014].

Penetrance is unknown.

Management

There are no described treatments for this group of disorders. Anticipatory guidance should focus on preventing complications and improving the presenting symptoms. This may include physical therapy for the contractures (since they tend to resolve over time), and monitoring for any signs of feeding or respiratory difficulties, in particular nocturnal hypoventilation. If the latter is present, then assisted non-interventional ventilation at night may be indicated.

Differential Diagnosis

- Bethlem and Ullrich myopathies (Collagen type VI-related disorders)
- Kyphoscoliotic EDS
- Hypermobile EDS
- Classical EDS
- Classical-like EDS

PERIODONTAL EDS (pEDS)

Synonyms: EDS type VIII, Ehlers–Danlos Syndrome periodontitis type, Ehlers–Danlos Syndrome periodontosis type.

The History of Periodontal EDS

McKusick [1972] described a "unique condition" in a patient with EDS-like features, that is, lesions on the shins, slow-healing breaks in the skin, atrophic scars, and absorptive periodontitis with early loss of the teeth. Five years later, Stewart et al. [1977] published a similar case and classified this new variant as EDS VIII. Since then, pEDS has been reported in 32 case reports and seven pedigree analyses. Extensive periodontal destruction with early onset is a core finding of periodontal EDS, mostly in combination with striking pre-tibial plaques and tissue fragility. There is greater variability in other clinical features.

In the past, the delineation of pEDS as a specific phenotype was hampered by the relatively high prevalence of chronic periodontitis, with an estimated range from 19 to 83% depending on age and severity [Demmer et al., 2010]. Therefore, periodontal disease in vascular and other EDS types could be a coincidence of two unrelated diseases. These historical overlaps between pEDS and other EDS subtypes have confused the phenotype. While the majority of pEDS patients had vEDS excluded through collagen protein analysis, this does not completely exclude a *COL3A1* variant being causative in some of the older cases.

Also, joint hypermobility is a common feature in the general population, which complicates accurately ascertaining co-segregation of these two traits. The Villefranche EDS nosology group noted these difficulties in distinguishing this rare disorder from other hereditary disorders of connective tissue [Beighton et al., 1998]. In 2003, pEDS was mapped to a 7 cM (5.8 MB) interval on

chromosome 12p13 in three families [Rahman et al., 2003], but no candidate gene was identified. In 2016, an international consortium published 19 independent families comprising 107 individuals with pEDS to identify the genetic locus [Kapferer-Seebacher et al., 2016]. Included were samples of eight previous case reports and pedigree studies [Stewart et al., 1977, Hartsfield and Kousseff, 1990, Rahman et al., 2003, Reinstein et al., 2011, Reinstein et al., 2012, Reinstein et al., 2013, Cıkla et al., 2014, George et al., 2016]. In 17 of these families, heterozygous missense or in-frame insertion/deletion mutations in *C1R* (15 families) or *C1S* (two families) were identified. *C1R* and *C1S* are contiguous genes in the previously reported linkage region on chromosome 12p13, and encode subunits C1r and C1s of the first component of the classical complement pathway.

The prevalence of pEDS is unknown.

The Mechanisms of Disease

Complement is a major element of antimicrobial host defense through its ability to recognize pathogens and limit infection in the early phase after exposure to microorganisms. The classical pathway of complement is triggered by C1, a complex comprising a recognition subunit C1q and two modular serine proteases (SPs) C1r and C1s [Budayova-Spano et al., 2002]. C1r and C1s are assembled into a Ca(2+)-dependent C1s—C1r—C1r—C1s tetramer which associates with the recognition protein C1q [Gaboriaud et al., 2014; Rossi et al., 2014]. After C1 binding to immune complexes, C1r auto-activates and then cleaves C1s which in turn cleaves C4 (into C4a and C4b) and C2 (into C2a and C2b) to form the classical pathway C3 convertase (C4b2a) [Patrick et al., 1970; Thielens et al., 1982; Amano et al., 2008].

One attractive hypothesis for the pathomechanism of pEDS is altered binding of the C1r—C1s tetramer or prematurely cleaved fragments to C1q or soluble procollagens. This could affect C1 function or interfere with procollagen processing within the ER. Moderate enlargement of the ER cisterns documented in vitro in dermal fibroblasts may reflect retention of malprocessed molecules but could also reflect boosted expression/production of collagen as a feed-back response to decreased deposition of mature collagen into the matrix. The exact pathomechanism of pEDS remains to be clarified.

Allelic Heterogeneity

Heterozygous missense or in-frame insertion/deletion variants in *C1R* were detected in 15 families (comprising 76 affected individuals), and heterozygous missense or in-frame insertion/deletion variants in *C1S* were detected in two families (comprising 16 affected individuals). These variants involve the C1r/C1s, C1r/C1r, or C1r/C1q interfaces or the hinges between interaction and catalytic domains of C1r and C1s. Variants never involved the catalytic domain of C1r or C1s [Kapferer-Seebacher et al., 2016].

Clinical Description

In the review on clinical features, we distinguished between individuals with confirmed mutations in *C1R* or *C1S* and other case reports. See Table S1 for the prevalence of clinical features in the molecularly confirmed patients (Representative pictures of the phenotype are given in Fig. 8).

- Craniofacial features
  Stewart et al. [1977] included a photograph of the reported patient with an "aesthenic build." Dysmorphic facial features were not described by Rahman et al. [2003]. In the dysmorphology literature, Cunniff and Williamson-Kruse [1995] described a triangular face, prominent eyes, long nose, and short philtrum. Biesecker described a paucity of subcutaneous fat with prominent nose and larynx [Biesecker et al., 1991]. Hartsfield noted the phenotypic overlap with vEDS [Hartsfield and Kousseff, 1990].

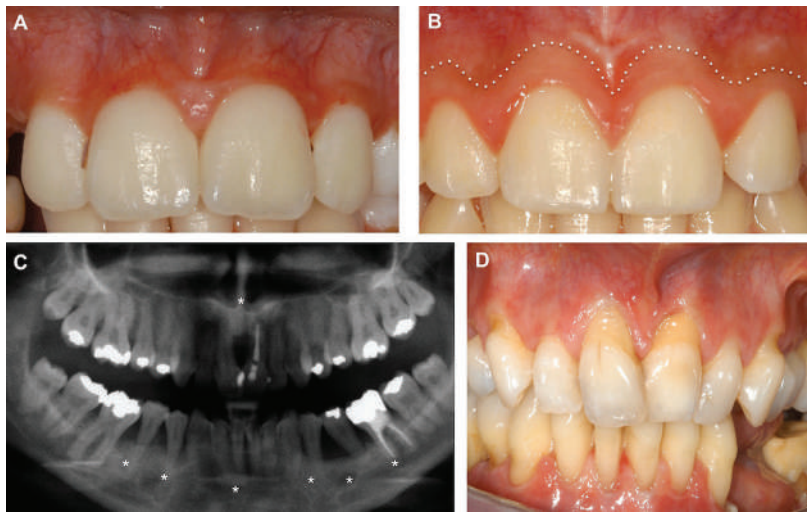

Figure 8. (**A**) Gingival tissues of a child affected with pEDS. The keratinized gingiva is missing; the oral mucosa extends to the free gingival margin and the interdental papillae and is very fragile. (**B**) Gingival tissues of a non-affected child. The gingiva is keratinized and is tightly bound to the underlying periostum via collagen structures, and performs a protective function during mastication. The border between gingiva and alveolar mucosa is the mucogingival junction (dotted line). The oral mucosa is non-keratinized and only loosely connected to the periostum; therefore, it is more fragile. (**C**) Dental radiograph of an affacted individual, at aged 29. Notice severe periodontal bone loss (asteriks). (**D**) Clinical picture of the same individual, at age 30. Premolars in the left mandible have been lost in the meantime without periodontal pocketing and despite good oral hygiene. Notice the lack of keratinized gingiva and gingival recessions (receeding gums) (Images kindly provided by Dr. Ines Kapferer-Seebacher, with permission).

- Musculoskeletal system
  In 93 individuals with *C1R* or *C1S* mutations reported by Kapferer-Seebacher et al. [2016] joint hypermobility was reported in 56% of patients, mostly affecting the fingers (30%), the elbows (19%), knees (11%), hips, wrist, and ankle (3%). Marfanoid habitus, scoliosis, osteoarthritis, flat feet, and hernia were not consistent features [Kapferer-Seebacher et al., 2016].
- Skin and integument
  Pretibial plaques with or without haemosiderosis are a consistent feature in most reports. Clinically, the lesions resemble necrobiosis lipoidica, but generally differ histologically. Fibrosis and haemosiderin deposits were reported, as opposed to interstitial and palisade granulomas and/or microangiopathy 19. Buckel and Zaenglein [2007] confirmed similar findings. Easy bruising, skin fragility, and (mild) hyperelasticity of the skin have been reported in the majority of cases. There is a single report of an associated vasculitis in the absence of pretibial lesions [Hoffman et al., 1991]. In 93 individuals with *C1R* or *C1S* mutations reported by Kapferer-Seebacher et al. [2016], consistent cutaneous findings were pretibial discolorations (83%), easy bruising (96%), skin fragility (83%), and (mild) hyperelasticity of the skin (73%). Atrophic scars were present in 50% of cases [Kapferer-Seebacher et al., 2016].
- Cardiovascular involvement
  Until recent, pEDS has not been associated with catastrophic vascular complications or hollow visceral rupture that arise in vEDS. It is of note that the father of the case reported by Stewart et al. [1977] had duodenal rupture and subsequent collagen protein analysis showed a normal collagen (I:III) ratio. Recently, a 42-year-old woman was reported with pEDS and a ruptured "blood blister" shaped aneurysm of her left middle cerebral artery [Cıkla et al., 2014].
  Kapferer-Seebacher et al. [2016] reported a prevalence of 16% for vascular complications (cerebral aneurisms or aortic dissection), and one individual with three events of organ rupture (once duodenum, twice lung). As pEDS patients are not routinely checked for aneurisms, there might be also unrecorded cases. Additionally, many of the reports describe pediatric patients and there is a great need for longterm follow-up.
- Dental involvement
  Early-onset periodontitis with extensive periodontal destruction and loss of teeth, starting in childhood or adolescence, is one of the defining hallmarks of pEDS, and was present in all reported cases and in 99% of individuals with confirmed *C1R/C1S* mutations. A clear demarcation to the diagnosis of chronic or aggressive periodontitis is essential. Typically, periodontal destruction in pEDS is not accompanied by periodontal pocket formation but by receding gums (personal observation IK). Prior to periodontitis, affected individuals may present with extensive gingival inflammation in response to mild dental plaque accumulation. A characteristic recently described feature is a striking lack of attached gingiva causing oral tissue fragility (Fig. 1) [Kapferer-Seebacher et al., 2016].
- Additional laboratory findings
  - Biochemistry:
    Biochemical analysis of collagen in cultured skin fibroblasts did not show abnormalities in the production and secretion of type I, III, and V collagens in several case reports and also in eight individuals with confirmed mutations in *C1S/C1R* [Biesecker et al., 1991; Cunniff and Williamson-Kruse, 1995; Kapferer-Seebacher et al., 2016]. In contrast, Mataix et al. [2008] reported a reduced rate of collagen (I) and collagen (III) synthesis compared to control samples. Lapiere and Nusgens [1981] initially reported a family with pEDS and reduced collagen III protein from skin, but later reported that a repeat analysis had not been able to replicate this.
  - Skin histology and ultrastructure:
    It is of note that there is variation in collagen ultrastructure depending on the site of biopsy in the general population (Pope and Vandersteen, personal observations). Many patients with pEDS in the literature had biopsy from pre-tibial lesions, others at the standard site. There were no consistent findings, but evidence of collagen fibril size, packing, morphology, and ER dilatation are all reported.
    Electron microscopy examination of skin reported in seven individuals with *C1R/C1S* mutations showed decreased collagen content, abnormal variation in collagen fibril diameter and some abnormally shaped fibrils [Rahman et al., 2003; Reinstein et al., 2012, 2013; Kapferer-Seebacher et al., 2016], which is in line with further reports [Kobayasi, 2004; Mataix et al., 2008]. Dermal collagen fibers showed some variability in the density of the packing and a few areas of kinking. The size uniformity does not support vEDS, while the kinking is nonspecific. Additionally, patients' fibroblasts showed an increased proportion of dilated rough ER (RER) cisternae [Reinstein et al., 2012; Kapferer-Seebacher et al., 2016].
    Dyne et al. [1993] reported collagen depletion and a larger number of small elastin fibrils; ultrastructure showed occasional serrated collagen fibrils, with normal fibril diameter.
  - Immunology:
    Hoffman et al. [1991] reported a patient with severe periodontitis, valvular heart disease, osteocondylar and phalangeal osteolysis in the absence of pretibial hyperpigmentation. This patient had intractable vasculitis and had a T cell response to type I collagen. Other patients have not had evidence of vasculitis. The case has some similarities to patients described with Singleton Merton syndrome, (premature dental loss, aortic calcification, and osteoporosis, OMIM 182250). It is doubtful whether this patient had true pEDS.

    Kapferer-Seebacher et al. [2016] reported a prevalence of 40% for recurrent infections like otitis media, herpes zoster, bladder infections, empyema, kidney infections, or

pneumonia. There were single patients with autoimmunologic disorders like Sjögren syndrome, rosacea, and Crohn's disease [Kapferer-Seebacher et al., 2016].

Management

There is no curative treatment for this disorder. A recent review of the dental management of EDS recommended special care regarding mucosal fragility, bleeding, temporomandibular joint hypermobility, and local anaesthetic resistance [Tulika and Kiran, 2015]. Management of periodontal disease requires lifelong biofilm management including intense oral hygiene instructions and nonsurgical debridement about every 3 months. Systemic antibiotics may be indicated. Conservative surgical management is recommended because of difficulties with fragile periosteal skin flaps and suture tears.

Differential Diagnosis

- Vascular EDS
- Classical EDS
- Hypermobile EDS
- Periodontal diseases

Periodontal diseases range from mild and reversible gingivitis to irreversible loss of periodontal attachment resulting in tooth loss. "(Plaque-induced) gingivitis" is an inflammation solely of the gums in response to bacterial biofilms, and is characterized by bleeding on probing. "Periodontitis" is characterized by inflammation of the gingiva and destruction of the periodontal tissues, which are the gingiva, the cementum, the periodontal ligament, and the alveolar bone. Periodontal bone loss is diagnosed radiologically or clinically with a periodontal probe. "Gingival recession" (receding gums) in general is the exposure of the tooth roots. It might be an accompanying feature of periodontitis, and in this case the tooth root is exposed also interdentally. Gingival recession might also present only on the buccal or lingual aspects of the tooth. In this case, it can, for example, be associated with a thin gingival biotype and intencse tooth brushing, but not with periodontitis.

"Chronic periodontitis" prevalence estimates ranged from 19 to 83% depending on age and severity [Demmer et al., 2010]. Severe periodontitis with a mean prevalence of 11.2% is the sixth-most prevalent condition in the world [Kassebaum et al., 2014]. The typical patient is over 30 years of age, and the amount of bone destruction is consistent with the presence of plaque and calculus [Armitage, 2004]. In general, the disease progresses slowly but there may be bursts of destruction. In addition, the rate of disease progression can be modified by local factors, systemic diseases, and extrinsic factors such as smoking or emotional stress.

"Aggressive periodontitis" prevalence estimates range from 0.1% in Caucasians residing in north and mid Europe to 5% in African populations [Albandar, 2014]. The primary features are rapid attachment loss in otherwise healthy individuals and familial aggregation, usually affecting persons under 30 years of age [Albandar, 2014]. Some types of aggressive periodontitis seem to be inherited in a Mendelian manner, and both autosomal modes and X-linked transmission have been proposed [Meng et al., 2011]. However, review of pedigree analysis, linkage and linkage disequilibrium studies have so far been inconclusive [Meng et al., 2011].

There are several "monogenic syndromes with significant periodontitis" as part of the clinical phenotype. The majority of syndromes with severe periodontal destruction in childhood are inherited as autosomal recessive or X-linked traits and are associated with neutrophil dysfunction, for example, congenital and cyclic neutropenia (OMIM 202700), Chediak–Higashi syndrome (OMIM 214500), leukocyte adhesion deficiencies types I, II, and III (OMIM 116920; OMIM 266265; OMIM 612840), WHIM (OMIM 193670), Cohen Syndrome (OMIM 216550), and agranulocytosis (OMIM 610738).

Conditions with more complex dermatological phenotypes include Kindler syndrome (hereditary acrokeratotic poikiloderma OMIM 173650), Papillon–Lefevre syndrome and cathepsin C associated phenotypes (*602635), hypotrichosis osteolysis periodontitis (OMIM 607658). Multiple loci associated with an aggressive periodontitis have been reported (OMIM 170650) [Hart and Atkinson, 2007]. The Singleton–Merten syndrome (OMIM 182250) with periodontal destruction and aortic calcification has recently been shown to result from dominant mutations in the *IF1H1* gene [Rutsch et al., 2015].

Hypophosphatasia (OMIM 146300) is a highly variable autosomal dominant disorder associated with enamel hypoplasia, early loss of primary dentition, bowed long bones, and osteopenia. Odontohypophosphatasia is the least severe form of hypophosphatasia, characterized by premature exfoliation of primary and/or permanent teeth in the absence of skeletal system abnormalities. It is associated with a low circulating alkaline phosphatase.

FUTURE RESEARCH AND GAPS

During the last decade, there has been an explosion of diverse but overlapping novel EDS or EDS-like phenotypes for which molecular defects have been identified in an array of new genes, as illustrated above. The genomic era promises to shed additional light on unsolved forms of Ehlers–Danlos syndrome. However, while our knowledge of the molecular basis of EDS has greatly progressed since the Villefranche Nosology, our understanding of the pathophysiological mechanisms underlying these conditions remains very limited, and elucidation of the genetic basis has not

translated to improved clinical management strategies.

However, while our knowledge of the molecular basis of EDS has greatly progressed since the Villefranche Nosology, our understanding of the pathophysiological mechanisms underlying these conditions remains very limited, and elucidation of the genetic basis has not translated to improved clinical management strategies.

Future research could focus on different aspects, including:

- Natural history studies
- Quality of life studies
- The creation of an international patient register, with prospective collection of detailed information regarding genotype and phenotype. This information should, among others, help address questions regarding:
  - genotype–phenotype correlations
  - prevalence
  - clinical variability (inter- and intrafamilial)
  - age-dependent organ-system involvement outcomes
  - risk related to pregnancy and delivery
- Development of surveillance, and management and care guidelines, including pain management
- Collection of tissue samples for the study of the pathogenetic basis of disease
- Development of animal models for study of pathogenetic mechanisms and for preclinical studies
- Identification of biomarkers to follow evolution of disease
- With the advent of next-generation sequencing techniques, many variants of unknown significance are being identified. As such there is a need for the development of functional tests to study the pathogenic nature of these variants
- Identification of therapeutic targets

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ARTICLE

The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents, and Adults Diagnosed With Joint Hypermobility Syndrome/Hypermobile Ehlers Danlos Syndrome

RAOUL H.H. ENGELBERT,* BIRGIT JUUL-KRISTENSEN, VERITY PACEY, INGE DE WANDELE, SANDY SMEENK, NICOLETA WOINAROSKY, STEPHANIE SABO, MARK C. SCHEPER, LESLIE RUSSEK, AND JANE V. SIMMONDS

New insights into the phenotype of Joint Hypermobility Syndrome (JHS) and Ehlers-Danlos Syndrome-hypermobile type (hEDS) have raised many issues in relation to classification, diagnosis, assessment, and treatment. Within the multidisciplinary team, physical therapy plays a central role in management of individuals with hypermobility related disorders. However, many physical therapists are not familiar with the diagnostic criteria, prevalence, common clinical presentation, and management. This guideline aims to provide practitioners with the state of the art regarding the assessment and management of children, adolescents, and adults with JHS/hEDS. Due to the complexity of the symptoms in the profile of JHS/hEDS, the International Classification of Functioning, Disability and Health (ICF) is adopted as a central framework whereby the umbrella

Dr. Jane Simmonds is Chair of the International Ehlers Danlos Syndrome Physical Therapy Clinical Guidelines working group. She is a Senior Teaching Fellow at Great Ormond Street Institute of Child Health, University College London and clinical lead in the Hypermobility Unit at the Hospital of St John and St Elizabeth in London. Jane is an active researcher and has more than 20 years of clinical experience working with this patient group. She is physiotherapy advisor to three UK patient charities and has published widely and presents regularly at international conferences in the field of hypermobility, bone health and Ehlers Danlos Syndrome.

Prof. Raoul Engelbert is Professor of Physiotherapy at the University of Amsterdam (AMC) where focussing on transition of care in complex patients. He is the Director of Research, Center of Research ACHIEVE, Faculty of Health, University of Applied Sciences Amsterdam and has researched for over two decades and published widely in the field of heritable disorders of connective tissue, hypermobility and Ehlers Danlos Syndrome.

Professor Birgit Juul Kristensen is Associate Professor, Research Unit of Musculoskeletal Function and Physiotherapy, University of Southern Denmark, and Professor at the Institute of Occupational Therapy, Physiotherapy and Radiography, Bergen University College, Norway. She is an active researcher and has published widely in the field of musculoskeletal dysfunction and hypermobility.

Dr. Verity Pacey is a Senior Lecturer in the Department of Health Professions, Macquarie University, and Senior Physiotherapist at The Children's Hospital at Westmead, with over 10 years clinical and research experience working with children and adolescents with symptomatic hypermobility. Verity's research focuses on the assessment, treatment and quality of life of children and adolescents with connective tissue disorders.

Dr. Inge De Wandele is a physiotherapist at the Center for Medical Genetics at Ghent University Hospital, Belgium. The topic of her PhD was the presence of dysautonomia in EDS. Her current clinical work and research focus on adapted physiotherapy for patients with heritable connective tissue disorders and generalized joint hypermobility.

Stephanie Sabo is a senior physical therapist who practices in outpatient developmental paediatrics evaluating and treating infants, children and adolescents. She is the leader of the Joint Hypermobility Evidence Based Practice Team at Cincinnati Children's Hospital Medical Center. She has also participated in program developmental for an intensive based therapy program for children with Joint Hypermobility Syndrome and EDS. She is involvement in multiple research studies that relate to intensive therapy services and patients with EDS/Hypermobility.

Nicoleta Woinarosky is a Health Resource Consultant for the Improving the Life of Children and Families Foundation (ILC), Nicoleta draws on her education (Master's thesis on The Effects of Exercise/Physical Activity on Chronic Pain and Pain Related Mental Health Issues), volunteer work (teaching chronic pain self-management and physical education to seniors), and experience (living with EDS and chronic pain) to provide evidence-based information to health professionals and persons living with chronic pain syndromes including EDS. While recognizing the need for pain medications, she is passionate about the physical and psychological benefits of exercise.

Sandy Smeenk is the co-Founder and Executive Director of the Improving the Lives of Children and Families with Chronic Pain Charitable Foundation ("ILC"), a national charity catalyzing efforts to address the burden of pain through evidence-based awareness and education, systems change and knowledge translation. She has led substantiate initiatives to influence Ministry of Health mandated programs for people with rare diseases utilizing Ehlers-Danlos Syndrome (EDS) as a model of optimal care.

Mark Scheper is a physiotherapist and clinical movement scientist. Currently working as a senior lecturer physiotherapy at the University of Applied sciences Amsterdam and a researcher affiliated to the Academic Medical Center Amsterdam, department of rehabilitation. His current research focus is on disability and chronicity in children with chronic diseases, with special attention for diseases of connective tissue.

Dr. Leslie Russek is an Associate Professor teaching musculoskeletal physical therapy and research courses in the Clarkson University Doctor of Physical Therapy program. She has been researching hypermobility syndrome for almost 20 years, and treats patients in her areas of specialty: hypermobility, fibromyalgia, and headaches.

*Correspondence to: Prof. Raoul H.H. Engelbert, ACHIEVE, Centre for Applied Research, Education of Physiotherapy, Faculty of Health, University of Applied Sciences Amsterdam, Amsterdam, The Netherlands. E-mail: r.h.h.engelbert@hva.nl

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term of disability is used to encompass functions, activities and participation, as well as environmental and personal factors. The current evidence-based literature regarding the management of JHS/hEDS is limited in size and quality and there is insufficient research exploring the clinical outcomes of a number of interventions. Multicenter randomized controlled trials are warranted to assess the clinical and cost-effectiveness of interventions for children and adults. Until further multicenter trials are conducted, clinical decision-making should be based on theoretical and the current limited research evidence. For all individuals diagnosed with JHS/hEDS, international consensus and combined efforts to identify risk profiles would create a better understanding of the pathological mechanisms and the potential for optimizing health care for affected individuals.

KEY WORDS: physical therapy; diagnostics; treatment; guidelines; joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome; international classification of functioning

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INTRODUCTION

In the last decade, scientific research in the area of hypermobility related disorders has grown. Scientific exploration has not only provided new insights into the phenotype of Joint Hypermobility Syndrome (JHS) and Ehlers-Danlos Syndrome-hypermobility type (hEDS), but it has also raised many issues in relation to classification, diagnosis, assessment, and treatment. We will refer to these overlapping/indistinguishable clinical entities [Tinkle et al., 2009; Remvig et al., 2011], in this paper as JHS/hEDS. Within the multidisciplinary team, physical therapy plays a central role in management of individuals with hypermobility related disorders [Simmonds and Keer, 2007; Grahame and Hakim, 2008; Scheper et al., 2013, 2016a]. The reported prevalence of JHS/hEDS in adult physical therapy outpatient musculoskeletal settings has been reported to be between 30% [Connelly et al., 2015] and 55% [Clarke and Simmonds, 2011]. Despite the relatively high incidence of JHS/hEDS, recent research has found that many physical therapists and other clinicians are not familiar with the diagnostic criteria, prevalence, or common clinical presentation of affected individuals [Billings et al., 2015; Lyell et al., 2016; Russek et al., 2016], whereas clinicians also experience a lack of awareness of this condition [Billings et al., 2015; Rombaut et al., 2015a; Terry et al., 2015; Lyell et al., 2016]. This guideline aims to provide physical therapists and other clinicians with the state of the art regarding the assessment and management of children, adolescents, and adults with JHS/hEDS. In preparing the guideline, the quality of evidence is graded according to the GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation) [Balshem et al., 2011]. The paper has been written based on a synthesis of best evidence available and consensus opinion of an international group of researchers, clinicians, and patient representatives. Evidenced-based assessment and treatment strategies should be used where available. In the absence of these, therapists should be guided by clinical reasoning and assessment and treatment should be tailored to the individual patient's needs.

Due to the complexity of the symptoms in the profile of JHS/hEDS, the International Classification of Functioning, Disability and Health (ICF) is adopted as an overarching framework [Atkinson and Nixon-Cave, 2011]. Disability, according to the World Health Organization, is an umbrella term covering functions, activities and participation, as well as environmental and personal factors [WHO, 2015]. In children, adolescents and adults with JHS/hEDS, impairments in the ICF domain body and function may result in decreased functional capacity and restrictions in participation.

The Beighton tests for assessing generalized joint hypermobility (GJH) are widely used and were described about 40 years ago, but only with photos and unclear legends accompanying [Beighton et al., 1973]. Considerable variation exists in the utilization of this tool, the cut-off level used for a positive test and in the criteria definition of GJH [Remvig et al., 2007]. The Beighton score, consisting of five clinical maneuvers, is scored dichotomously (0/1) from which a total score, ranging from 0 to 9, is calculated. It is a widespread belief that GJH is present in adults with a Beighton score of $\geq$4 as described in the diagnostic Brighton criteria [Grahame et al., 2000] and for hEDS $\geq$5 [Beighton et al., 1998]. Other cut-off points for detecting the presence of GJH have been proposed, especially for children, among others $\geq$6, $\geq$7, and $\geq$8 [Jansson et al., 2004]. Although these testing procedures and diagnostic criteria have been in place for years and are considered the gold standard from infancy to old age [Adib et al., 2005], criticism has arisen from clinicians and researchers about its diagnostic and clinical usefulness and predictive validity [Juul-Kristensen et al., 2017]. Beyond the Beighton scale, other assessment measures should be utilized within each domain of the ICF and clinical reasoning should underpin where appropriate, and where possible evidence-based, tailored treatment strategy.

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JHS/hEDS IN CHILDHOOD

Children with JHS/hEDS may experience multiple impairments as a result of increased laxity of the connective tissues, incorporating complaints in all domains of the ICF as illustrated in Figure 1 [Pacey, 2014].

Pain and Health Related Quality of Life

In JHS/hEDS pain is often present. It is not known why some children develop pain and other symptoms, while others do not. The primary hypothesis regarding the development of musculoskeletal complaints is localized biomechanical overload during activity, with a high risk of repetitive trauma. Generalized joint instability may cause the occurrence of micro-traumas in joint surfaces, leading toward adaptation and compensation of movement patterns, consequently causing overload in other areas of the musculoskeletal system [Ferrell et al., 2004]. Pain exacerbated by activity is a distinguishing feature of JHS/hEDS. Eighty-one percent of children with JHS attending a rheumatology service reported that their pain was exacerbated by exercise [Adib et al., 2005]. All of these children reported experiencing pain in the 24 hr following exercise: 65% immediately post exercise, 59% later that evening, and 50% the following morning. The knee, a weight-bearing joint of the lower limb, and the shoulder, are the most commonly affected sites of pain in children with JHS/hEDS [Adib et al., 2005; Pacey et al., 2015a]. Parent and child self-reported pain intensity is highly correlated [Pacey et al., 2015b], although parents have been shown to underestimate their child's perception of pain [Kemp et al., 2010]. Recently it was shown that children and adults diagnosed with JHS/hEDS are not only characterized by GJH, and chronic pain, but also by the presence of generalized hyperalgesia (GHA) [Scheper et al., 2016b]. The presence of GHA may indicate involvement of the central nervous system in the development of chronic pain and may not only provide insights as to the phenotype of GJH related disorders, but also indicates diagnostic qualities that may be useful in clinical practice [Scheper et al., 2016c].

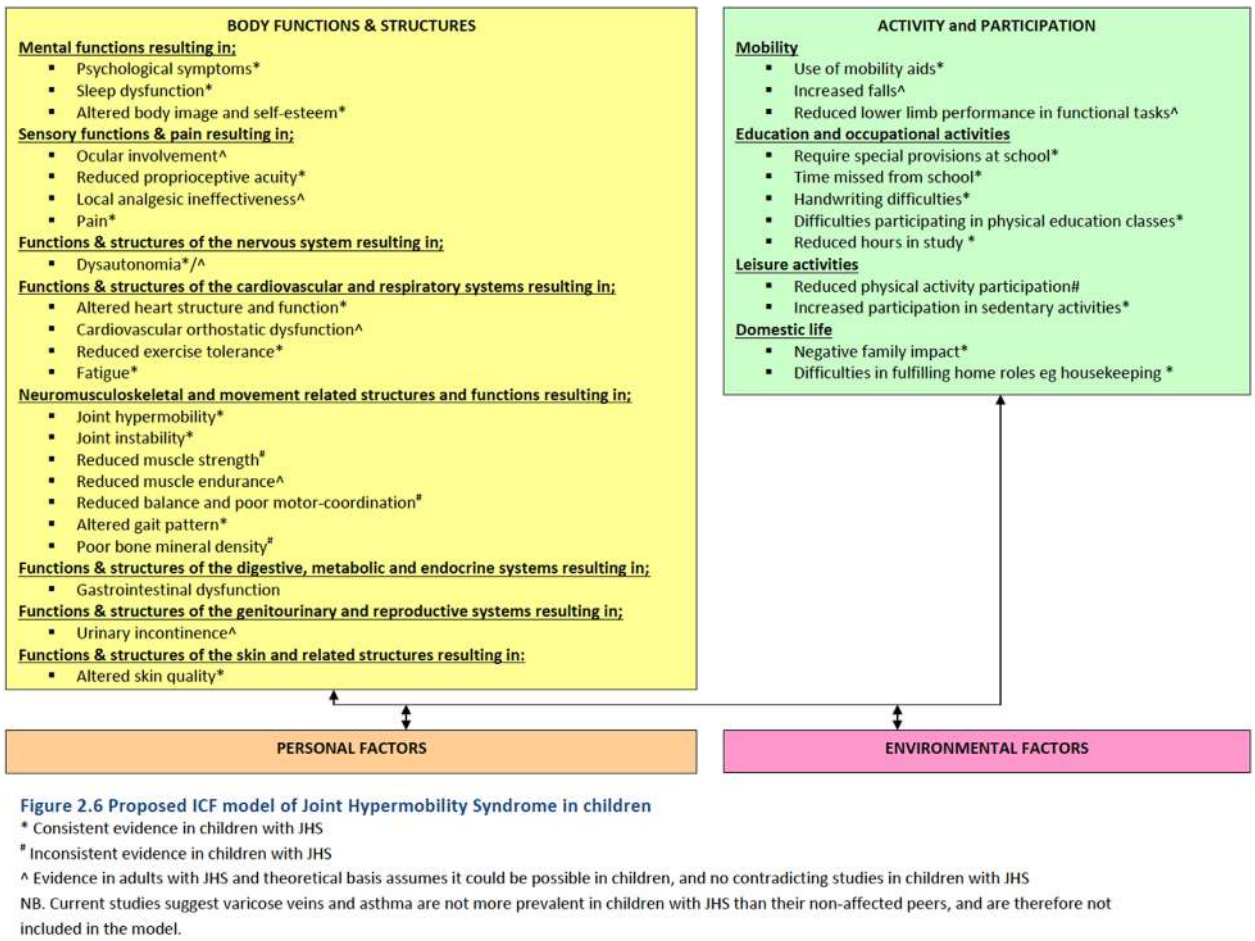

Figure 1. Proposed ICF model for JHS in children by Pacey [2014].

Children aged 9–12 years old with JHS/hEDS and knee pain report lower Health Related Quality of Life (HRQL) than healthy children at the same age [El-Metwally et al., 2005; Fatoye et al., 2011]. Children with JHS/hEDS experience poor HRQL and disabling fatigue, with parent scores providing a good proxy. Pain, fatigue, and the presence of stress incontinence symptoms have been demonstrated to have the greatest impact on their HRQL [Pacey et al., 2015a].

Dysfunction in JHS/hEDS can be the result of chronic pain but also due to involvement of multiple systems, psychological distress and related disability. How chronic pain and systemic deficits come into effect and interact with each other is currently unknown. The specific problems related to the GJH related syndromes as compared with other chronic pain syndromes are still challenging for most clinicians and scientists due to many issues surrounding etiology, disease classification, diagnostics, and treatment [Scheper et al., 2015].

Proprioception, Muscle Strength, and Balance

Another important factor within the biomechanical pathway in JHS/hEDS patients may be reduced proprioceptive acuity, which has been suggested to be important for the occurrence of gait abnormalities and musculoskeletal pain [Smith et al., 2013]. Decreased knee joint proprioception in combination with decreased knee flexor and extensor muscle strength has also been reported in children with JHS/hEDS [Fatoye et al., 2009]. This was partly confirmed in another study of adolescents and adults with JHS/hEDS where the reflex in the knee extensors was absent in 47% of 15 patients, compared with a healthy control group in which this reflex was present in all subjects [Ferrell et al., 2007]. Decreased muscle strength is associated with activity limitations in JHS/hEDS patients. Joint proprioception has been found to influence this association and should be considered in the development of new treatment strategies for patients with JHS/hEDS [Scheper et al., 2016a]. Children between 8 and 16 years of age with JHS/hEDS assessed by the balance subsection of the Bruininks–Oseretsky test of motor proficiency (2nd edition), have been found to have significantly reduced balance [Schubert-Hajlmarsson et al., 2012].

Decreased muscle strength is associated with activity limitations in JHS/hEDS patients. Joint proprioception has been found to influence this association and should be considered in the development of new treatment strategies for patients with JHS/hEDS.

Joint Instability

Dislocations or subluxations in more than one joint, or in one joint on more than one occasion, form part of the diagnostic criteria for JHS/hEDS. Consequently, recurrent joint instability episodes are commonly reported by children with JHS/hEDS, with the knee, ankle, and shoulder as the most affected joints [Pacey et al., 2015b].

Extra-Articular Features

In children with JHS/hEDS involvement of not only the skin and joints but also other organ systems consisting of different types of collagen, for example, bone and blood vessels, indicates a more systemic rather than local involvement. In children 8–9 years old with JHS/hEDS, lower ultrasound values in bone, higher degradation products in urine, higher skin extensibility, and lower blood pressure have been observed in comparison with a non-symptomatic hypermobile group [Engelbert et al., 2003]. High levels of urinary incontinence are reported in children with JHS/hEDS [Pacey et al., 2015a], where such systemic concerns cause significant discomfort and impacts significantly on function and quality of life, a referral to a pediatrician or system specialist is required [de Kort et al., 2003].

A relationship between JHS/hEDS and a characteristic neurodevelopmental profile affecting coordination is emerging. Common symptoms shared between children with JHS/hEDS and those with developmental coordination disorder (DCD) have been highlighted [Kirby and Davies, 2007]. Multiple clinical features of JHS/hEDS, such as "double-jointedness," joint pain, flat feet, easy bruising and dysautonomic symptoms, have been found to be significantly more frequent in children with DCD than in children without [Kirby and Davies, 2007]. Among children with JHS presenting to health care services, 36% report poor coordination and 48% report clumsiness, and problems with gait, falls, and coordination are the second most common presenting complaint [Adib et al., 2005]. Overall gross motor abilities have been shown to be reduced in 22% of children (mean 8 years of age) with JHS/hEDS measured with the Movement Assessment Battery for Children [Hanewinkel-van Kleef et al., 2009].

Symptoms of gastrointestinal dysfunction (GID) and dysautonomia may commence very early in a child's life. The most common GID symptoms include gastrointestinal reflux, abdominal pain, and slow transit constipation or long standing intractable diarrhea; however, abnormalities from the mouth to the anus have been reported [Abonia et al., 2013].

Psychological Symptoms

Children and adolescents with JHS/hEDS aged 8–15 years report significantly poorer emotional functioning on the Pediatric Quality of Life Inventory compared to their non-hypermobile peers [Pacey et al., 2015b]. Furthermore, self-esteem, behavior, and psychosocial functioning of children with JHS/hEDS have been shown to be significantly lower than population norms prior to commencing a treatment program [Pacey et al., 2013].

Activities: Motor Development, Gait Pattern, Physical Fitness

The medical history often reveals developmental delay during early childhood and DCD may coexist [Kirby et al., 2005; Kirby and Davies, 2007]. Congenital hypotonia or "floppy infant" syndrome and joint hypermobility (JH) have been recognized by a number of researchers [Mintz-Itkin et al., 2009]. Late walking and clumsiness are characteristics commonly reported by parents [Adib et al., 2005]. In JHS/hEDS, non-physiological gait-patterns (absolute comparisons: spatio-temporal, kinematics, and kinetics) have been demonstrated in children. These patterns were not consistent and a high variability within patients was present [Fatoye et al., 2011], and children with JHS/hEDS and multiple joint pain, had significantly decreased knee flexion in the swing phase, as well as increased knee extension in mid-stance during walking. Also, decreased lateral joint stability and different stabilization strategies (kinetic patterns) in children and adults with GJH have been shown [Falkerslev et al., 2013].

As far as the gait pattern of children with JHS/hEDS is concerned, it has been reported that "hypermobile joints, reduced proprioception, weak muscles, and reduced stamina (endurance) can profoundly affect the gait of a child with JHS/hEDS. To correct this, the causes of the abnormalities need to be identified and worked on separately, before the gait will improve" [Murray, 2006]. Problems with gait, falls and coordination are the second most common presenting complaint of children with JHS/hEDS presenting to an outpatient rheumatology clinic [Adib et al., 2005].

In children with JHS/hEDS, a relationship was found with exercise induced pain and reduced aerobic fitness and physical capacity fitness compared with a healthy reference group, measured as absolute and relative (related to body mass) peak VO_2 [Engelbert et al., 2006], and also when assessed with a sub-maximal 6 min walk test [Hanewinkel-van Kleef et al., 2009]. The reason for this poor aerobic fitness was assumed to be due to musculoskeletal pain, resulting in inactivity and deconditioning, which could then result in exercise-induced pain and intolerance.

Participation: Hobbies, Sport, and Social Activities

Children with GJH are less active in sports and miss education more often in comparison with their healthy peers with normal joint mobility [Jansson et al., 2004]. Qualitative research with children with JHS/hEDS and their parents has identified "difficulties at school" as being one of the six main themes, when discussing symptoms prior to commencing a treatment program [Birt et al., 2014]. A retrospective chart audit also showed that 40% of affected children report handwriting difficulties, 24% report "problems at school," 41% report missing time from school, and 48% were unable to participate in physical education classes as a result of their condition [Adib et al., 2005]. A recent study showed that children 8–16 years with JHS/hEDS had significantly decreased participation in housework, riding a bicycle, taking part in sport or outdoor games, as assessed by the Frequency of Participation Questionnaire, in conjunction with a higher frequency of participation in non-sporting games and a higher need to rest [Schubert-Hajlmarsson et al., 2012]. Withdrawal from physical activity due to their condition has also been reported by children and their parents [Birt et al., 2014].

Qualitative research with children with JHS/hEDS and their parents has identified "difficulties at school" as being one of the six main themes, when discussing symptoms prior to commencing a treatment program.

It is essential therefore for clinicians to explore and understand the impact of the child's problems on school, home and social life. Some children have poor school attendance records due to recurrent injury, pain, and systemic issues. Many children reduce physical activity and stop participating in physical education due to fear of re-injury or pain.

Finding out about hobbies, ambitions, and sports that a child enjoys is very helpful in driving the management plan. Physical therapists and parents have difficulty when searching for sports and hobbies that suit the child, because many sports involve movement or activities with high risk of injuries in unstable joints. Contact sports for example have been suggested to be an injury risk factor for knee injuries amongst individuals with GJH [Pacey et al., 2010]. In reality many children with JHS/hEDS cannot keep participating in their preferred hobbies, sports and activities, despite their hypermobility originally being considered an asset. It can therefore be very challenging to find activities which young people like and which do not exacerbate pain and joint instability

JHS/EDS-HT IN ADULTHOOD

Pain, Fatigue, and Health Related Quality of Life

Adults diagnosed with JHS/hEDS often experience joint pain in multiple joints, which can vary from localized to widespread pain, in nature and severity [Remvig et al., 2011; Connelly et al., 2015]. Chronic widespread pain is frequently present in patients with the JHS/hEDS. In half of the patient group, a predominantly neuropathic pain component was present [Rombaut et al., 2011a]. This study provides evidence for the existence of hyperalgesia even in asymptomatic areas (generalized secondary hyperalgesia). The GHA (generalised

hyperalgesia) may represent the involvement of a sensitized central nervous system, which requires an adapted pain management approach for this patient group [Rombaut et al., 2015b].

Fatigue symptoms are heterogeneous in nature and can vary from mild to severe. However, patients often report fatigue symptoms as the most disabling complaint. In addition, neurologically oriented symptoms (proprioceptive deficits, central mediated hyperalgesia), psychological dysfunction (anxiety, depression), and systemic complaints (organ dysfunction, dysautonomia) are often highly prevalent in JHS/hEDS [Voermans and Knoop, 2011; De Paepe and Malfait, 2012].

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Muscle Strength, Proprioception, and Balance

Rombaut et al. [2012] demonstrated severely reduced quantitative muscle function and impairment in physical function in patients with JHS/hEDS compared to age- and sex-matched controls. The muscle weakness may be due to muscle dysfunction rather than reduced muscle mass. Whether muscle strength and endurance can be improved by appropriate exercise programs needs evaluation in further studies. Compared with healthy participants, individuals with JHS/hEDS showed significantly impaired balance, reflected by increased sway velocity, mediolateral and anteroposterior sway excursion, and sway area during modified Clinical Test of Sensory Interaction on Balance (mCTSIB) and the Tandem Stance test (TS). Gait velocity, step length, and stride length were significantly smaller during all walking conditions, and a significant dual-task-related decrement was found for gait velocity, step and stride length, and cadence in the JHS/hEDS subjects compared with the control group. Ninety-five percent of the patients fell during the past year, and some fear of falling was further measured [Rombaut et al., 2011b]. DCD may persist into adulthood. In a case control study, 56% of those with JHS/EDS-HT met the criteria for adult DCD [Clark et al., 2014]. Proprioception has been shown to be impaired in a number of studies [Smith et al., 2013].

Extra-Articular Features

Dysautonomia, defined as a term for various conditions in which the autonomic nervous system does not work correctly, provides a complex challenge for the multidisciplinary team. Dysautonomia consisting of cardiovascular dysfunction is found to be present in JHS/hEDS. Neuropathy, connective tissue laxity, and vasoactive medication are likely to play a role in its development [De Wandele et al., 2014]. Gastrointestinal symptoms are also commonly reported [Zarate et al., 2010], impact significantly on quality of life and are managed in a variety of ways. Specialist medical referral may be necessary. Constipation requires active treatment usually including dietary advice, however sustained use of laxatives is often required. Adult women with JHS/hEDS have an increased rate of incontinence. Both case-control and cross-sectional studies consistently report that 60–73.3% of adult women with JHS/hEDS have urinary incontinence, compared with only 30–48.3% in non-affected women [Mastoroudes et al., 2013]. The increased rate seen in women with JHS/hEDS is present with various types of incontinence, including urgency incontinence, nocturnal enuresis, and intercourse incontinence [Nijs et al., 2000]. Other symptoms of lower urinary tract dysfunction including nocturia (waking one or more times at night to void), urgency, bladder pain, urinary tract infections, and voiding difficulties (poor stream, straining, incomplete bladder emptying, postmicturition dribble) have also been reported to be significantly more prevalent in women with JHS/hEDS [Mastoroudes et al., 2013]. No studies have yet investigated incontinence or other lower urinary tract symptoms in adult men with JHS/hEDS.

Impaired bone health in adults with JHS/hEDS has been demonstrated by significant reductions in volumetric bone density measured at the distal radius site using peripheral quantitative computed tomography in comparison with age and gender matched peers [Nijs et al., 2000]. However, in contrast Carbone et al. [2000] found that after correction for height, weight, and amount of physical activity, no significant differences between bone density measured by dual energy absorptiometry was found in adults with JHS/hEDS and controls.

Activities and Participation

Significant disability has been shown in patients with JHS/hEDS in ambulation (walking, running, stair climbing), activities of daily living (personal hygiene, self-care) and sports activities, influencing quality of life. The high number and severity of complaints in JHS/hEDS result in substantial care and treatment seeking. In a group of 78 adults with JHS/hEDS registered as patients in a rehabilitation medicine department, 92.4% were medication consumers, 70.9% had underwent several surgical interventions, and 51.9% had received physiotherapy treatment [Rombaut et al., 2011a]. The main objective of rehabilitation is to reduce disability and to improve quality of life, however, evidence concerning effectiveness of treatment for reducing disability is limited, as are the actual factors related to disability. A recent meta-analysis showed that pain, fatigue, and psychological distress had a significant impact on disability [Scheper et al., 2016b].

Psychological Symptoms

A systematic review has demonstrated that compared with their non-affected peers, adults with JHS/hEDS have

greater risk of anxiety, depression and panic disorders [Smith et al., 2014a]. A nationwide population-based cohort study showed a high incidence of psychiatric disorders including anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorder in the JHS/hEDS patient population [Cederlöf et al., 2016].

PRINCIPLES OF MANAGEMENT OF INDIVIDUALS WITH JHS/EDS-HT IN CHILDHOOD, ADOLESCENCE, AND ADULTHOOD

In children and adults with JHS/hEDS with symptomatic joints or intestinal and systemic problems, differential diagnostics have to be performed to exclude other diseases or disorders that are characterized by GJH. In individuals with GJH, easy bruising and frequent fracturing, the presence of a collagen disease such as osteogenesis imperfecta or osteopenia due to vitamin D deficiency should be considered. When GJH and musculoskeletal complaints as well as a Marfanoid habitus is present, Marfan or Loeys-Dietz syndrome should be considered. Severe collagen diseases, such as the other types of EDS should be excluded. In case of progressive muscle weakness central of peripheral neurological conditions including myopathies should be ruled out. Additionally, rheumatology conditions should also be considered and ruled out.

Kemp et al. [2010] performed the first prospective randomized controlled trial (RCT) in children comparing a 6-week generalized program, improving muscular strength and fitness, with a targeted program aimed at correcting motion control of symptomatic joints. It was demonstrated in 57 children that significant improvements in both the children's and parental pain scores were reached in both groups. A recent RCT study of children with JHS/hEDS and hypermobile knees found an increased effect on psychosocial/self-esteem in the group that performed knee exercises into the hypermobile range of motion (ROM) compared with the control group performing knee exercises into neutral ROM. Both groups improved knee strength and reduced knee pain [Pacey et al., 2013]. Evidence-based guidelines suggest that children with flexible flat foot presenting with pain or impaired function, particularly in the presence of GJH, such as that commonly seen in children with JHS/hEDS, should use orthotics and/or sensible footwear [Evans and Rome, 2011]. Preliminary findings of a small RCT suggests that use of orthotics may improve the efficiency of gait of children with GJH and DCD [Morrison et al., 2013].

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Only one RCT study of adults with JHS/hEDS has been performed, showing reduced knee pain and increased proprioception, in the group receiving exercises of proprioception, balance and plyometrics, compared with a matched control group receiving no exercises [Sahin et al., 2008].

A number of cohort/uncontrolled clinical studies of JHS/hEDS in children and adults report positive effects of strength, core stability and endurance training in addition to education in pain management [Bathen et al., 2013], different intensity of resistive training alone [Ferrell et al., 2004; Møller et al., 2014], and education in pain management alone [Rahman et al., 2014]; however, these reports need to be further evidenced with more rigorous research designs. Existing consensus based hospital and UK paediatric rheumatology guidelines may also offer helpful advice and treatment strategies to clinicians [The British Society for Pediatric and Adolescent Rheumatology, 2013; Cincinnati Children's Hospital Medical Center, 2014]. Qualitative interviews with 28 families with children with JHS/hEDS (5–17 years) on prerequisites for the best adherence to exercise is reported to be parental motivation adapting family routines, making exercise a family activity and seeing the benefit [Birt et al., 2014]. On the other hand are factors for non-adherence to exercise for these children, lower levels of parental supervision, not understanding the treatment, not seeing the benefit and not having specific time to dedicate for doing exercises [Birt et al., 2014].

There is some evidence for that JHS/hEDS improves with exercise, but there is no convincing evidence for specific types of exercise or that exercise is better than control [Smith et al., 2013; Palmer et al., 2014]. Both reviews recommend that longer term, rigorous high-quality multicentre RCT's are warranted for children and adults with JHS/hEDS.

Education, reassurance, manual therapy, tape, hydrotherapy, and relaxation training are used by physical therapists [Lyell et al., 2015; Palmer et al., 2015; Rombaut et al., 2011b, 2015b; Billings et al., 2015] and clinical experts recommend these strategies [Russek, 2000; Simmonds and Keer, 2007; Keer and Simmonds, 2011], based on clinical experience and some evidence of their efficacy from other patient groups. Currently there are no RCT's or comparative trials to support the efficacy of these strategies in individuals with JHS/hEDS. Therapies should be individualized [Simmonds and Keer, 2007, 2008; Simmonds et al., 2016a] and applied carefully to avoid exacerbation of pain as peripheral

and central sensitization is commonly observed [Rombaut et al., 2011b]. Although Adib et al. [2005] refer to 25% of children using mobility aids in a selected population and splints are sometimes recommended, limited effect of these aids, and splinting for hands/wrists in individuals with JHS/hEDS has been found [Smith et al., 2013].

Cardiovascular, musculoskeletal and physical fitness training parameters should be encouraged in both children and adults according to the criteria of the National Strength and Conditioning Association (NSCA) and American College of Sports Medicine (ACSM) [Faigenbaum et al., 2009; Faigenbaum and Myer, 2010; Garber et al., 2011]. In general, specialists recommend a carefully graduate exercise training prescription, underpinned by motor learning theory [Smith et al., 2014b] to avoid injury and overtraining as this may lead to loss of confidence in the physical therapist. Pain, fatigue, and fear of injury are commonly reported barriers to exercise [Simmonds et al., 2016b]. A graduated return to higher levels of sport or dance is recommended, and training loads should be observed to ensure adequate recovery.

Patients with JHS/hEDS have numerous complaints and an impaired functional status that strongly determine their high rate of treatment consumption. The outcome of surgical and physical therapy treatment is largely disappointing, which illustrates the need for a stronger evidence base [Rombaut et al., 2011a]. Education for health professionals [Billings et al., 2015; Rombaut et al., 2015b; Terry et al., 2015; Lyell et al., 2016; Russek et al., 2016] is paramount in order to optimize physical therapy provision. A recent feasibility study of a six session package of treatment demonstrates future potential [Palmer et al., 2016a,b] and further research is required to explore the specific therapeutic actions of physical therapy for managing JHS/hEDS. Recently, a meta-analysis revealed that for treatment of adults, a significant pain reduction was achieved by a variety of physical and cognitive approaches. Active modes of physical therapy are the recommended approach. However, the effectiveness on disability still needs to be established [Scheper et al., 2016c].

In cases where significant systemic signs and symptoms are observed and reported by individuals, such as cardiac dysautonomia, gastrointestinal, urinary and bladder dysfunction, referral to specialist medical teams is indicated. Readers are referred to care guidelines in these specialist areas. Physiotherapists play an important role in management through exercise prescription and patient education for many of these conditions. Relatively recent developed masterclass courses, papers, and symposia provide clinicians with information on how to adapt and apply therapies [Simmonds and Keer, 2007, 2008; Simmonds et al., 2016c].

CONCLUSION

Children, adolescents, and adults suffering from JHS/hEDS frequently present with complex symptoms and are therefore challenging for physical therapists to manage effectively. Based on the ICF, a literature overview has been presented for the assessment and management based on the best evidence available to help guiding clinicians. The current evidence-base for the physical therapy assessment and management of JHS/hEDS is limited in size and quality.

In future directions longer term, rigorous multicenter randomized controlled trials are warranted to assess the clinical and cost-effectiveness of interventions for children and adults with JHS/hEDS. There is a need for further identification and validation of suitable outcome measures. Until further multicenter trials are conducted, clinical decision-making should be theoretically applied based, underpinned by the available evidence where available. In patients diagnosed with JHS/hEDS international consensus and combined efforts to identify patient risk profiles would create a better understanding of the pathological mechanisms with the possibility of optimizing health care for affected individuals.

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ARTICLE

Cardiovascular Autonomic Dysfunction in Ehlers–Danlos Syndrome—Hypermobile Type

ALAN HAKIM,* CHRIS O'CALLAGHAN, INGE DE WANDELE, LAUREN STILES, ALAN POCINKI, AND PETER ROWE

Autonomic dysfunction contributes to health-related impairment of quality of life in the hypermobile type of Ehlers–Danlos syndrome (hEDS). Typical signs and symptoms include tachycardia, hypotension, gastrointestinal dysmotility, and disturbed bladder function and sweating regulation. Cardiovascular autonomic dysfunction may present as Orthostatic Intolerance, Orthostatic Hypotension, Postural Orthostatic Tachycardia Syndrome, or Neurally Mediated Hypotension. The incidence, prevalence, and natural history of these conditions remain unquantified, but observations from specialist clinics suggest they are frequently seen in hEDS. There is growing understanding of how hEDS-related physical and physiological pathology contributes to the development of these conditions. Evaluation of cardiovascular symptoms in hEDS should include a careful history and clinical examination. Tests of cardiovascular function range from clinic room observation to tilt-table assessment to other laboratory investigations such as supine and standing catecholamine levels. Non-pharmacologic treatments include education, managing the environment to reduce exposure to triggers, improving cardiovascular fitness, and maintaining hydration. Although there are limited clinical trials, the response to drug treatments in hEDS is supported by evidence from case and cohort observational data, and short-term physiological studies. Pharmacologic therapy is indicated for patients with moderate-severe impairment of daily function and who have inadequate response or tolerance to conservative treatment. Treatment in hEDS often requires a focus on functional maintenance. Also, the negative impact of cardiovascular symptoms on physical and psycho-social well-being may generate a need for a more general evaluation and on-going management and support.

KEY WORDS: Ehlers–Danlos; autonomic; orthostatic; tachcardia; hypotension

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INTRODUCTION AND METHODS

There is growing recognition of an association between autonomic dysfunction and Ehlers–Danlos syndrome—hypermobile type (hEDS). While many symptoms of autonomic dysfunction have been observed clinically in hEDS, including cardiovascular, pupil, bladder, sweating dysfunction, and gastrointestinal dysmotility (see "Gastrointestinal Involvement in Ehlers Danlos Syndrome," by Aziz et al. in this issue), the purpose of this review is to explore

Alan Hakim is a Consultant in Rheumatology and Adult General Medicine and a Senior Lecturer with a specialist interest in the diagnosis and management of hereditary connective tissue disorders. He is co-author of more than 100 papers and reviews in international journals, author and editor of five books, and numerous book chapters.

Chris O'Callaghan is an Associate Professor and clinical pharmacologist and general physician. His broad clinical and research interests in autonomic medicine extend from heritable disorders of connective tissue to pharmacokinetics of insulin in diabetes mellitus to blood pressure regulation in spinal cord injury. He is also the pending author of a series of books that provide education to patients about common medical conditions.

Inge De Wandele is a physiotherapist. The topic of her PhD was the presence of dysautonomia in EDS. Her current clinical work and research focus on adapted physiotherapy for patients with heritable connective tissue disorders and generalized joint hypermobility.

Lauren Stiles is an attorney turned patient scientist, and co-founder of Dysautonomia International. She collaborates in autonomics research with Vanderbilt University, University of Texas Southwestern, and Mayo Clinic, and has lectured at numerous institutions including Harvard University, Duke University, and the National Institutes of Health.

Alan Pocinki is a General Internist and an Associate Clinical Professor who has over 25 years clinical experience treating people with, studying, and lecturing widely on EDS and related syndromes.

Peter Rowe is a General Pediatrician and Professor of Pediatrics, Johns Hopkins University School of Medicine. He specializes in the evaluation and treatment of adolescents and young adults with conditions characterized by chronic fatigue, including chronic fatigue syndrome, orthostatic intolerance, and joint hypermobility.

*Correspondence to: Alan Hakim, The Hospital of St John and St Elizabeth—Hypermobility Unit, 60 Grove End Road London NW8 9NH, United Kingdom of Great Britain and Northern Ireland. E-mail: contact@alanhakim.com

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what is known of the association between cardiovascular autonomic dysfunction and hEDS; provide guidance on the assessment and management of these in the context of hEDS; and, consider areas for further research in this field.

The committee on Cardiovascular Dysautonomia of the International Ehlers–Danlos Syndrome Consortium met by teleconference or through electronic correspondence throughout 2015 and 2016 to discuss the associations of cardiovascular autonomic dysfunction with hEDS and its assessment and management. The following reflects the Committee's literature review and professional experience as well as insights from various contributing members of the international effort on EDS through the Consortium.

LITERATURE REVIEW

There has been no general hEDS population cohort study of cardiovascular autonomic dysfunction, and there has been one published case-control study of symptom reporting. Equally the causal relationships in hEDS are unclear though there are plausible mechanisms, and the evidence for the management in hEDS is lacking in that there are no published clinical trials.

That said tachycardia and hypotension are recognized complications in hEDS [Rowe et al., 1999; Gazit et al., 2003; Hakim and Grahame, 2004; Mathias et al., 2011; Wallman et al., 2014; De Wandele et al., 2014a, 2016]. Typically one of the following four presentations may arise:

- Postural tachycardia syndrome (POTS),
- neurally mediated hypotension (NMH), also referred to as vaso-vagal syncope or neuro-cardiogenic syncope,
- orthostatic hypotension (OH) or delayed orthostatic hypotension,
- orthostatic intolerance (OI).

Symptoms can be highly debilitating in hEDS [Rowe et al., 1999; Hakim and Grahame, 2004; Mathias et al., 2011; De Wandele et al., 2014b]. There is recognition of an association of POTS with fatigue [Schondorf et al., 1999], reduced quality of life [Benrud-Larson et al., 2002], and a greater incidence of migraine and syncope with POTS in patients with joint hypermobility syndrome compared to those without [Kanjwal et al., 2010]. When poorly controlled, these symptoms may also restrict treatment strategies for other symptomatic management including physical therapies.

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In the general literature on the management of autonomic dysfunction there is evidence for the effectiveness of treatment strategies. This and the definitions of the different cardiovascular presentations are discussed later. Such treatments have been applied to individual cases of hEDS, based on physiological findings. However, there are no clinical trials of treatment in hEDS, either in general or in specific subgroups based on pathophysiology.

CAUSAL ASSOCIATIONS WITH hEDS

The causes of cardiovascular autonomic dysfunction in hEDS are unclear. Suggested mechanisms include (listed based on clinical experience and in order of most common occurrence):

- Low blood pressure,
- increased peripheral venous dilation and blood pooling,
- low circulating blood volume,
- medications with side effects that trigger or impair autonomic responses, for example tricyclics,
- elevated circulating catecholamines,
- auto-immunity, particularly auto-antibodies directed against receptors which play a role in the regulation of heart rate and blood pressure, and other autonomic functions,
- excess systemic levels of histamine, and
- rarely, brainstem or cervical cord impingement from Chiari malformation or cranio-cervical instability.

EVIDENCE FOR UNDERLYING MECHANISMS IN hEDS

Handler et al. [1985] identified through continuous wave Doppler ultrasound measurement increased aortic wall compliance in 10 of 13 study cases with joint hypermobility syndrome. Rowe et al. [1999] suggested that in some cases the association of OI with hEDS could be attributed to abnormal connective tissue in dependent blood vessels with veins distending excessively in response to ordinary hydrostatic pressures. This in turn leads to increased venous pooling and its hemodynamic and symptomatic consequences. Studies by Mathias et al. [2011] and De Wandele et al. [2014a] suggest that neuropathy, connective tissue laxity, and vasoactive medication play a role in development of cardiovascular dysfunction in hEDS.

Gazit et al. [2003] identified evidence of alpha-adrenergic and beta-adrenergic hyper-responsiveness. In support of the hypothesis that this is one mechanism in hEDS, a study by Thieben et al. [2007] identified a hyperadrenergic state in 29% of cases of POTS from a general cohort though cases of hEDS were not specifically identified. Also in the general literature, research has identified potentially pathogenic adrenergic [Fedorowski et al., 2016], muscarinic [Yu et al., 2012; Dubey et al., 2016], and other neural autoantibodies [Thieben et al., 2007; Li et al., 2014; Singer et al., 2016] in a significant percentage of cases with POTS and a subset of those

with OH. Current, ongoing research may identify this as applicable to patients with hEDS.

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Histamine can induce hypotension and tachycardia [Frieri et al., 2013]. More recently mast cell activation, and excessive histamine release has been identified in cases of hEDS [Louisias et al., 2013; Cheung and Vadas, 2015] and an intriguing association reported between multi-systemic pathologies including autonomic disturbances and germline duplications and triplications of the TSPAB1 gene encoding alpha 1 tryptase [Lyons et al., 2016]. High circulating levels of histamine may be another mechanism contributing to cardiovascular dysfunction (see also "Mast Cell Activation Syndrome in Ehlers–Danlos syndrome" by Seneviratne et al. in this issue).

Arnold Chiari malformation may also trigger cardiovascular autonomic disturbances that resolve following decompressive surgery [Ireland et al., 1996]. Milhorat et al. [2007] demonstrated an association between Arnold Chiari and hEDS. In some cases this may also be a contributing factor (see also "Neurologic Manifestations in Ehlers–Danlos Syndrome" by Henderson et al. in this issue).

CONTROVERSIES

Screening for Mitral Valve Prolapse

Mitral valve prolapse (MVP) can be associated with excessive catecholamines, orthostatic intolerance, and occasionally with dysrhythmias. MVP is not common (approx. 6%) in patients with hEDS [Dolan et al., 1997; McDonnell et al., 2006; Atzinger et al., 2011], and in most cases this is unlikely to be of clinical significance. Also, normal cardiac anatomy does not rule out cardiovascular dysfunction. Screening for MVP in hEDS is not indicated. Echocardiography should be limited to those in whom there is concern regarding cardiac function, or a personal or family history of cardiac or aortic root/arch disease [Atzinger et al., 2011].

The Role of Physical Therapy in Improving POTS, OI, and OH

Physical deconditioning and poor aerobic fitness are common findings in patients chronically unwell with hEDS. A history of onset of symptoms of cardiovascular dysfunction following a prolonged period of reduced physical activity is not uncommon.

OI has been related to deconditioning [Fu et al., 2010; Parsaik et al., 2012]. However, as to which is the cause and which is the consequence remains open to debate. Increased physical fitness may counteract OI. Fu et al. [2011] and George et al. [2016] have shown that after a 3-month training programme, moderate gradual endurance and strength training can decrease upright heart rate, improve baroreflex sensitivity and heart rate variability, and improve quality of life.

The extent to which physical deconditioning triggers cardiovascular dysfunction, and to which physical reconditioning has a fundamental role in managing symptoms related to OI, OH, and POTS, warrants further research and long-term follow up.

MANAGEMENT AND CARE GUIDELINES

Using the standard nomenclature for guidelines Level I to III evidence for the management of cardiovascular autonomic dysfunction in hEDS is lacking; there are no published clinical trials. Level IV evidence of the associations with EDS arises from small cohort studies, case reports, and expert opinion. Even where evidence exists, it is confounded by imprecision in definitions and diagnostic methods that further confound extrapolation from data to individual patients. As such guidance is principally based on expert consensus, but draws on Level I to III guidance published by international groups on the assessment and management of POTS and OI per se [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al., 2015].

History, Examination, and Investigations

History

The clinical history should focus on defining the symptoms, triggers, modifying factors, impact on daily life, chronicity of the condition, possible causes, and family history.

Many of the common symptoms relate to changes in posture. They occur when changing from a lying or sitting to a standing position, or with maintaining upright posture, and are improved but not always completely relieved by sitting or lying down.

The more common symptoms and signs that suggest cardiovascular dysfunction are:

- Fast heart rate (palpitations),
- light-headedness, sometimes with a sense of being about to blackout (pre-syncope),
- visual impairment including altered acuity, partial or complete visual loss, and light sensitivity due to pupillary dilation,
- cognitive complaints including word-finding difficulties, limited concentration and poor memory (often described in lay terms as "brain fog"),
- chest pain,
- tremulousness,
- chronic fatigue,
- exercise intolerance and post exercise malaise,

- swelling and/or discolouration (dusky purple/red) in the legs after standing for only relatively short (e.g., 5 min) periods of time (as seen in OI),
- peripheral vasoconstriction (cold, dusky hands, and feet),
- fainting (syncope),
- temperature dysregulation,
- sleep disturbance.

The history may reveal states that trigger or exacerbate symptoms. Such things include:

- Medication side effects,
- dehydration,
- hot environments,
- exercise or after exercise,
- valsalva manouevers for example lifting a heavy object, defecation,
- after alcohol or caffeine intake,
- after eating, particularly carbohydrate,
- during other illness including infection,
- stressful situations for example blood tests, arguments, exams,
- painful stimuli,
- high altitude (aircraft travel, etc.),
- after long periods of rest,
- surgery involving general anesthesia,
- allergic reactions (histamine reactions).

Physical examination

A detailed examination is always warranted. Other common causes of low blood pressure or palpitations should be considered in an assessment. These include:

- Anaemia,
- hyperthyroidism (e.g., tachycardia and heat intolerance),
- hyper adrenergic states (e.g., tachycardia and flushing),
- addison's disease (e.g., low blood pressure and fatigue).

There are a number of causes of autonomic neuropathy, many of which are rare and more pertinent to the older adult population. It is not the purpose of this guideline to describe these. Some of the more common conditions to consider in the younger adult population are:

- Diabetes mellitus,
- coeliac disease,
- Sjögren syndrome and other autoimmune rheumatic conditions,
- pregnancy,
- toxicity (e.g., alcohol),
- trauma (e.g., surgery),
- vitamin deficiencies: vitamin E, B1 (thiamine), B3 (niacin) B6 (pyridoxine), and B12.

Investigations

POTS, OH, and some forms of OI can be diagnosed in clinic without the need for complex tests. The diagnosis of NMH that is associated with recurrent syncope can be made clinically, and in most cases does not require formal tilt table testing. A simple clinic room standing test can help assess whether a brief period of standing can provoke orthostatic symptoms in those with NMH, but provocation of hypotension usually requires more prolonged tilt table testing.

Orthostatic testing should take place in a quiet room, ideally at a temperature between 20 and 24°C. The patient should rest while supine for 5 min before testing. Emptying the bladder before testing is recommended.

The following consensus definitions[1] [Freeman et al., 2011; Sheldon et al., 2015] are applied:

- POTS: is a clinical syndrome usually characterized by: (i) frequent symptoms that occur with standing, such as lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (ii) a sustained increase in heart rate of $\geq$30 beats per minute (bpm) within 10 min of standing or head-up tilt (or $\geq$40 bpm in individuals 12–19 years of age); and (iii) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure).
- OH: a sustained reduction of systolic blood pressure by at least 20 mm Hg systolic or diastolic blood pressure of at least 10 mm Hg within 3 min of standing or head-up tilt to at least 60° angle on a tilt table.
- NMH: requires the reproduction of orthostatic symptoms and a 25 mm Hg drop in systolic BP during standing or tilt testing. The drop in blood pressure can be associated with junctional rhythm (recognized by a loss of P waves on an electrocardiogram) at the time of pre-syncope or syncope. Syncope need not be present to make the diagnosis of NMH, as individuals with this hemodynamic pattern have daily lightheadedness and other symptoms but have adopted habits such as sitting or lying down, or tensing the calf muscles to avoid losing consciousness.
- OI: the development of symptoms during 10 min upright posture which improve upon lying down and do not meet the above criteria for POTS, OH, or NMH.

If orthostatic signs are normal on testing in the clinic but the clinical suspicion of autonomic dysfunction remains high, or signs are present and simple, non-pharmacologic treatments have not helped, for most individuals a haematocrit, electrocardiogram, blood pressure monitoring, and echocardiogram are sufficient to screen for a potential cardiovascular or systemic disorder.

If orthostatic signs are normal on testing in the clinic but the clinical suspicion of autonomic dysfunction remains high, a haematocrit, electrocardiogram, blood pressure monitoring, and echocardiogram may be sufficient further screening.

Symptoms of OI can overlap with some features of cardiac dysrhythmias.

[1]The authors are aware of limitations of the criteria that have been traditionally used to classify the types of cardiovascular disease that are seen in hEDS. This document uses definitions already proposed by international consensus and published in the general literature.

If there is clinical concern that a dysrhythmia is present, a 24-hr Holter monitoring is indicated. If these tests are normal but clinical suspicion remains high, a tilt-table test might be helpful as it assesses the patient over a more prolonged period than a standing test. The test may also be used to provoke syncope in a controlled environment and where there is doubt as to the diagnosis.

More extensive evaluation by an expert Autonomic Unit might be required. An extended approach to evaluation might include:

- Thermoregulatory sweat test or QSART testing to detect autonomic neuropathy,
- supine and upright plasma epinephrine and norepinephrine level tests,
- 24-hr urine sample to assess sodium intake.

Tests of autonomic function may identify autonomic neuropathy that is not usually a component of the cardiovascular dysfunction of EDS.

Treatment

None of the treatments available is universally effective, and several treatments, used together, are likely to be needed. There is no evidence that specific treatments should be targeted at subgroups of patients with hEDS.

Education, advice, and non-pharmacologic treatments should be offered first in all patients, and include education on:

- Avoiding or reducing exposure to triggering factors,
- withdrawing medications that might worsen symptoms,
- maintaining good hydration and electrolyte balance,
- reducing venous pooling by lower limb elevation or by abdominal and/or lower limb compression garments,
- increasing exercise adapted where necessary for the presence of joint hypermobility, instability, and injury.

When prescribing exercise, the program might be adapted to account for OI in several ways that include the:

- Exercise modality: in general, aerobic activities with a local resistive component for the lower limbs are preferred, such as (reclined) cycling and swimming.
- Type of exercise: dynamic exercise may be better tolerated than isometric exercise. The latter is more prone to provoke valsalva manoeuvers, which decrease blood pressure.
- Prevention of peripheral blood pooling: exercising in the supine position is better tolerated than the upright position. Exercising in water may also help decrease peripheral blood pooling, because of the greater pressure exerted by the water on the lower limbs. However, an over-heated pool may cause venous dilation and be poorly tolerated.
- Intensity and frequency: training at a target heart rate of 75% of the estimated maximal heart rate for about 30 min per session, 2–3 times per week is advised [Fu et al., 2011; George et al., 2016]. This should be adapted according to level of disability.
- Increase of fluid intake, preferably with added sodium, and if helpful, the use of pressure garments during and after exercise.
- Avoidance of meals 1 hr prior to an exercise session, because vasodilatation in the gastrointestinal tract lowers the capacity of the circulatory system.
- Prevention of sudden drop in blood pressure after a training session by engaging in low-intensity cooling-down activity.

In those with moderate-severe impairment of daily function, and poor response to or tolerance of non-pharmacologic treatments, pharmacologic treatments are available [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al., 2015]. These include:

- Fludrocortisone is a first line drug therapy for OI at doses of 100–200 mg daily (Level III evidence).
- Midodrine significantly reduces POTS symptoms and reduces the frequency of neurally mediated syncope (Level I evidence). The initial dosage is 2.5 mg orally every 4 hr while awake, usually for two to three doses daily, increasing gradually up to 10 mg every 4 hr while awake if needed. Midodrine may also be used with fludrocortisone.
- Beta blockers can help with management of recurrent syncope, NMH, POTS, and OI (Level I evidence). Lower doses tend to be better tolerated, but there is substantial inter-individual variability.
- Ivabradine slows sinus heart rate without affecting blood pressure, and has been reported to be helpful in those with POTS (Level III evidence).

Other agents include:

- Stimulants: medications such as methylphenidate [Grubb et al., 1996] and dextroamphetamine [Susmano et al., 1993] have vasoconstricting properties, and can help reduce peripheral pooling of blood. They can be particularly helpful if inattention is a prominent symptom.
- Hormonal contraceptives can help manage OI symptoms in young women. This option can be first line therapy for OI in those who have comorbid dysmenorrhea, menstrual irregularity, heavy periods, or worse fatigue and OI symptoms during the menstrual cycle [Boehm et al., 1997].
- Desmopressin may be given as nasal spray (10–40 μg) or orally (100–200 μg) at night to prevent volume loss due to frequent urination at night [Raj, 2006]. Additional doses of 100–200 μg during the day may be beneficial as well, but must include monitoring for hyponatremia. At 200 ug orally it may also reduce tachycardia [Coffin et al., 2012].
- Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine in the autonomic ganglia and at peripheral muscarinic receptors [Raj et al., 2005]. The drug can be effective for neurally mediated syncope and for POTS (Level I evidence).
- Clonidine is a central sympatholytic agent that can be useful if there is comorbid anxiety, and can be useful in patients with the central hyper adrenergic form of POTS [Robertson et al., 1983].

- Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors can be helpful in some patients with OI, and can be beneficial in the setting of co-morbid pain, anxiety, or depression [Di Girolamo et al., 1999]. Dihydroxyphenylserine titrated 100–200 mg three times daily reduces OH (Level I evidence).
- Octreotide given subcutaneously in doses of 25–150 μg for 30 min before a meal may be used to reduce postprandial OH.
- Tolerance of upright posture and autonomic tone may improve after the administration of 1–2 L of intravenous normal saline infused over 1–2 hr [Burklow et al., 1999; Takenaka et al., 2002], or other forms of sodium loading [Rosen and Cryer, 1982]. Some physicians use IV saline to manage acute episodic exacerbations of OI [Moak et al., 2016]. The use of IV saline on a weekly basis can help improve function for selected individuals who are intolerant of or unresponsive to medications. The administration of IV saline via indwelling central catheters creates a risk of bacteremia and thrombosis, and should be avoided if at all possible.
- Ruscus aculeatus (butcher's broom) [Altern, 2000].

WHAT WE NEED TO KNOW

The incidence, prevalence, and natural history of cardiovascular autonomic dysfunction in the hEDS population are unknown, as are the distribution and types of (co-associated) mechanisms that may trigger or influence these phenomena.

Subgroup (by risk factors/mechanism of disorder) clinical trials of efficacy and safety of treatments are required to move beyond the limitations of case study and expert opinion evidence. Studies also need to assess the effect of treatment on quality of life and fatigue.

SUMMARY

Individuals with hEDS can develop cardiovascular autonomic dysfunction. Its manifestations include symptoms related to inadequate cerebral perfusion and symptoms of heightened adrenergic tone. Specific conditions include POTS and NMH.

The diagnosis is predominantly based upon taking a detailed personal and family history of symptoms, provoking circumstances, and accompanying complaints.

Simple clinic room tests can provide support for the diagnosis and other tests may be useful to exclude other diseases that can present in a similar manner.

Consideration should also be given to the possibilities that symptoms are due to medications and supplements, cardiac valvular disease, venous pooling, allergy, autoimmunity, or rarely Chiari malformation.

Although pharmacological therapies are often required, non-drug treatments should always be employed. Foremost amongst these are education about the causes of symptoms and physical measures that might be used to control them. Other non-pharmacological measures include increased dietary salt intake, use of compression garments and graded exercise therapy.

Pharmacological therapy begins with minimizing or removing medications that are either ineffective or producing deleterious effects. Drug treatments include volume expansion (e.g., fludrocortisone, saline infusion), vasoconstriction (e.g., midodrine), modulators of autonomic tone including beta-blockade, and others.

The prognosis remains uncertain with the outcomes ranging from virtually complete resolution of symptoms to long-term disability, which may be so severe as to affect education, employment, or socialization.

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ARTICLE

Chronic Fatigue in Ehlers–Danlos Syndrome—Hypermobile Type

ALAN HAKIM,* INGE DE WANDELE, CHRIS O'CALLAGHAN, ALAN POCINKI, AND PETER ROWE

Chronic fatigue is an important contributor to impaired health-related quality of life in Ehlers–Danlos syndrome. There is overlap in the symptoms and findings of EDS and chronic fatigue syndrome. A proportion of those with CFS likely have EDS that has not been identified. The evaluation of chronic fatigue in EDS needs to include a careful clinical examination and laboratory testing to exclude common causes of fatigue including anemia, hypothyroidisim, and chronic infection, as well as dysfunction of major physiological or organ systems. Other problems that commonly contribute to fatigue in EDS include sleep disorders, chronic pain, deconditioning, cardiovascular autonomic dysfunction, bowel and bladder dysfunction, psychological issues, and nutritional deficiencies. While there is no specific pharmacological treatment for fatigue, many medications are effective for specific symptoms (such as headache, menstrual dysfunction, or myalgia) and for co-morbid conditions that result in fatigue, including orthostatic intolerance and insomnia. Comprehensive treatment of fatigue needs to also evaluate for biomechanical problems that are common in EDS, and usually involves skilled physical therapy and attention to methods to prevent deconditioning. In addition to managing specific symptoms, treatment of fatigue in EDS also needs to focus on maintaining function and providing social, physical, and nutritional support, as well as providing on-going medical evaluation of new problems and review of new evidence about proposed treatments.

KEY WORDS: hypermobility; fatigue; Ehlers Danlos

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INTRODUCTION

Fatigue can be temporally categorized as recent, prolonged, or chronic that is less than 1, 1–6, and more than 6 months, respectively. Its persistence and impact on daily activities and quality of life are recognized in the descriptors of the condition Chronic Fatigue Syndrome (CFS), also known as myalgic encephalomyelitis (ME).

Fatigue may be a principal presenting symptom in Ehlers–Danlos syndrome—hypermobile type (hEDS). However a clinician may diagnose CFS without appreciating the presence or pre-existence of features that may have led to a diagnosis of hEDS. The risk then is attention may be taken away from specific triggering factors for fatigue and adaptations to management specific to hEDS such as physical therapies.

Fatigue may be a principal presenting symptom in Ehlers–Danlos syndrome—hypermobile type (hEDS). However a clinician may diagnose CFS without

Alan Hakim is a Consultant in Rheumatology and Adult General Medicine and a Senior Lecturer with a specialist interest in the diagnosis and management of hereditary connective tissue disorders. He is co-author of more than 100 papers and reviews in international journals, author and editor of five books, and numerous book chapters.

Inge De Wandele is a physiotherapist. The topic of her PhD was the presence of dysautonomia in EDS. Her current clinical work and research focus on adapted physiotherapy for patients with heritable connective tissue disorders and generalized joint hypermobility.

Chris O'Callaghan is an Associate Professor and clinical pharmacologist and general physician. His broad clinical and research interests in autonomic medicine extend from heritable disorders of connective tissue to pharmacokinetics of insulin in diabetes mellitus to blood pressure regulation in spinal cord injury. He is also the pending author of a series of books that provide education to patients about common medical conditions.

Alan Pocinki is a General Internist and an Associate Clinical Professor who has over 25 years clinical experience treating people with, studying, and lecturing widely on EDS and related syndromes.

Peter Rowe is a General Pediatrician and Professor of Pediatrics. He specializes in the evaluation and treatment of adolescents and young adults with conditions characterized by chronic fatigue, including chronic fatigue syndrome, orthostatic intolerance, and joint hypermobility.

*Correspondence to: Alan Hakim, The Hospital of St John and St Elizabeth—Hypermobility Unit, 60 Grove End Road London NW8 9NH, United Kingdom of Great Britain and Northern Ireland. E-mail: contact@alanhakim.com

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appreciating the presence or pre-existence of features that may have led to a diagnosis of hEDS.

The purpose of this review is to explore what is known of the assocation between fatigue and hEDS; provide guidance on the assessment and management of fatigue in the context of hEDS; and consider areas for further research in this field.

METHODS

The committee on Chronic Fatigue of the International Ehlers–Danlos Syndrome Consortium met by teleconference or through electronic correspondence throughout 2015 and 2016 to discuss the associations of chronic fatigue with hEDS and its assessment and management. The following reflects the Committee's literature review and professional experience as well as insights from various contributing members of the international effort on EDS through the Consortium.

LITERATURE REVIEW

Fatigue is common and often disabling in hEDS [Rowe et al., 1999; Hakim and Grahame, 2004; Voermans et al., 2010; Castori et al., 2011; Voermans and Knoop, 2011; Murray et al., 2013; Scheper et al., 2016]. It has been associated in hEDS with muscle weakness [Voermans et al., 2011; Celletti et al., 2012], and kinesiophobia [Celletti et al., 2013]. However, there are no large randomized trials of the management of fatigue in EDS. The few publications that offer management advice are based on either small cohort studies or expert opinion.

There is no specific definition for chronic fatigue in hEDS. The authors recommend the following definitions of fatigue, similar in concept and substance to that published by the Institute of Medicine [2015]. Chronic fatigue is defined by:

- Persistent and/or recurrent fatigue, that has been present for more than 6 months,
- unexplained by other conditions,
- not the result of ongoing exertion,
- not substantially alleviated by rest,
- resulting in a substantial reduction or impairment in the ability to engage in normal levels of activities.

CAUSAL ASSOCIATIONS

A full history (including exacerbating and alleviating factors, sleep disturbance and stressors, and perceived impact on wellbeing) should be taken, and include assessment of psychological wellbeing both as a cause and an impact. Because fatigue is such a common symptom in systemic illnesses not related to hEDS, and can be associated with disease in any organ system, it is fundamentally important that a thorough history and physical examination is undertaken.

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The following causes for fatigue are common findings in hEDS.

- Poor sleep quality—in hEDS initiation, maintenance and restoration of sleep may be disturbed by factors such as pain, nocturnal tachycardia, or sleep disordered breathing.[1]
- Chronic pain—typically both neuropathic in nature and from acute and chronic mechanical joint and soft tissue injury.
- Physical deconditioning (as opposed to physical "weakness")—that arises from poor physical activity.
- Orthostatic intolerance [De Wandele et al., 2016], and cardiovascular dysregulation (e.g., tachycardia, hypotension, syncope).
- Bowel dysfunction (e.g., malabsorption and subsequent nutritional deficiencies).
- Nocturnal micturition due to bladder dysfunction or polyuria which is usually secondary to increased fluid consumption but may also be a consequence of increased urine production during recumbent posture, eliminating fluid "pooled" in the lower body during the day.
- Anxiety and/or depression.
- Headaches/migraines.

It is important to recognize that chronic fatigue may be the result of a co-existing condition. "Red flag" alerts of a serious different condition include:

- Weight loss,
- significant lymphadenopathy,
- clubbing,
- persistent shortness of breath on exertion (exertional dyspnoea is often a consequence of cardiovascular dysfunction),
- fevers,
- red, swollen joints,
- bronzing of the skin,
- abnormalities on the neurological examination,
- later age of onset.

The following should then be excluded or investigated further if thought to be present:

- Chronic infection (e.g., hepatitis, tuberculosis, brucellosis, endocarditis, Lyme disease),
- endocrine disorders (e.g, diabetes, thyroid disease, adrenal insufficiency),
- autoimmune inflammatory conditions (e.g., joints, skin, bowel, liver, and renal disorders),
- cardiorespiratory disease,
- sleep disordered breathing,
- neurological disorders (e.g., myasthenia gravis, multiple sclerosis).

CONTROVERSIES

It is the authors' opinion that the criteria used for diagnosing CFS and hEDS are

[1]While daytime napping may be beneficial as part of rest and relaxation, it may in some cases lead to either a shift or reversal of the day–night sleep cycle, with resultant difficulty sleeping at night and daytime somnolence, and therefore be more detrimental than beneficial.

inadequate and contribute to diagnostic confusion. To meet a diagnosis of CFS, fatigue must be "unexplained by other conditions." Therefore, a diagnosis of hEDS must exclude a diagnosis of CFS. However, hEDS is likely to be substantially under-diagnosed and it is likely that some patients diagnosed with CFS may meet or would previously have met the criteria for diagnosis of hEDS. Also it is the authors' opinion that the literature and diagnostic methods for CFS and hEDS are of insufficient strength to reliably differentiate between these conditions in a given individual. We would conclude that in the context of hEDS one would simply use the term chronic fatigue.

Treatment of fatigue in hEDS is based on guidance from the general literature on management of chronic fatigue, and expert opinion. There is no evidence for use of specific pharmacological therapies in hEDS, though these are, within licencing regulation, recommended.

MANAGEMENT AND CARE GUIDELINES

Assessment of Severity and Impact of Fatigue

There is no single tool for the assessment of patients with fatigue that allows a global appraisal of its severity and impact. Also fatigue may be an expression of an underlying disorder, and it is the severity and impact of that disorder per se that is the issue.

More formal questionnaires that address fatigue include the Multidimensional Fatigue Inventory—Short Form (MFI-SF), a 30-item self-report instrument designed to measure fatigue. The full MFI is 83 questions [Smets et al., 1995]. It explores general, physical, and mental fatigue, reduced motivation and reduced activity. Subsections of it can be used to look at specific areas such as mental fatigue.

Simple tools such as the Wood Mental Fatigue Inventory can be used in the clinic to explore the cognitive symptoms of fatigue [Bentall et al., 1993].

Scales for functional assessment, such as the Medical Outcomes Study Short-Form General Health Survey (SF-36®) and Sickness Impact Profile (SIP) may be helpful.

Simple tools such as the Wood Mental Fatigue Inventory can be used in the clinic to explore the cognitive symptoms of fatigue.

Scales for functional assessment, such as the Medical Outcomes Study Short-Form General Health Survey (SF-36®) and Sickness Impact Profile (SIP) may be helpful.

Whitehead [2009] analized of the scales most often used in research. The review identified three short instruments demonstrate good psychometric properties (namely the Fatigue Severity Scale [FSS], Fatigue Impact Scale [FIS], and Brief Fatigue Inventory [BFI]), as did three comprehensive instruments (namely the Fatigue Symptom Inventory [FSI], Multidimensional Assessment of Fatigue [MAF], and Multidimensional Fatigue Symptom Inventory [MFSI]). Of these four measures (BFI, FSS, FSI, and MAF) demonstrated the ability to detect change over time and might therefore be more suitable in the assessment of chronic long-term conditions.

Perhaps the most useful information clinically is that gained from patient self-record of their daily activities, general function, and the degree of disability perceived, for example how far a patient can walk without having to stop to rest, or how many flights of stairs. By logging a list of these activities and functions, the patient has a baseline from which to set goals, and the opportunity to judge improvement in wellbeing by achieving these goals. This process can be repeated to challenge and record further improvements over time.

Personal electronic devices are now available to measure activity and these can be useful in monitoring physical exertion particularly during therapeutic programs.

Advice and Treatment

General principles

To facilitate effective management the clinician needs to establish a collaborative relationship with the patient and their carers. Engagement with the family is particularly important for children and young people, and for people with severe fatigue.

The patient and their clinician should share decision making both in identifying the causes of, recognising the impact of, and the phases in the management of fatigue. Together this might include:

- Understanding the need to exclude underlying diseases and disorders.
- Recognizing the reality and impact (physical, emotional, social [including education and employment]) of the condition and the symptoms.
- Setting realistic goals and timelines for improvement, being prepared to manage set-backs/relapses.
- Exploring the range of interventions and management strategies available, taking account of the patients' age (particularly for children), the severity of their symptoms, their preferences and experiences, and the outcome of previous treatment.
- Negotiating other areas of healthcare provision, supporting applications for financial benefits and social care, as well as concerns related to education or employment.

People with severe fatigue may need support from a multidisciplinary team for example, nursing, occupational therapy, dietetics, psychology, physiotherapy, and pain management. This should be coordinated by a named

healthcare professional, and usually their general practitioner/general physician.

Treatment is based on addressing the underlying issues. These might include medications directed at orthostatic intolerance, antidepressants, anti-anxiety drugs, management of allergies, use of sleep aids, and pain management [Castori et al., 2012], as well as a lifestyle changes including pacing, changing sleep pattern, exercise, and even a change of job or hours of work.

There is no known pharmacological treatment or cure for fatigue per se. Large systematic reviews have not identified consistently effective medications for CFS symptoms in general, but many medications are effective for specific symptoms (e.g., headaches) and co-morbid conditions that result in fatigue [Smith et al., 2014]. Unless there is an underlying medical disorder, the following medications should be avoided as they may cause harm if used inappropriately:

- Glucocorticoids (in the absence of other indications),
- thyroxine (in the absence of hypothyroidism),
- antiviral agents[2] (in the absence of confirmed active viral infection).

There is insufficient evidence to recommend the use of complementary therapies and supplements for fatigue. However, some patients choose to use these therapies and find them helpful, and there is little evidence of harm. Typical agents include co-enzyme Q10, Carnitine, alpha-lipoic acid, magnesium, nicotinamide adenine dinucleotide (NADH), and multivitamins and minerals. Co-enzyme Q and Riboflavin have been shown to be effective in migraine prophylaxis.

There is insufficient evidence to recommend the use of complementary therapies and supplements for fatigue.

[2]The authors recognize that clinicians try these, however, there is very little evidence of efficacy in the literature.

However, some patients choose to use these therapies and find them helpful, and there is little evidence of harm.

In some cases, patients with bowel dysfunction may need supplements because of a restricted diet. A dietician's expertise may be required in this situation if the attending clinician is not confident to advise.

Clinicians and patients should remain aware that some patients do not show meaningful responses to therapy. Patients with intractable, chronic and disabling conditions are prone to feelings of abandonment and may be vulnerable to potentially toxic therapies or exploitative practitioners. For such patients, the long-term supportive and protective role of the physician can be invaluable.

Maintaining independence

For people with moderate or severe fatigue that has not responded to treatment, equipment and adaptations (e.g., a wheelchair) should be considered as part of the management plan, after assessing the risks and benefits for the individual patient. Such adaptations may be valued ways of gaining more independence and improving quality of life.

Disruption of education or employment is generally detrimental to health and wellbeing. The ability to continue in these should be addressed early. The clinician should assist, following consent from their patient, by proactively and as needs be regularly advising colleagues on their patients' fitness for work and education, and the adjustments or adaptations required for them to remain in or return to studies or work.

Treatment modalities

Sleep management, rest, and relaxation and key approaches. Advice on sleep management includes:

- Explaining the effect disordered sleep or a poor sleep pattern can have on causing and exacerbating fatigue can help an individual understand how their behaviors might affect the normal day–night sleep cycle.
- Identifying poor sleep patterns such as insomnia, hypersomnia, an altered sleep–wake cycle, and non-refreshing sleep despite either an apparent normal cycle or prolonged sleep.
- Providing general advice on what good sleep hygiene means (see below).
- Introducing changes to sleep patterns gradually.

Good sleep hygiene includes:

- Avoiding stimulants such as caffeine or nicotine too close to bedtime.
- Exercise during the day to promote good sleep.
- Avoiding large meals too close to bedtime.
- Relaxation techniques—establishing a regular relaxing bedtime routine, avoiding emotional upset/dwelling on problems before trying to go to sleep. Calm music or reading may be relaxing for some.
- Associate bed with sleep. Avoid watching TV, playing computer games, sending text messages, e-mails, etc. Calm music or reading may be relaxing for some.
- The sleep environment should be pleasant and relaxing. The bed should be comfortable, and the room dark, quiet, and neither too hot or too cold.

During the day, exercise may also encourage wakefulness, as should adequate exposure to natural light. Especially early in the day, light exposure helps to maintain a healthy sleep–wake cycle.

During the day, exercise may also encourage wakefulness, as should adequate exposure to natural light. Especially early in the day, light exposure helps to maintain a healthy sleep–wake cycle.

Chronic pain may be a dominant influence on sleep; it should be managed accordingly. Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered.

Other medications may assist sleep. These include:

- Melatonin,
- doxepin,
- cyproheptadine,
- diphenhydramine,
- trazodone,
- propranolol,
- clonazepam,
- zolpidem,
- a variety of others including benzodiazepines, beta blockers, muscle relaxants, and eszopiclone.

As part of pacing, rest periods may be required. Rest periods can be introduced into daily routine, but the frequency, length, and types of activities undertaken should be adapted for each individual. It is important to maintain as normal a level of activity as possible, whilst avoiding overexertion. There is always a balance here and advice requires individual assessment. Rest advice might include:

- Limiting the length of rest period to, say, 30 min.
- Undertaking low-level physical (arts, crafts, etc.) and cognitive (reading, puzzles, etc.) activities depending on the severity of symptoms.
- Using relaxation techniques.
- Trying to avoid complete rest as the only management during a setback/relapse.

Prolonged bed rest should be avoided if possible. It is associated with significant physical deconditioning, psychological risks, and medical disorders including severe postural hypotension, venous thrombosis, osteoporosis, and pressure sores.

Relaxation techniques may help in the management of pain, sleep problems, and comorbid stress or anxiety. It is important that patients rest when tired, and not use caffeine or stimulating medications to "push through" periods of severe fatigue. Common relaxation techniques include:

- Progressive muscle relaxation. In this technique the individual focuses on slowly tensing and then relaxing each muscle group.
- Visualization. For example the individual may imagine a peaceful setting and then focus on controlled, relaxing breathing, slowing the heart rate.
- Other techniques include:
  - Massage,
  - meditation,
  - yoga,
  - music and/or art therapy.

Graded exercise therapy (GET) and management of daily activities are also fundamental therapeutic approaches. Before advising on exercise the clinician should consider the impact of joint hypermobility and joint instability in EDS, as well as the negative influence on exercise that arises from uncontrolled pain, fear of movement (kinesiophobia), and other associated conditions such as cardiovascular autonomic dysfunction.

Gradual exercise programmes may be beneficial for some patients, improving physical, psychological, and cognitive aspects of wellbeing. The main objectives in EDS of an exercise programme are the progressive prevention of physical deterioration, optimization of functional capacity without triggering injury, and pain control.

A suitably trained therapist or instructor should deliver GET. Recommendations such as "go to the gym," "exercise more," or "go swimming" are not helpful without supported advice on what this actually means, and should be avoided. It is recommended that exercise should be supervised, structured, and gradually increased in intensity (both in muscle strengthening and aerobic fitness as appropriate). Unstructured and unsupervised exercise may worsen symptoms, as can a rigid or inflexible escalation of activity.

GET should be based on the individuals' current level of activity and individual goals. When planning GET, it is important clinicians and/or therapists:

- Undertake an assessment of current activity analysis—while also ensuring that this does not of itself already lead to a "boom and bust" cycle.
- Discuss both short and long-term goals important and relevant to the individual.
- Agree on a level of additional low-intensity exercise that is sustainable
- Recognize that it can take weeks, months, or even years to achieve goals, and ensure that this is taken into account in the therapy structure and the ways services deliver treatment.
- Advise that increased levels of exercise may increase symptoms for a few days (e.g., stiffness and fatigue), but explain that this is normal.

Before completing a GET programme, it is important the individual has been advised on maintaining the exercise and strategies for managing set backs, including access to their clinician and/or therapist. Treatment of existing movement restrictions and biomechanical dysfunction using manual techniques can be a bridge to tolerating exercise for some individuals.

Activity management is a form of pacing, controlling activities by means that include:

- Planning daily activities to allow for a balance and variety of different types of activity, rest, and sleep.
- Spreading out difficult or demanding tasks over the day or week.
- Splitting activities into small achievable tasks.
- Monitoring, regulating, and planning activities to avoid a "boom and bust" cycle.
- Goal setting, planning, and prioritising activities.

Cognitive Behavioral Therapy (CBT) has both formal and informal approaches.[3] At an informal level, this involves education about symptoms, demystification of the medical problems, and explanation of how inactivity can aggravate a number of the problems that contribute to fatigue (e.g., deconditioning, orthostatic intolerance).

[3]The authors caution that the effect size of CBT is modest, that improvements are not always sustained, and that CBT has not been studied in those with more severe symptoms and impairment.

An individualized, person-centred programme should be offered to people with fatigue. The objectives of the programme should be to:

- Sustain or gradually extend, the person's physical, emotional, and cognitive capacity.
- Manage the physical and emotional impact of their symptoms.

The components, and progression throughout the programme should be based on the person's age, preferences and needs, and should be delivered only by a healthcare professional with appropriate training in CBT.

WHAT WE NEED TO KNOW

The incidence, prevalence, and natural history of fatigue in the hEDS population is unknown, so therefore also the distribution and types of (co-associated) mechanisms that trigger this phenomenon.

Also, it is unclear as to how many patients diagnosed with CFS actually really have EDS, not CFS.

Subgroup clinical trials of efficacy and safety of treatments are required to move beyond the limitations of case study and expert opinion evidence. Future studies are also needed to assess the effect of treatment on quality of life and fatigue.

The influence of anxiety disorders/mental health factors on presentation and response to treatment are also not clear.

SUMMARY

Fatigue is a common finding in EDS. It may present in a manner that is indistinguishable from CFS. Diagnosis of fatigue remains an area of uncertainty: the definition of fatigue remains uncertain and diagnostic tests are not available. The initial approach to fatigue in EDS is to exclude other conditions that may produce fatigue.

Conditions which are commonly seen in EDS and which may manifest as or exacerbate fatigue include sleep disorder, chronic pain, deconditioning, cardiovascular dysregulation, bowel and bladder dysfunction, psychological issues and nutritional deficiencies.

Treatment algorithms for fatigue are poorly defined and therapy is frequently ineffective and so aims of treatment should be realistic. Treatment should focus on improving symptoms, maintaining function and providing social, physical and nutritional support.

Where medical and physical interventions fail to provide substantial symptomatic or functional improvement, it is essential that clinicians provide on-going support to patients who are at risk of feelings of abandonment.

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ARTICLE

Gastrointestinal Involvement in the Ehlers–Danlos Syndromes

ASMA FIKREE, GISELA CHELIMSKY, HEIDI COLLINS, KATCHA KOVACIC, AND QASIM AZIZ*

Current evidence suggests that an association exists between non-inflammatory hereditary disorders of connective tissue such as the Ehlers–Danlos syndromes (EDS) and gastrointestinal (GI) symptoms. Patients with EDS can present with both structural problems such as hiatus hernias, visceroptosis, rectoceles, and rectal prolapse as well as functional problems such as disordered gut motility. It has recently been demonstrated that patients with hypermobile EDS (hEDS) present with GI symptoms related to the fore and hind-gut and these patients frequently meet the criteria for functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome. Presence of GI symptoms in EDS patients influences their quality of life. Specific evidence based management guidelines for the management of GI symptoms in EDS patients do not exist and these patients are often treated symptomatically. There is, however, recognition that certain precautions need to be taken for those patients undergoing surgical treatment. Future studies are required to identify the mechanisms that lead to GI symptoms in patients with EDS and more specific treatment guidelines are required.

KEY WORDS: Ehlers–Danlos syndrome; gut motility; abdominal pain; constipation; diarrhea

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INTRODUCTION

The current information on the gastrointestinal manifestations of Ehlers–Danlos syndrome (EDS) are summarized in this review. Information about management principles based on current evidence is provided together with suggestions for future research in the field.

METHODS

The gastrointestinal (GI) group had a number of telephone conferences to discuss the content of the literature review. It was agreed that a comprehensive literature search should be conducted and each member should provide a list of references relevant to specific areas.

The search terms used were "Ehlers–Danlos and gastrointestinal," "Ehlers–Danlos and GI," "Joint-hypermobility and joint hypermobility syndrome (JHS) and gastrointestinal," "Ehlers–Danlos hypermobility (EDS-HT)," "Ehlers–Danlos and perforation," "Ehlers–Danlos vascular," "Ehlers–Danlos type IV and gastrointestinal."

Management and Care Guidelines

There are currently no well validated national or international management and care guidelines for the management of EDS-related GI symptoms. GI symptoms are normally managed on empirical grounds using best practice models and evidence.

There are anecdotal reports of global improvement of hypermobile type of Ehlers–Danlos syndrome (hEDS) related symptoms following patient-led "trial and error" diet-based interventions, as well as through the use of enteral nutrition via nasogastric feeding, percutaneous endoscopic gastrostomy/jejunostomy feeding, and total parenteral nutrition. In 2005, a novel and theoretical approach to symptom management in

Dr. Asma Fikree is a consultant gastroenterologist at the Royal London Hospital, London, UK. Her Ph.D. was on gut manifestations of hypermobile EDS.

Dr. Gisela Chelimsky is a pediatric gastroenterologist in Milwaukee, Wisconsin, and is affiliated to Children's Hospital of Wisconsin and the Medical College of Wisconsin.

Dr. Heidi Collins is a physical medicine and rehabilitation specialist. She is chair of the EDNF Professional Advisory Network and works at Beacon Medical Group, Memorial Hospital, South Bend, IN.

Dr. Kovacic is assistant professor and a Pediatric Gastroenterologist. She is part of the nationally recognized GI motility program at the Children's Hospital of Wisconsin, Center for Pediatric Neurogastroenterology, Motility and Autonomic Disorders.

Prof. Qasim Aziz is a professor of neurogastroenterology at Barts and The London School of Medicine and Dentistry, and specialists in disorders of gut function.

*Correspondence to: Professor Qasim Aziz, The Wingate Institute of Neurogastroenterology, 26 Ashfield Street, London E1 2AJ.
E-mail: q.aziz@qmul.ac.uk
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EDS was described by Mantle et al. [2005]. The authors suggested that attention to nutrient intake, by use of supplements, may impact on symptom severity in EDS. Tinkle [2009] has also reported his experience with similar selected nutraceuticals in hEDS. In a 2015 review of gastrointestinal and nutritional issues in hEDS, Castori et al. [2015] suggested that there is a theoretical basis which suggests that lifestyle and nutrients may be beneficial in hEDS. Consequently, it is reasonable to postulate that these features may be managed or improved by nutritional supplementation and lifestyle modifications. In the author's own clinical practice, low FODMAP (Fructose, Oligosaccharides, Disaccharides, Monoamines, and Polyols) diet is frequently used to good effect for abdominal bloating, pain, and diarrhea, these features often overlap with irritable bowel syndrome (IBS) where the efficacy of this diet is now well established. Given that approximately 37% of patients with a diagnosis of IBS meet the criteria of hEDS [Fikree et al., 2015], it is not surprising that efficacy of this diet is being seen. However, further controlled studies are required to determine efficacy of the diet based interventions in patients with GI symptoms associated with hEDS.

In the author's own clinical practice, low FODMAP (Fructose, Oligosaccharides, Disaccharides, Monoamines, and Polyols) diet is frequently used to good effect for abdominal bloating, pain, and diarrhea, these features often overlap with irritable bowel syndrome (IBS) where the efficacy of this diet is now well established.

Surgical management of patients with vascular EDS who develop acute GI complications such as bleeding or perforation has been described in the literature. These approaches range from refrain from intervention with conservative non-surgical management of intestinal perforation [Casey et al., 2014] to more conventional surgical management with resections of appropriate segments of the gut. It has been suggested that during surgery, all organs must be treated gently due to tissue fragility [Omori et al., 2011]. A systematic review of GI surgery and related complications in EDS [Burcharth and Rosenberg, 2012] suggests that surgery in patients with EDS is associated with a high risk of complications, which is why preoperative indications should be carefully considered. Furthermore, optimal therapy for these patients includes the awareness that EDS is a systemic disease involving fragility, bleeding, and spontaneous perforations from almost all organ systems. The authors suggested that a nonsurgical approach can be the best choice for these patients, depending on the condition.

Desmopressin has been used in a preliminary study of hEDS associated bleeding symptoms such as easy bruising, epistaxis, menorrhagia, and gum bleeding [Mast et al., 2009]. In these patients, desmopressin was given intranasally or intravenously and led to significantly reduced bleeding time. In the same study, desmopressin was also given to patient's pre-surgery (non-GI surgery) and none of these patients suffered from any post-surgical bleeding complications, in contrast, 30% of the patients who did not receive desmopressin developed post-operative bleeding complications. This suggests that desmopressin may have a role in the management of GI peri-surgical bleeding complications in EDS patients but further studies are required to test this hypothesis.

Recently, Fikree et al. [2015] have demonstrated that a significant proportion of patients with Functional Gastrointestinal Disorders (FGID) meet the criteria for hEDS. Patients with this overlap have a different phenotype with more chronic pain, somatization, autonomic symptoms and anxiety, and poorer pain-related quality of life compared to those without the overlap. Thus, it is likely that management of FGID patients with and without EDS overlap may differ. For instance, those with overlap may require earlier identification and holistic multidisciplinary management involving for instance rheumatologists, autonomic neurologists, and pain specialists.

Chronic musculoskeletal and visceral pain is common in patients with EDS. It is, therefore, likely that opioids will be considered in the management of these patients, which can significantly influence GI function and lead to deterioration in symptoms. Hence, avoidance of opioids should be a consideration in those with GI involvement.

Chronic musculoskeletal and visceral pain is common in patients with EDS. It is, therefore, likely that opioids will be considered in the management of these patients, which can significantly influence GI function and lead to deterioration in symptoms. Hence, avoidance of opioids should be a consideration in those with GI involvement.

Recognition that anatomical abnormalities such as diverticulosis, rectoceles, and prolapse can occur in patients with EDS may help to plan investigation and treatment in patients with GI symptoms. For instance, constipation is common in patients with hEDS [Fikree et al., 2014], and recognition that symptoms may at least partly be due to rectal evacuatory dysfunction due to the anatomic abnormalities such as rectocele and or prolapse may help to guide the management toward nurse led therapy aimed at improving defecatory dynamics or in some severe cased

surgical correction of the anatomic abnormality.

GI Connective Tissue Abnormalities in Disease

Localized abnormalities in connective tissue have been described in association with GI pathology. In diverticular disease, there is increased elastin deposition in the taenia of the colon, and structural changes in the collagen of the smooth muscle [Whiteway and Morson, 1985]. Patients with hiatus hernias have fragmentation and distortion of elastin in their gastro-hepatic and phreno-esophageal ligaments [Curci et al., 2008]. Children with megacolon have atrophy of collagen in the tendinous connective tissue membrane of the myenteric plexus and muscularis propria, referred to as "atrophic desmosis" [Meier-Ruge, 1998]. Evidence also exists for the association between GI pathology and both inflammatory and non-inflammatory connective tissue disorders [Braun and Sieper, 1999]. A rationale, therefore, exists for an influence of connective tissue disorders on gut structure and function. Evidence now exists of involvement of the entire GI tract in EDS.

EDS AND ABNORMAL GI TRACT

EDS and Abnormal GI Anatomy

In a study of EDS patients, only 11 out of 143 (7.7%) who underwent endoscopic assessment had a hiatus hernia [Nelson et al., 2015]. A study in patients with lower urinary tract dysfunction demonstrated that patients with hEDS were significantly more likely to have symptoms of rectal evacuatory dysfunction and evidence of rectal morphological anomalies, for example, rectal prolapses, compared to those without hEDS [Manning et al., 2003]. In a case series of EDS patients at the Mayo clinic, all 4 patients who underwent an MR proctogram had an anterior rectocele [Nelson et al., 2015]. In the same study, 12 (11%) out of 110 who underwent colonoscopy had diverticulosis or diverticulitis.

Case reports of patients with hEDS describe further anatomical abnormalities in small numbers of patients. Diverticular disease has been described in association with EDS [Lindor and Bristow, 2005]. Visceroptosis of the bowel has been described in two patients with hEDS [Reinstein et al., 2012]. This refers to the downward displacement of abdominal organs below their natural position. It is rare and its aetiology is unknown. It can cause kinking of thin walled structures such as blood vessels and nerves and thereby cause symptoms, which can be severe. In the case described, the patient presented with a 4 year history of abdominal distension and bloating that interfered with her eating and activities of daily living.

EDS and Abnormal GI Physiology

Results of gastrointestinal physiological studies were reported in a retrospective observational study from the Mayo clinic in EDS patients of whom the vast majority had hEDS (71.7%) [Nelson et al., 2015]. About 13 out of 46 (28%) patients who underwent colonic transit studies had abnormal results; nine with slow transit and four with fast transit. A total of 60% of these patients with abnormal colonic transit had hEDS In the same study, 17 out of 76 (22%) patients had abnormal gastric emptying half being fast and half being slow Abnormal oesophageal manometry was present in 5 out of 11 (31%) patients. About 7 out of 16 patients (44%) had pathological acid reflux on reflux testing.

Association Between hEDS and GI Symptoms

The association between hEDS and GI symptoms was first described 12 years ago by Hakim and Grahame [2004]. They found that hEDS patients attending a hypermobility clinic had significantly more GI symptoms compared to age and sex matched controls (37% vs. 11%). The most common GI symptoms were nausea, abdominal pain, constipation, and diarrhea. It was felt that dysautonomia was one mechanism by which this may occur [Gazit et al., 2003; Hakim and Grahame, 2004], and since then it has been shown that Postural Tachycardia Syndrome (PoTS) is associated with GI symptoms such as nausea, reflux, bloating, constipation, and diarrhea [Mathias et al., 2011]. Thus, it would appear that hEDS, autonomic symptoms, and GI symptoms are indeed linked, though the exact mechanism for the association is unknown.

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As that landmark study, other studies in various hospital settings and countries, have confirmed that GI symptoms are common in patients with an existing diagnosis of hEDS. In a study of 21 hEDS patients attending a genetics clinic in Italy, 87% of patients were found to have GI symptoms, most commonly dyspepsia (67%), gastro-oesophageal reflux (57%), recurrent abdominal pain (62%), alternating constipation and diarrhea (33%), and abdominal hernias (5%) [Castori et al., 2010]. Furthermore, the same author demonstrated that the incidence of GI symptoms increased with age, and that older hEDS patients were more likely to have GI symptoms than their younger counterparts.

In a prospective cross-sectional study of over 600 new patients in

secondary care GI clinics, Fikree et al. [2014] looked at three groups of patients including those with established hEDS from rheumatology clinics (hEDS-Rh), those with hEDS albeit previously undiagnosed (hEDS) and those without hEDS (non-hEDS). They demonstrated that approximately one-third of unselected patients attending GI clinics have previously undiagnosed hEDS based on validated clinical criteria; however, the GI symptom profile in these patients is less severe than that observed in patients with established hEDS referred from rheumatology clinics. In the newly diagnosed hEDS patients, there was a significant association with gastro-oesophageal reflux and dyspeptic symptoms but not with alternating bowel habit, chronic abdominal pain, dysphagia, globus, and bloating; however, these symptoms were more common in the hEDS-Rh group. Autonomic dysfunction, chronic pain, and analgesic use, but not psychopathology, showed increasing trends across the three groups, being highest in patients with hEDS-Rh. Thus, they concluded that hEDS is common in GI clinics, with increased burden of upper GI and extra intestinal symptoms.

Studies from a Genetics Department in Belgium not only confirm that GI symptoms such as constipation, diarrhea, bloating, and swallowing problems are present in hEDS, but that these GI symptoms are associated with clusters of other extra-articular symptoms, in particular cognitive problems, insomnia, postural dizziness, and syncope [Rombaut et al., 2011]. This group also recognized that there was large heterogeneity in presentation and not all patients had the same cluster of symptoms. Consequently, they performed a cluster analysis and identified that two main clusters. In both clusters, musculoskeletal symptoms were most prominent; however, the pattern of extra-articular symptoms differed. GI symptoms were particularly prominent in the cluster, which also had high levels of fatigue, cutaneous changes, orthostatic, immune, urogynecological, visual, and respiratory problems [De Wandele et al., 2013].

hEDS and Organic GI Disorders

Only two published studies exist which demonstrate a possible association between hypermobility and organic disorders, and these were done in patients with inflammatory bowel disease (IBD) and celiac disease. The first was performed in a Greek Hospital setting [Vounotrypidis et al., 2009] which described that the prevalence of hEDS in Crohn's disease (12.2%) was higher than that in UC (3.6%) but this difference was not statistically significant. Fikree et al. [2015] also demonstrated a relatively high prevalence of JHS in Crohn's disease and ulcerative colitis patients (32% and 21%, respectively). No other studies have further examined this association between EDS and IBD.

One small study demonstrated a high prevalence of celiac disease in hEDS patients [Danese et al., 2011]. Thirty-one patients attending a genetics clinic with an established hEDS diagnosis were screened for celiac disease using IgA/G endomysial antibodies and/or anti-tissue transglutaminase, of which six (19%) tested positive. Duodenal biopsies from five had features consistent with celiac disease. The prevalence of celiac disease (16%) in the hEDS group was, therefore, significantly higher than the estimated population prevalence (1%) [Danese et al., 2011]. However, there are a number of limitations to this study. First, the population prevalence of celiac disease was estimated rather than calculated. Second, the basis on which hEDS patients were selected for testing for celiac disease is not described and, therefore, there may be a degree of selection bias. Nevertheless, these results were broadly corroborated in another study with a small sample size, where hEDS was diagnosed in four out of 13 (30%) patients attending GI clinics with a new diagnosis of celiac disease [Fikree et al., 2015].

hEDS and Functional GI Disorders

Direct evidence for an association between FGID and generalized joint hypermobility initially came from a retrospective observational study in tertiary gastroenterology setting [Zarate et al., 2009]. A subgroup of these patients were assessed further by a rheumatologist, and found to have hEDS. Patients with hEDS tended to have motility problems in their gut on physiological testing, for example, small bowel dysmotility, delayed gastric emptying and delayed colonic transit. This study suggested that in a tertiary neurogastroenterology setting, hEDS was associated with GI dysmotility.

In studies demonstrating the presence of GI Symptoms in hEDS, GI symptoms were often attributable to FGID subtypes such as IBS, rectal evacuatory dysfunction, and functional constipation [Manning et al., 2003; Castori et al., 2010; Zeitoun et al., 2013], all of which are ROME III categories of FGID. In another paper, two-thirds of patients with hEDS who reported having appendectomies for abdominal pain did not have a positive outcome of surgery, suggesting that the pain was more likely to be secondary to a functional cause rather than appendicitis [Rombaut et al., 2011].

Fikree et al. [2015] further studied the association between hEDS and FGID and the impact of this association on comorbidities and quality of life (QOL). In a prospective case-control study in secondary care GI clinics over 2 years, hEDS was assessed prior to consultation in consecutive new patients. It was demonstrated that hEDS prevalence was higher in FGID compared to organic GI disorders (39.0% vs. 27.5%, ORadj: 1.51, CI: 1.07–2.12, $P = 0.02$), and particularly associated with functional gastroduodenal disorders (44.1%, ORadj: 2.08, CI: 1.25–3.46, $P = 0.005$), specifically postprandial distress syndrome (51%, ORadj: 1.99, CI: 1.06–3.76, $P = 0.03$). FGID patients with hEDS had increased chronic pain, fibromyalgia, somatization scores, urinary autonomic scores, and worse pain-related QOL scores. The authors concluded that hEDS is significantly associated with FGID, and this subgroup of patients have increased comorbidity and decreased QOL.

hEDS and GI Symptoms in Children

Data on gastrointestinal manifestations in children with hEDS is limited.

However, several studies link constipation with childhood generalized joint hypermobility (GJH) as determined by the Beighton score. These studies found constipation rates ranging from 11% to 38% in hypermobile children. Constipation was more common in hypermobile boys [de Kort et al., 2003; Adib et al., 2005; Reilly et al., 2008].

A variety of gastrointestinal symptoms and functional GI disorders have also been linked to joint hypermobility in children. Pacey et al. [2015] reported gastrointestinal symptoms in 54% of children with GJH. Kovacic et al. [2014] found a 56% prevalence of GJH in adolescents diagnosed with complex functional GI disorders. In these patients, fibromyalgia appeared associated with GJH. A large population study in India found a high prevalence of GJH and a possible link of this condition with moderate-severe malnutrition [Hasija et al., 2008].

GI Symptoms in Other Subtypes of EDS

GI symptoms have been described in EDS I, II, and IV subtypes as well as in patients with Tenascin X deficiency.

In classic EDS (cEDS), diverticular disease has been described [Kitsiou-Tzeli et al., 2010]. Although spontaneous acute pancreatitis has been described in cEDS, it is not clear if this is a true association or an incidental finding [Sarra-Carbonell and Jimenez, 1989].

Various GI manifestation of the vascular type of EDS (vEDS) has been described. Most of these relate to organ perforation and or bleeding [Pepin et al., 2000; Baichi et al., 2005; Diz et al., 2009; Omori et al., 2011; Anderson and Sweetser, 2014; Yoneda et al., 2014]. Familial cases of sigmoid perforation have also been described [Surgey et al., 2011]. There also appears to be increased risk of colonic perforation during colonoscopy [Rana et al., 2011]. Occult and overt small bowel perforation can also occur [Aldridge, 1967; Leake et al., 2010]. Even esophageal perforation has been described [Habein, 1977]. Furthermore, congenital diaphragmatic hernia (CDH) has been reported in two siblings with a suspected diagnosis of vEDS with consanguineous parents [Lin et al., 2006]. The index case was a 3-year-old girl who had surgery for CDH at 5 months of age, with recurrence 6 months later followed by further surgery. Recurrence at 3 years of age prompted further investigations. Two-dimensional echocardiography revealed an atrial septal defect, dilatation of the pulmonary arteries, and suspected abnormally tortuous aorta. Subsequent contrast-enhanced magnetic resonance angiography revealed marked tortuousity of the aorta and the innominate, left common carotid, left subclavian, and bilateral vertebral arteries, that was suggestive of EDS. Further detailed evaluation of the patient revealed hyper elastic skin and mild hypermobility of the knee joints. A chromosome study did not demonstrate an obvious abnormality but diagnosis of vEDS was made on clinical grounds. Subsequently, her 1-year-old brother was also diagnosed with CDH.

Various GI manifestation of the vascular type of EDS (vEDS) has been described. Most of these relate to organ perforation and or bleeding. Familial cases of sigmoid perforation have also been described.

vEDS complicated by eventration of the diaphragm and colonic and jujenal perforation has been described [Iwama et al., 1989]. Post-operative celiac artery thrombosis [Debnath et al., 2007] and other complications [Freeman et al., 1996] can also occur in vEDS. In addition, spontaneous rupture of the liver [Gelbmann et al., 1997; Mistry et al., 2000; Ng and Muiesan, 2005] and spleen [Privitera et al., 2009] as well as post-operative bleeding into the liver capsule [Blaker et al., 2007] has been reported in these patients.

In a review of surgical complications of vEDS by Freeman et al. [1996], 44 gastrointestinal and 45 vascular complications of vEDS have been reported in the literature between January 1975 and July 1995. This included 41 colon perforations, two paraesophageal hernias, 22 spontaneous haemorrhages, 17 aneurysms, and 5 arterial dissections. A total of 27 colonic perforations were treated with resection and diversion, 11 with total abdominal colectomy (TAC), and 3 with primary colon repair. Re-perforation occurred in 15 resection/diversion patients versus none treated with TAC ($P < 0.05$). Seven patients (23.3%) died from their gastrointestinal complications. Twelve (30%) patients died from vascular complications of vEDS, seven of whom had been treated with arterial reconstruction ($P < 0.05$). This review supports treating colon perforations in vEDS patients with TAC and end ileostomy to avoid a re-perforation or an anastomotic leak. Stillman et al. [1991] have described spontaneous colonic perforation, a complication traditionally treated by primary closure of the perforated segment and creation of an end colostomy, while attempts at bowel re-anastomosis often result in repeated colon perforations. They present a patient with vEDS with colonic perforation proximal to an end colostomy, and describe the surgical strategy to prevent recurrences of this and other postoperative complications associated with the syndrome.

GI symptoms have been described in patients with Tenascin X (TNX) deficiency including abdominal pain [Lindor and Bristow, 2005] episodes of spontaneous and secondary ileus and perforations (sigmoid and duodenum), with post-operative incisional hernia and incarceration. Chronic constipation and rectal prolapse, pan colonic diverticulosis with diverticulitis, uterine prolapse, and moderate sized hiatus hernia [Lindor and Bristow, 2005] have also been described. Increased incidence of GI problems in family members of TNX deficiency patients have been described including chronic constipation since childhood, and rectal prolapse. Spontaneous perforation of colonic diverticulum,

multiple intra-abdominal abscesses, duodenal and sigmoid diverticulae have also been reported in TNX deficient patients. Gastric ulceration [Hendriks et al., 2012] and GI bleeding [Schalkwijk et al., 2001] has also been described in a male patient with homozygous for TNX deficiency.

FUTURE DIRECTIONS

It is clear from the above literature review that GI symptoms can occur in all EDS subtypes. GI perforations and bleeding complications are less likely in hEDS and most likely in vEDS than in the other subtypes. There is a high prevalence of hEDS in patients presenting with the features of FGID especially functional dyspepsia. hEDS patients with GI symptoms also often have a combination of musculoskeletal, autonomic, and urinary tract symptoms.

There remain several knowledge gaps and future work will be needed to address these on an epidemiological, physiological, cellular, molecular, and genetic level. The aetiology of GI symptoms in individuals with EDS will need to be determined and this will require investigation of biomechanical, autonomic, and sensorimotor function of the upper GI tract. The understanding of which EDS individuals will develop GI symptoms and how they progress over time, what other factors such as poor nutrition, traumatic life events, viral infections, and so on, precipitate the worsening of GI and extra-intestinal symptoms in these patients will require longitudinal studies. Improving our understanding of the above-mentioned factors will enable better treatment strategies to be devised.

Identification of the nature of the connective tissue defect in EDS and its relation to the functioning of the GI tract is undeniably an important question now and will require genetic studies in humans and validation studies in animal models. The mechanism of the link between EDS and PoTS also needs further study. Furthermore, signaling between the extracellular matrix (component of connective tissue) and intracellular structures is now recognized as being critical to normal cellular function, and there has been increasing research into various signaling components (e.g., growth factors) which might provide treatable targets in the future. Genetic studies such as exome sequencing on families of patients with hEDS, and in patients who have had deep phenotypic profiling perform are some of the methods that may pave the way of identification of the molecular abnormalities that underlie this hitherto difficult to understand disorders.

CONCLUSION

Current literature suggests an association between all subtypes of EDS and GI symptoms. This association is common and has hitherto been underestimated. The group observed that evidence for GI symptoms to be included as a major EDS diagnostic criteria is compelling. However, a causative relationship between abnormalities in connective tissue and GI symptoms has not yet been established. Similarly, specific evidence based guidelines for the management of EDS patients with GI symptoms are not yet available.

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ARTICLE

Orthopaedic Management of the Ehlers–Danlos Syndromes

WILLIAM B. ERICSON JR.* AND ROGER WOLMAN

The role of orthopedic surgery in Ehlers–Danlos syndrome is inherently controversial, opaque to most patients and many medical providers, and difficult to discern from available medical literature. Non-operative treatment is preferable, but for carefully selected patients, specific joint stabilization and nerve decompression procedures can provide symptomatic relief when conservative measures fail.

KEY WORDS: orthopedic surgery; Ehlers–Danlos syndrome; joint stabilization; nerve decompression; musculoskeletal treatment

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INTRODUCTION

Ehlers–Danlos Syndrome (EDS) is a connective disorder that in the orthopedic realm involves joint hypermobility (JH). JH is not always painful, but if so, (1) is difficult to diagnose without highly specialized training, (2) does not show on standard diagnostic tests, (3) does not respond to standard treatment protocols, (4) lowers the threshold for associated joint injuries, (5) causes premature wearing of joints, and (6) results in a higher failure rate for treatment, both medical and surgical.

EDS is often either not diagnosed or misdiagnosed, and the situation can be extremely frustrating for the patient as well as the physician and other caregivers. In spite of this, there is much that can be done for EDS patients. The role of the musculoskeletal specialist (e.g., orthopedic surgeon, physiatrist, rehabilitation medicine specialist, rheumatologist) in the care of EDS patients is to help determine the cause of the patient's complaints, and recommend treatment, based on the specific musculoskeletal diagnosis or diagnoses. It is extremely important for the physician to understand the context in which the joint problem occurs, and that the physician understands the individual patient's specific needs and expectations. This requires a thorough understanding of the bodily manifestations of EDS as well as extensive knowledge of the pathophysiology other painful conditions that cause similar, overlapping symptoms, and appreciating how these problems are affecting the individual person being treated.

The role of the musculoskeletal specialist (e.g., orthopedic surgeon, physiatrist, rehabilitation medicine specialist, rheumatologist) in the care of EDS patients is to help determine the cause of the patient's complaints, and recommend treatment, based on the specific musculoskeletal diagnosis or diagnoses.

The authors have extensive experience with patients with JH issues, and the following is a brief summary, describing a general approach to patients with EDS and JH. The authors do not specifically endorse, approve, recommend, or certify any specific procedure or technique, and provide these opinions for general information only. Such information should not be considered medical advice and is not intended to

William B. Ericson Jr., M.D., F.A.A.O.S., F.A.C.S., F.A.E.N.S., is a board certified orthopedic hand surgeon, and a graduate of MIT and Harvard Medical School. He has a special interest in painful conditions that do not show on standard diagnostic tests, which include small joint instability and peripheral nerve disorders. He has a large experience with Ehlers–Danlos syndrome patients.

Roger Wolman, M.D., F.R.C.P., F.F.S.E.M., trained in Rheumatology and Sport and Exercise Medicine. He has written on Exercise following Brain injury and Exercise and Arthritis. He practices holistic medicine and has a strong belief in the health benefits of exercise. In the NHS, he runs an Exercise Prescription clinic with the aim of replacing medication with Exercise as the most effective way of managing many chronic diseases. His practice at Spire Bushey incorporates these areas into his general Rheumatology and Sports Medicine clinics.

*Correspondence to: William B. Ericson Jr., M.D., F.A.A.O.S., F.A.C.S., F.A.E.N.S., Ericson Hand Center—Research, 6100 219th Street SW Suite 540, Mountlake Terrace, WA 98043. E-mail: wbe@wbericson.org; ericsonhandcenter@icloud.com

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replace consultation with a qualified physician. Complex musculoskeletal problems may best be served by a Multi-Disciplinary Team (MDT) approach including physicians (surgeons, rheumatologists, pain consultants), physiotherapists, occupational therapists, psychologists, and nurses. A coordinated team can help to plan management more effectively and can include a comprehensive inpatient (or outpatient) pain management program.

MEDICAL LITERATURE

There is sparse information in the medical literature regarding the role of orthopedic surgery in patients with EDS, particularly successful surgery. For example, a recent review article on EDS in the Journal of Hand Surgery discusses the presentation of patients with EDS and reviews the phenotypes, but does not discuss any surgical procedures that might be appropriate for patients with EDS [Christophersen and Adams, 2014]. Many journal articles refer obliquely to the higher rate of complications, treatment failure, and patient/provider dissatisfaction with surgical intervention [Freeman et al., 1996] but often lack detailed analysis or explanation of why surgery did not go well [Weinberg et al., 1999]. Under the best of circumstances, it would be difficult to form discrete, reliable generalizations about the role of orthopedic surgery in EDS patients from the available medical literature. Determining the correct and complete diagnoses in an EDS patient can be a difficult task, and the risks of all of the known hazards of surgical intervention are distinctly higher in EDS patients.

The multiple forms of EDS also have widely varying clinical manifestations [Shirely et al., 2012], and there is inherent genetic heterogeneity that further complicates any attempt at abstraction of published data. There is also considerable unfamiliarity among medical professionals regarding the clinical history, physical exam, diagnostic testing, treatment, or long-term implications of joint instability. And, unfortunately, diagnosing joint instability is not something that can be learned from medical literature or online courses; one must be educated by a hands-on approach, with direct physical contact.

Not all JH is related to EDS, and there is controversy regarding labeling EDS patients with their specific phenotype. It would be helpful in terms of tracking patients and further determining likely patterns of associated clinical problems to know their exact genetic group, but, in a practical sense, one must still deal with the involved painful joints, whether or not the group or subgroup is known. Labeling patients can increase their fear and anxiety, particularly when unfiltered information is freely available on the internet, and once labeled, the resulting bias can cause misinterpretation of subsequent symptoms by treating physicians for other conditions that may not be related to EDS.

BASICS

The medical term for partial dislocation of a joint is "subluxation," and EDS patients have frequent subluxation and occasional dislocation of large and small joints. The asymmetric loading of the joint surfaces as the joint subluxes contributes to the early wear of the joint surface, and it takes very little injury to make a "loose" joint "loose and painful." At least some of the pain is from stretch receptors near the joints, and/or from swelling of the lining of the joints. This source of pain is not reflected by diagnostic studies, at least in the early stages, and physical examination for joint instability is not routinely taught outside of orthopedics, and is not taught consistently for all joints within orthopedics.

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In a sense, EDS causes premature aging of the musculoskeletal system. Many of the musculoskeletal problems that can afflict anyone, if they live long enough, occur simultaneously in EDS patients, at an earlier age, and unfortunately also tend to cause overlapping symptoms. It can be particularly challenging for a physician to "disambiguate" the root cause(s) of the patient's symptoms.

EDS patients often have nerve pain, presumed to be related to traction and/or compression of the peripheral nerves. This type of nerve problem does not typically damage the nerves, but causes pain where the nerves end, not where they are compressed, and unfortunately does not show on electrodiagnostic tests, and can be refractory to treatment. Referred pain from nerve problems can mimic joint pain from instability, and this feature of EDS/JH seriously complicates the lives of EDS patients and their physicians.

CLINICAL PRESENTATION

EDS patients tend to present with multiple complaints, specifically vague, intermittent pain involving the limbs or spine. Doctors have a tendency to seek a simple, single diagnosis or unifying approach (the invocation of Occam's Razor), such as a attributing joint pain to a "sprain," even when there has been no injury per se, or invoking the label "fibromyalgia" when there is widespread pain. As the treatment fails, and diagnostic testing become more exhaustive but remains negative, patients often drift between different specialists—rheumatology, neurology, orthopedics, pain management—without a firm diagnosis or successful treatment plan. Patients with EDS have increased rates of

clinical depression [Berglund et al., 2015], which can seriously complicate physician and patient interpretation of strictly subjective complaints. Patients with EDS are often labeled as the problem, rather than their arm or leg. Physician burnout (emotional exhaustion, depersonalization, and low job satisfaction) in orthopedic surgeons is endemic in the United States [Daniels et al., 2016], and is likely to have more of an impact on EDS patients, with their numerous, unexplained symptoms, and seemingly unsolvable problems.

Successful surgery in general depends on the correct diagnosis (or in the case of EDS patients, diagnoses), establishing realistic expectations, and superlative technical expertise. In EDS patients, it tends to be much harder to determine the exact cause or causes of the patients' pain, expectations of the patient and/or physician may be unrealistic, and technical difficulties can have much more serious consequences. In spite of this, for patients with painful instability of joints or peripheral nerve compression, surgery may be the only treatment that reliably results in persistent pain relief.

PAIN RELIEF

Pain relief is a clear goal of every EDS patient. Surgery is often the last resort for EDS patients, and may be the only reasonable option for some conditions, such as wrist or thumb instability, but also may not be an option at all. For example, the tissues around an unstable joint may be so lax that NO surgical procedure will ever be successful. EDS patients have a higher incidence of bleeding complications, and wider scars, and less predictable healing. This does not mean they should not have surgery, but optimal treatment would include involvement of a surgeon with knowledge and experience specifically with EDS patients. Managing patients prior to considering surgical intervention is best performed by a comprehensive, multifaceted approach to care delivered by knowledgeable EDS providers.

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NON-SURGICAL TREATMENT OPTIONS FOR EDS PATIENTS

Generally speaking, non-surgical options for treatment of joint pain should be exhausted prior to recommending surgery. The following is a partial list of treatments that may help avoid the risks of surgery.

Acute Pain

Pain may be from an acute event, or a chronic pattern. In the acute setting, the standard orthopedic "R-I-C-E" (Rest, Ice, Compression, Elevation) treatment is safe and can be effective. It is not particularly effective or practical in the chronic setting. Associated joint injuries such as anterior cruciate ligament and meniscal tears in the knee, labral and rotator cuff tears in the shoulder, wrist instability, thumb joint subluxation, labral tears in the hip, and lateral ankle ligament tears are much more common in the EDS patient population; the usual treatment options for any patient with an acute musculoskeletal injury are appropriate for most EDS patients.

Chronic Pain

In the chronic setting, there are multiple options that may be effective. Patients and physicians would both appreciate an "oral medication" that results in effective pain relief, especially when diagnostic testing is normal but patients are obviously suffering. EDS patients often have multiple joints that are sore simultaneously, and a medication that reduced pain in all sore joints would be beneficial and desirable. Unfortunately, oral medication for EDS patients is problematic: Medications do not change the underlying cause of the pain, and often have side effects that negate their efficacy.

EDS patients often have a high incidence of gastroesophageal reflux [Castori, 2012], and often cannot take non-steroidal anti-inflammatory drugs (NSAIDs), or require a second medication (e.g., acid blocking, acid reducing, or antihistamine) to protect the stomach. Acetaminophen does not irritate the stomach, but is often insufficient for pain relief, and large doses can be toxic to the liver [Fontana, 2008]. Chronic use of opioid medications tends to result in tolerance and patients are at risk for dependence. Opioids are also central depressants, and tend to make postural issues worse, and can result in "central sensitization," where normal physical stimulus becomes interpreted as painful. There is also a growing legislative trend to restrict or suppress doctors from prescribing narcotics, owing to the recent rapid increase in fatal overdoses. Gabapentin and Pregabelin are similar and also anxiolytic, but associated with weight gain. Naltrexone has been used off-label for chronic pain with some success [Younger et al., 2014].

"Splints" can be quite helpful for specific types of joint instability. Several splint manufacturers make braces for most large joints, including the spine, which can be extremely helpful as part of a coordinated treatment program. Splints limit joint motion, and can therefore limit pain, but may or may not result in increased stability, and if used consistently can make muscles weaker through disuse. Special purpose finger splints are particularly effective for "Swan Neck" hyperextension deformities of the finger proximal interphalangeal (PIP) joints, and can also be effective in many patients for the thumb metacarpal–phalangeal (MP) and carpal–metacarpal (CMC) joints.

"Physical therapy" and "exercise" programs are essential components to successful pain relief in patients with

EDS (See also "The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents and Adults Diagnosed With Joint Hypermoblity Syndrome/Hypermobilie Ehlers–Danlos Syndrome" by Engelbert et al., this issue). Exercises that emphasize low-impact, isometric and eccentric strengthening, proprioception, and improved posture can be extremely helpful. Physical therapy can be used effectively to increase core muscle strength, and to stabilize specific joints such as the spine, shoulder, and knee. Exercise programs, often self-directed, that do not take into account that EDS patients have loose joints but tight muscles are doomed to failure. Exercise programs that emphasize "range of motion" exercises or repetitive, forceful actions such as "work hardening" are inappropriate and can make patients' joint symptoms worse.

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"Local anesthesia" injections can be helpful in determining the source of pain. It should be noted that the most common forms of local anesthesia, xylocaine, and bupivacaine, are now known to be specifically and highly cytotoxic to chondrocytes [Chu et al., 2010], and ropivacaine should be used preferentially for intra-articular injections. EDS patients are often resistant to lidocaine and bupivacaine [Hakim et al., 2005], a fact underappreciated by most physicians. Anecdotally, carbocaine tends to work better in EDS patients.

"Dietary considerations" are becoming more important and the so-called "anti-inflammatory" diets are in vogue these days. There may be clearer indications for specific dietary recommendations in the future. "Weight control" is a major imperative for any patient with EDS. "Bone health," with adequate calcium intake and appropriate vitamin D levels, is very important. Exercise is also an important component of bone health, but is problematic as physical activities can easily exacerbate pain related to instability.

SURGICAL TREATMENT OPTIONS FOR EDS PATIENTS

EDS patients are at increased risk from any form of surgery, and the outcomes are less predictable. The decision to recommend an orthopedic operation needs to be carefully considered, ideally through close collaboration between the patient, the musculoskeletal physician, the orthopedic surgeon, and the multidisciplinary team.

Surgery is an option for a select number of specific conditions in EDS patients, but there remains very little in the surgical literature to support this approach. The rate of failure of surgical intervention is clearly higher in EDS patients, particularly for conditions where ligaments are repaired, but another cause of failure is the fundamental assumption errors that are made during the diagnostic process. That is to say, the cause of the patient's pain was something other than what was operated on. In the opinion of one author (Ericson), this is particularly true in the upper extremity. This type of error is more likely to occur when the patient and his/her concerns are not the complete focus of the medical appointment.

In spite of this, EDS patients have multiple problems for which surgery may be the only reasonable option, if the diagnosis can be made correctly. With upper extremity surgery, at least in one author's experience (Ericson), most EDS patients do not have significant problems with wound healing or bleeding. Scars tend to be wider, so smaller incisions are advisable. Joint stabilization procedures in EDS patients have a higher rate of recurrence of instability, but it is lower for non-weight bearing joints such as the wrist and thumb. The lower extremity is less forgiving. Normal diagnostic tests and a higher failure rate should not preclude surgical intervention in the EDS population, but serious prudence is advised.

Cervical Spine

Craniocervical instability and Arnold–Chiari malformation may absolutely require surgical intervention. Upright MRIs are advisable when evaluating the cervical spine. Cervical spondylosis is common, and discectomy and fusion may be necessary. However, making one segment of the spine rigid tends to increase the load at each end of the fusion site, and "next-segment" disease has a much higher incidence in patients with JH. Minimally invasive techniques, when appropriate, are preferred. JH is a relative contraindication for artificial disks.

Thoracic Outlet

Thoracic outlet "symptoms" are common in EDS patients, and are often related to Thoracic Outlet Syndrome (TOS). The thoracic outlet is the space where nerves and blood vessels to the arm pass from the neck/chest area into the arm. The nerves in this area are subject to compression from the anterior scalene and pectoralis minor muscles, and the 1st rib. They are also subject to tension from inferior shoulder subluxation in patients with JH (causing thoracic outlet "symptoms" related to posture and joint laxity). Compression and/or tension on the nerves in this area cause symptoms where the nerves end, not where they are pinched or pulled. The result is vague hand/arm pain that unfortunately overlaps with the other areas that tend to be painful in patients with loose joints. Physical therapy is essential for this condition. Botox injections into the anterior scalene or pectoralis minor muscles can give tremendous relief if the patient has

TOS. Surgery may be indicated in recalcitrant cases, but detaching stabilizing muscles in loose-jointed patients can definitely make patients worse. TOS is an inherently complex and controversial topic in the medical community [Moore, 1986; Parker and Parker, 2002; Wehbe, 2004; Illig et al., 2013] and seriously complicates the lives of many patients with EDS.

Shoulder

Shoulder instability is a very common problem in EDS patients, but fortunately responds well to physical therapy in most patients. The goal of therapy is to increase the resting tone of the rotator cuff muscles, without overpowering the deltoid, which can cause bursitis and/or impingement. Radiographs and MRI are typically normal. Surgery in the form of a Neer Inferior Capsular Shift can be extremely helpful in stabilizing the shoulder [Neer and Foster, 1980; Pollock et al., 2000]. Possible complications include recurrent instability, and joint stiffness. In patients with very, very loose shoulders this procedure has a high failure rate and should be approached cautiously.

Rotator cuff and labral tears are not uncommon and are more likely in patients with excess joint motion. Surgery is indicated for full thickness tears that remain painful. Possible complications include recurrent tears and joint stiffness.

Elbow

Both lateral and medial humeral epicondylitis are more common in EDS patients. Radial tunnel syndrome is also very common in EDS patients. These problems often resolve spontaneously or with physical therapy or other modalities, such as Platelet Rich Plasma (PRP) injections [Rabago et al., 2009; Glanzmann and Audigé, 2015], but when persistent and refractory to other treatment modalities, surgery can be a reasonable option. Literature support is lacking. Posterolateral rotatory instability of the elbow may also be an issue in patients with JH and EDS.

Wrist

Wrist pain is a common complaint in EDS patients. EDS patients tend to have unstable ankles, knees, and hips, and frequently fall on their outstretched hands. This wrist trauma can convert loose wrist joints into painful loose wrist joints. Physical therapy and hand exercise often make this type of wrist pain worse. Surgical stabilization of the wrist works reasonably well for radiocarpal, midcarpal, and distal radioulnar joint instability [Büchler, 1996]. Intercarpal fusions have a role, but can create load imbalance and loss of motion that can also be painful. Painful instability of the pisiform is common, and responds well to surgery. Proximal median nerve entrapment causes intermittent severe wrist pain with pronation, and can be treated successfully with surgery if the diagnosis can be made.

Thumb

Thumb problems are almost universal in EDS patients. A painful unstable non-arthritic thumb CMC joint can be stabilized surgically, with a good prognosis [Eaton and Littler, 1973]. Unfortunately, radiographs do not correlate with symptoms [Hoffler et al., 2015], and patients must be examined carefully by specialists with extensive subspecialty training. Thumb MP joint hyperextension instability can be treated with soft tissue stabilization and/or extensor pollicus brevis tenodesis, or more reliably with arthrodesis. Painful clicking at the thumb interphalangeal joint is caused by sesamoiditis, and is treated with sesamoidectomy.

Fingers

Hyperextension of the proximal interphalangeal joints of the fingers is common in EDS patients. This may be entirely asymptomatic. If painful, or if the fingers catch or lock because of this, digital Figure-of-eight splints are extremely helpful. Surgery is an option if the splints fail, but this type of surgery is technically challenging and has a higher failure rate. Tendinopathies that can occur in anyone [Adams and Habbu, 2015] can also be present in EDS patients, and respond well to surgery, if necessary and the diagnosis is correct.

Lumbar Spine

Lumbar spondylosis is common, and spine surgery in terms of laminectomy or fusion is not uncommon. Cauda Equina Syndrome is a concern for any patient with EDS or JH who presents with severe back pain and radicular symptoms, particularly with leg weakness or perineal numbness, incontinence or sudden onset of sexual dysfunction. This can require emergency surgery to prevent permanent paralysis and loss of bladder/bowel control.

Hip

Hip pain is common in EDS patients. Lateral hip pain is common and may occur as a result of the iliotibial band subluxing over the greater trochanter. This often produces a painful, loud clunking sensation (which the patient often interprets as the hip dislocating). This can lead to trochanteric bursitis which makes if difficult for patients to sleep on their sides. This may show edema in the bursa on MRI, and usually responds to physical therapy and steroid injections (which should be avoided if possible). In recalcitrant cases, endoscopic surgery can give tremendous relief, if the diagnosis is correct [Redmond et al., 2016]. Labral tears are much more common in EDS patients, and hip arthroscopy to remove or repair this type of tear can give tremendous relief of pain, although long term evidence for this procedure is lacking. Sacroiliac (SI) joint instability is very common in EDS patients, and presents as vague low back/pelvic pain. This often responds well to physical therapy, if the diagnosis is made. Prolotherapy for isolated SI joint instability can be helpful but remains controversial. Braces to stabilize the SI joint can be helpful for episodic pain. Surgery for SI joint instability is rarely necessary but can give immediate and permanent relief of pain. Hip pain may

also be radicular pain from disk failure at L4–L5. If the radiographs and/or MRI of the hip are normal, the pain is likely referred pain from the lumbar spine. In this setting, if the lumbar spine is normal, the patient could also have Piriformis syndrome, which usually responds to physical therapy or chiropractic are if the diagnosis is made.

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Knee

Knee instability is common in EDS patients, particularly patella subluxation or patella dislocation. This usually responds to physical therapy and occasionally requires a knee support. This can eventually lead to premature patellofemoral arthritis. This excess motion at the knee can also results in a much higher incidence of meniscal tears and ligament tears. Surgery can be utilized in these cases to restore the anatomic relations. Physical therapy can be quite helpful in creating dynamic stability of the knee joint. Advances in implant design have made surgery a more viable option for patellofemoral arthritis [Shaner and Lonner, 2015].

Ankle

Ankle instability is a common problem with EDS patients. The ankle tends to give out on uneven ground, and often causes falling. The ankle may also be injured by the fall, and can become more unstable. Ankle braces and orthotics work reasonably well in many patients, but are cumbersome. Soft tissue procedures around the ankle have a high failure rate, and wound problems are common. Malalignment of the hindfoot can result in imbalance that exacerbates any underlying knee, hip or back instability or malalignment. Physical therapy and orthotics are the mainstay of treatment, but talotarsal stabilization surgery can be helpful [Graham, 2015].

Foot

Bunions are common in EDS patients. If the bunion is not painful it should best be left alone. Metatarsalgia is also common. Steroid injections may seem like a good idea for metatarsalgia, but will often weaken the soft tissues and make this problem worse. Orthotics are the mainstay of treatment for foot deformities.

Nerve

Peripheral nerve problems are common in EDS patients. Decompressive surgery for peripheral nerve compression is extremely reliable if the diagnosis is correct. Unfortunately, EDS patients often present with multiple, simultaneously overlapping nerve complaints, and sorting out the cause of the nerve complaints can be tedious, time-consuming, and resource-intensive. Electrodiagnostic studies are often ordered to assess for nerve damage, but are not helpful when the results are normal, which is common. Understanding the contribution of the patient's cervical spine and thoracic outlet to their nerve complaints is advised as a starting point.

SUMMARY

EDS results in a tendency toward premature wear of all the major joints in the body, without causing diagnostic tests to become abnormal. Painful joint instability usually responds to conservative treatment. If this is unsuccessful, it can dramatically to surgical intervention, if the correct diagnosis can be made and the right patient population is selected. Peripheral nerve compression also responds well to surgical decompression, if the correct diagnosis can be made. With multiple overlapping complaints that are linked anatomically, it is no wonder that patients and providers struggle to provide answers and solutions. Successful treatment of EDS patients requires the caregivers to have extensive knowledge of anatomy and physiology, as well as treatment options, including surgery, and extensive resources in terms of diagnostic testing, physical therapy, and consultation/coordination of treatment with knowledgeable providers.

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RESEARCH REVIEW

Neurological and Spinal Manifestations of the Ehlers–Danlos Syndromes

FRASER C. HENDERSON SR.,* CLAUDIU AUSTIN, EDWARD BENZEL, PAOLO BOLOGNESE, RICHARD ELLENBOGEN, CLAIR A. FRANCOMANO, CANDACE IRETON, PETRA KLINGE, MYLES KOBY, DONLIN LONG, SUNIL PATEL, ERIC L. SINGMAN, AND NICOL C. VOERMANS

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin extensibility, and tissue fragility. This communication briefly reports upon the neurological manifestations that arise including the weakness of the ligaments of the craniocervical junction and spine, early disc degeneration, and the weakness of the epineurium and perineurium surrounding peripheral nerves. Entrapment, deformation, and biophysical deformative stresses exerted upon the nervous system may alter gene expression, neuronal function and phenotypic expression. This report also discusses

Fraser Cummins Henderson Sr., M.D., was fellowship trained in disorders of the craniocervical junction at the National Hospitals for Neurology and Neurosurgery, Queens Square London, before returning to complete his commitment to the U.S. Navy. He was then Professor and Director of Neurosurgery of the Spine and Craniocervical Junction at Georgetown University before entering private practice. He has concentrated on the diagnosis and treatment of hypermobility connective tissue disorders and other rare diseases of the spine. He serves on the Executive Boards of the Ehlers–Danlos Society, the Chiari Syringomyelia Foundation, the ILC, and the TCAPP Foundations.

Myles Koby, M.D. is a neuroradiologist, formerly at the National Institutes of Health and now at Doctors Community Hospital, Lanham, MD. He has special clinical interest in the use of dynamic imaging in the investigation of spinal instability disorders.

Claudiu Austin, M.D., is an internist at Doctors Community Hospital in Lanham, MD, with special interest in pharmacology and physiology. He specializes in treating complex EDS patients, including those with movement disorders, adult PANDAS, and severe autonomic dysfunction.

Clair Francomano, M.D., is a clinical geneticist with a long interest in the hereditary disorders of connective tissue. Her professional work in the last 10 years has centered on Ehlers–Danlos Syndrome. She is Director of Adult Genetics and of the Ehlers-Danlos Society Center for Clinical Care and Research at the Harvey Institute for Human Genetics, and Associate Professor of Medicine at Johns Hopkins University School of Medicine. She serves on the Executive Board and the Medical and Scientific Board of the Ehlers-Danlos Society.

Edward Benzel, M.D., Ph.D., is a neurosurgeon who was Professor Chairman of Neurosurgery at the Cleveland pathophysiology treatment of spinal disorders.

Paolo Bolognese, M.D., is a neurosurgeon in New Hyde Park, New York, and is affiliated with North Shore University Hospital. He received his medical degree from University of Torino Faculty of Medicine and has been in practice for more than 20 years. He specializes in Chiari I malformation, syringomyelia, and related disorders.

Richard Ellenbogen, M.D., is Professor Chairman of the Department of Neurological adult brain tumors trauma surgery craniofacial abnormalities Chiari malformations congenital conditions. He also conducts research on molecular imaging nanoparticles on traumatic brain injury.

Candace Ireton, M.D., is a Board Certified Family Physician with special interest in caring for Ehlers–Danlos syndrome patients. Dr. Ireton received her BS in Physical Education with Exercise Physiology emphasis from the University of California at Davis. She is currently piloting a group visit program for the primary care of EDS patients in Asheville, NC and has been in practice for more than 20 years.

Petra M. Klinge, M.D., Ph.D., is a neurosurgeon who completed training in Germany and is currently Professor of Neurosurgery at the Medical School of Brown University. She specializes in hydrocephalus, tethered cord and Chiari malformation, and developmental cerebrospinal fluid disorders.

Donlin M. Long, M.D., Ph.D., was Professor Chairman of Neurosurgery at The Johns where he took special interest in the development of infrastructure for patient care while developing new insights into pathophysiology of pain, spinal disorders, and brain tumors. He presently specializes in diagnosing the various comorbid conditions of EDS.

Sunil Patel, M.D., is Professor and Chairman of Neurosurgery at the Medical University of South Carolina. He completed fellowship training in Skull base Surgery, Cerebrovascular Surgery, and Microneurosurgery, and is presently focused on developing the understanding and treatment of vascular and neoplastic brain disorders, complex spine disorders, and the treatment of craniocervical and spinal manifestations of EDS.

Eric L. Singman, M.D., Ph.D., is Professor of Ophthalmology and Director of the Wilmer Eye Institute at The Johns Hopkins Hospital. His clinical expertise includes diagnosis of visual dysfunction after brain injury. Dr. Singman also has a particular interest in teaching health-care providers to recognize the visual sequelae of complex disorders such as traumatic brain injury, Lyme disease, and EDS.

Dr. Nicol Voermans is a neurologist the Neuromuscular Centre of Radboud University Medical Center, Nijmegen, The Netherlands. Her main research focus is inherited myopathies, in particular congenital myopathies, fascioscapulohumeral muscular dystrophy, and the neuromuscular features of inherited connective tissue disorders. She completed a doctoral dissertation on neuromuscular features in Ehlers–Danlos and Marfan syndromes.

Conflicts of interest: The senior author is a consultant to LifeSpine, Inc., and is developing technology to improve craniocervical stabilization. The senior author holds patents on finite element analysis methodology that could be used to assess stress in the brainstem and upper spinal cord. The other authors declare they have no conflict of interest.

*Correspondence to: Fraser Cummins Henderson Sr., M.D., Ehlers–Danlos Society Center for Clinical Care and Research, Greater Baltimore Medical Center, The Metropolitan Neurosurgery Group, 8401 Connecticut Avenue, Suite 220, Chevy Chase, Baltimore, MD 20815. E-mail: henderson@fraserhendersonMD.com

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increased prevalence of migraine, idiopathic intracranial hypertension, Tarlov cysts, tethered cord syndrome, and dystonia, where associations with EDS have been anecdotally reported, but where epidemiological evidence is not yet available. Chiari Malformation Type I (CMI) has been reported to be a comorbid condition to EDS, and may be complicated by craniocervical instability or basilar invagination. Motor delay, headache, and quadriparesis have been attributed to ligamentous laxity and instability at the atlanto-occipital and atlantoaxial joints, which may complicate all forms of EDS. Discopathy and early degenerative spondylotic disease manifest by spinal segmental instability and kyphosis, rendering EDS patients prone to mechanical pain, and myelopathy. Musculoskeletal pain starts early, is chronic and debilitating, and the neuromuscular disease of EDS manifests symptomatically with weakness, myalgia, easy fatigability, limited walking, reduction of vibration sense, and mild impairment of mobility and daily activities. Consensus criteria and clinical practice guidelines, based upon stronger epidemiological and pathophysiological evidence, are needed to refine diagnosis and treatment of the various neurological and spinal manifestations of EDS.

KEY WORDS: Ehlers–Danlos syndrome; headache; craniocervical instability; atlantoaxial instability; tethered cord syndrome

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INTRODUCTION

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin extensibility, and tissue fragility. The significance of neurological findings of EDS have been recently proposed and reviewed [Voermans et al., 2009a; Savasta et al., 2011; Castori and Voermans, 2014]. The following article discusses the etiology and clinical findings related to neurological and spinal manifestations commonly observed, yet often poorly recognized, in EDS patients, and proposes treatment options and areas of research needed.

METHODS

On the basis of a large shared experience in the treatment of EDS, the authors were solicited to contribute a review of the neurological and spinal manifestations of EDS. The authors represent a working group within the International Consortium on the Ehlers–Danlos Syndromes. In preparation for the EDS International Symposium 2016, the authors formed subcommittees to research individual topics relating to EDS and its neurological presentations, and here present those findings in synthesized, topic-based fashion designed to assist a wider audience of medical practitioners in caring for EDS patients, and in advancing research needs for this population.

HEADACHE IN EHLERS–DANLOS SYNDROME

EDS patients commonly suffer a variety of headache types [Jacome, 1999; Martin and Neilson, 2014; Castori et al., 2015]. These include headaches due to migraines, muscle tension, intracranial hypertension, craniocervical instability, and cervical spine disorders, temporomandibular joint disease, carotid dissection, and other physical conditions. Though a patient may suffer status migrainosis, constant pain is less likely to represent a migrainous headache [Headache Classification Committee of the International Headache Society (IHS), 2013].

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Migraine in EDS

Epidemiology

Migraine, common in the general population, is more prevalent in women [Nappi and Nappi, 2012]. Migraine is also more prevalent among EDS which also has a female predilection [Bendik et al., 2011; Castori and Voermans, 2014; Castori et al., 2015]. Therefore, EDS may be considered a risk factor for migraine.

Etiology

Migraine often presents as a comorbid disorder with many other medical conditions [Schurks et al., 2009; Casucci et al., 2012; Pierangeli et al., 2012; Gelfand et al., 2013; van Hemert et al., 2014]. The final common pathway appears to be abnormal regulation of cerebral vasculature following a spread of depression of cortical electrical activity [Burstein et al., 2015; Ferrari et al., 2015].

Clinical and diagnostic findings

Defined as a primary headache disorder, with recurrent attacks of moderate or severe intensity, lasting 4–72 hr, migraine headaches are more often unilateral, pulsating, associated with nausea, photophobia, and phonophobia, which are disabling and worse with physical activity [Headache Classification Committee of the International Headache Society (IHS), 2013]. Migraine is usually preceded by a prodrome and followed by fatigue, nausea, and dizziness (postdrome). A careful history may

elucidate triggers such as foods, stress, weather changes, sleep changes, menses, seasonal allergies, and caffeine. Physical findings may include vertigo, hypersensitivity to pressure on certain muscles and tendons, elevated blood pressure, and heart murmur. Migraines may cause a benign episodic mydriasis. Findings may be suggestive of a stroke. Diagnostic testing should exclude sleep disorders [Kothari et al., 2000], menstrual cycle dysfunction including menopause [Nappi and Nappi, 2012; Ripa et al., 2015], and patent foramen ovale [Volman et al., 2013].

Treatment

Migraine therapies (e.g., botulinum toxin, triptans, caffeine, acupuncture, meditation) are legion, and testify to the diverse causes of migraine. Recognition that migraine patients suffer multiple pain disorders should prompt a holistic treatment strategy or combination therapies [Estemalik and Tepper, 2013; Kress et al., 2015].

Areas needing investigation

(1) Connection between migraine, EDS and mast cell activation syndrome (MCAS), and cardiac functional/structural defects, such as postural orthostatic tachycardia syndrome (POTS) and patent foramen ovale.
(2) Connection between migraine and diet in EDS.
(3) Prevalence and impact of migraine in all types of EDS.
(4) Treatment of migraine in EDS.
(5) Effect of other co-morbidities, medications, and nutrition in EDS related to migraine prevalence, severity, or treatment.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

Epidemiology

IIH, or pseudotumor cerebri, is a poorly understood entity characterized by an increased intracranial pressure (ICP), headaches, visual disturbances and photophobia, and occasionally tinnitus, nausea, and vomiting. Affected patients may have objective changes in vision with 10% developing blindness [Corbett et al., 1982]. Female to male ratios range from 4:1 to 15:1, and obesity is an added risk factor [Radhakrishnan et al., 1993]. Anecdotal reports from large case series have suggested an association between EDS and IIH, but no such association has been formally reported in the biomedical literature.

Etiology

Hypotheses proposed for the etiology of IIH include excess cerebrospinal fluid (CSF) production, reduced CSF absorption, excessive brain water content, and increased cerebral venous pressure leading to reduced CSF reabsorption [Ball and Clarke, 2006]. Recent studies demonstrate that up to 93% of patients with IIH have focal venous sinus stenosis on MR venography, most commonly proximal to the transverse sigmoid sinuses junction, suggesting that venous abnormalities may play a role in the pathophysiology of IIH [Farb et al., 2003].

Clinical and Diagnostic Findings

The diagnosis of IIH requires symptoms of increased ICP. The visual disturbances are often associated with the finding of papilledema or visual field defects. The diagnosis is supported by increased ICP: >25 cm of H_2O in the obese population, or >20 cm H_2O in the non-obese population. There should be normal composition of CSF, thus, excluding inflammatory conditions, absence on MRI, or contrast-enhanced CT of hydrocephalus and of mass, structural, or vascular lesions, and no other cause of intracranial hypertension.

Treatment

Treatments include lifestyle modifications targeting weight loss including bariatric surgery, decreasing CSF production with acetazolamide, or serial lumbar punctures, CSF diversion with a ventriculo-peritoneal or lumbo-peritoneal shunt, optic nerve sheath fenestration, or subtemporal decompression. Stenting has emerged as an effective treatment for IIH in select patients with radiographic cerebral sinus stenosis and evidence of pressure gradients [Satti et al., 2015].

Areas Needing Investigation

(1) The epidemiology and etiology of pseudotumor cerebri in EDS.
(2) Longitudinal studies to assess the efficacy and risks of medical therapy, shunting, and stenting in the EDS population.

CHIARI I MALFORMATION (CMI)

Epidemiology

Chiari malformation Type I (CMI) has been reported as a comorbid condition in hypermobile EDS (hEDS) [Milhorat et al., 2007]. The precise incidence of the CMI and EDS association is unknown, but the female to male ratio is higher (9:1) in the CMI and EDS subgroup than in the general CMI population (3:1). The average age of onset tends to be younger in the CMI and EDS subgroup, when compared to the general CMI population.

Chiari malformation Type I (CMI) has been reported as a comorbid condition in hypermobile EDS (hEDS). The precise incidence of the CMI and EDS association is unknown, but the female to male ratio is higher (9:1) in the CMI and EDS subgroup than in the general CMI population (3:1).

Etiology

CMI is a mesenchymal disorder affecting the hindbrain, in which a developmentally

small posterior fossa results in downward migration of the brainstem and cerebellar tonsils through the foramen magnum into the spinal canal [Batzdorf et al., 2015]. The herniation causes obstruction to the normal regional circulation of the cerebrospinal fluid (CSF) and compartmentalization of CSF circulation [Ellenbogen et al., 2000], which may result in suboccipital pressure headaches. Obstruction of the CSF circulation may result in empty sella syndrome, with flattening of the pituitary gland and resulting hormonal changes. A syrinx may form, which exerts a mass effect on the spinal cord, and rarely the brainstem [Kahn et al., 2015]. There is increasing recognition of CMI variants [Milhorat et al., 1999]. Some have suggested an association of tethered cord syndrome and CMI [Royo-Salvador, 1996].

The incidence, prevalence, and etiology of CMI and EDS occurring together are not fully understood. However, Milhorat et al. [2007, 2010] found a high prevalence of patients with hereditary disorders of connective tissue in their retrospective series of CMI post-decompression failures that needed further intervention, including craniocervical fusion and/or tethered cord release. While this may indicate a co-existence of these conditions, it does not provide evidence of a causal relationship, but suggests that EDS and other disorders of connective tissue should not be overlooked in CMI.

Clinical and Diagnostic Findings

The CMI is traditionally defined radiologically by 5 mm of tonsillar herniation through the foramen magnum, though others have suggested a herniation of 3 mm, or 7 mm. The behavior of CMI is often unrelated to the size of the herniation, and CMI can be asymptomatic.

CM is best characterized by a tussive headache (worse with cough, strain, or yelling), dizziness, cerebellar findings—dysarthria, incoordination, imbalance, and unsteady gait—hearing and vestibular deficits. Romberg's sign, and deficits of cranial nerves. There is sometimes trigeminal neuralgia [Milhorat et al., 1999; Tubbs et al., 2011a; Yarbrough et al., 2011]. Brainstem findings, such as sleep apnea and dysautonomia, are often found in CM that are complicated by craniocervical instability or basilar invagination, the so-called "complex Chiari."

Treatment

There is no universally agreed upon surgical threshold for CMI, but surgery should be urgently performed in the presence of progressive neurological deficits, and expanding syringomyelia (Fig. 1) [Yarbrough et al., 2011].

The association of CMI and EDS is burdened by distinct management challenges, including craniocervical instability, and possibly an increased risk of CSF leaks. CMI may be asymptomatic (incidence unknown), or mildly symptomatic, so that surgical intervention may not be required [Novegno et al., 2008; Strahle et al., 2011]. Sporadic cases of spontaneous resolution of CMI

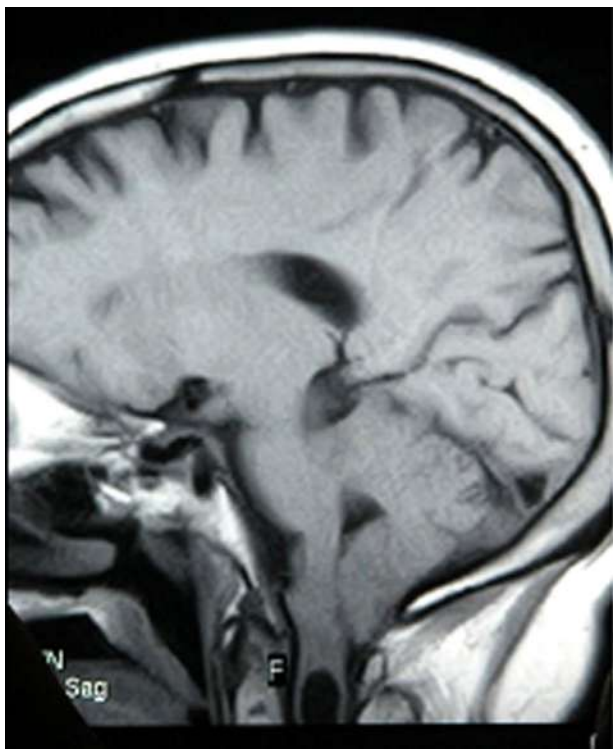

Figure 1. CMI with syrinx in the cervical spinal cord (sagittal view, T1 weighted MRI of the cervical spine).

have been described [Castillo and Wilson, 1995].

Areas Needing Investigation

(1) The incidence, prevalence, and etiology of CMI and its variants CM0 and CM 1.5 in the EDS population remains unclear and needs larger data registry
(2) The Complex Chiari malformation, though well described in the literature (see section on craniocervical instability), is not universally recognized among those who perform Chiari surgery. Prospective studies in EDS patients with Complex Chiari malformation are needed to compare outcomes following decompression alone versus those undergoing decompression with fusion/stabilization.

ATLANTOAXIAL INSTABILITY

Epidemiology

Atlantoaxial instability (AAI) is a potential complication of all forms of EDS. Motor delay [Jelsma et al., 2013], headache associated with "connective tissue pathological relaxation" and quadri-paresis have all been attributed to ligamentous laxity and instability at the atlantooccipital, and atlantoaxial joints [Nagashima et al., 1981; Halko et al., 1995].

Epidemiology

The epidemiology of AAI in hEDS is unknown. AAI was seen in two of three patients with vascular EDS [Halko et al., 1995]. A high risk of AAI is apparent in other disorders affecting connective tissue, including Down syndrome, Marfan syndrome, and rheumatoid arthritis [MacKenzie and Rankin, 2003; Hankinson and Anderson, 2010].

Etiology

A proclivity to ligamentous incompetence renders the atlanto-axial joint a higher risk for instability. The atlantoaxial junction (AAJ) is the most mobile joint of the body. The AAJ mechanical properties are determined by ligamentous structures, most prominent of which are the transverse and alar ligaments [Tubbs et al., 2011b].

Hypermobility of the AAJ is common in children, and over 40° of rotation may be observed in each direction, but in the adult there is substantially less than 40° of rotation [Zhang and Bai, 2007; Martin et al., 2010]. At 35° of rotation of C1 upon C2, there is stretching and kinking of the contralateral vertebral artery [Selecki, 1969]. At 45°, both vertebral arteries become occluded [Menezes and Traynelis, 2008].

Clinical and Diagnostic Findings

The diagnosis of AAI is predicated upon disabling neck pain or suboccipital pain, and

(1) history and clinical findings of cervical medullary syndrome, or syncopal (or pre-syncopal) episodes,
(2) demonstrable neurological findings, and
(3) radiological evidence of instability or compression of the neuroaxis.

Neck pain and suboccipital headache are the most common findings, with the caveats that headache is a common occurrence in EDS patients [Castori and Voermans, 2014]. There may be symptoms referable to the vertebral artery blood flow, including visual changes, as well as headache resulting from vertebral artery torsion. Syncopal and pre-syncopal events are frequent. Other symptoms include dizziness, nausea, sometimes facial pain, dysphagia, choking, and respiratory issues. Symptoms usually improve with a neck brace.

Neurological examination demonstrates tenderness over spinous process of C1 and C2, altered mechanics of neck rotation, hyperreflexia, dysdiadochokinesia, and hypoesthesia to pinprick. Weakness is not a constant feature of AAI.

A number of radiological features have been described, including rotation of C1 upon C2 $> 41°$ (as assessed by CT scan of C1-2) and retro-odontoid pannus on MRI [Fielding et al., 1978; Taniguchi et al., 2008]. The difficulty of recognizing rotary instability on standard X-ray, CT, and MRI images has resulted in failure to diagnose [Kothari et al., 2000].

Treatment

The first line of treatment should be neck brace, physical therapy, and avoidance of activities that provoke exacerbation of the AAI symptoms. If the non-operative treatment fails, fusion stabilization of C1/C2 is required. Incompetence of the alar ligament requires dorsal surgical fusion [Menendez and Wright, 2007]. Occiput to C1/C2 fusion should be considered in the presence of craniocervical instability, basilar invagination, or complex Chiari malformation.

Areas Needing Investigation

(1) The prevalence and natural history of AAI in the EDS population.
(2) The importance of dynamic imaging studies (such as CT with rotation of the cervical spine to extreme left and right, requires further validation to promote a generalized adoption of these studies to diagnose AAI, and to prompt greater availability of dynamic imaging facilities).
(3) Surgical outcomes for treatment of rotational instability and the long-term outcome in EDS.

CRANIOCERVICAL INSTABILITY

Epidemiology

Craniocervical instability (CCI) is recognized as a manifestation of ligamentous laxity in EDS [Nagashima et al., 1981; Milhorat et al., 2010]. Ligamentous laxity has been shown to result in neuraxial injury [Lindenburg and Freytag, 1970; Henderson et al., 1993; Menezes and Traynelis, 2008].

Etiology

CCI is a pathological condition in which ligamentous connections from the skull to the spine are incompetent. Motor delay, developmental coordination disorder, headaches secondary to spinal compression, clumsiness, and the relatively high rate of dyslexia and dyspraxia in the EDS population merit investigation as possible consequences of early onset degenerative changes resulting from ligamentous laxity upon the central nervous system [Nagashima et al., 1981; Adib et al., 2005]. The most prominent movement of the atlanto-occipital joint is flexion-extension; axial rotation is normally limited to <5 degrees of rotation [Dvorak et al., 1987].

There is increased recognition of mechanisms of neuronal injury that result from stretching, or deformative stress [Jafari et al., 1997; Maxwell et al., 1999; Shi and Whitebone, 2006]. The consequent formation of axon retraction balls is similar to that seen in diffuse axonal injury of the brain (Fig. 2) [Geddes et al., 2000; Henderson et al., 2005]. Stretching of neurons causes pathological calcium influx [Wolf et al., 2001], altered gene expression [Arundine et al., 2004], and apoptosis [Liu et al., 1997; Arundine et al., 2004].

Clinical and Diagnostic Findings

CCI-related symptoms result from deformation of the brainstem and upper spinal cord, traction on the vertebral artery, and possibly from the consequences of altered venous or CSF outflow from the cranium. CCI often occurs with basilar invagination or ventral brainstem compression, the findings of which are dominated by pyramidal and sensory changes: weakness of the limbs hyperreflexia and pathological reflexes (e.g., Babinski, Hoffman's sign, absence of the abdominal reflex), paresthesias, and a plethora of other symptoms—including sphincter problems, headache, neck pain, dizziness, vertigo, dyspnea, dysphonia, altered vision, and hearing, syncope, emesis, altered sexual function, altered menses, and gait changes [Caetano de Barros et al., 1968]. These signs, in aggregate, constitute the cervical medullary syndrome [Batzdorf et al., 2015], elements of which are commonly recorded among EDS patients [Celletti et al., 2012].

Three metrics may be useful in the identification of CCI and basilar invagination: the clivo-axial angle, the Harris measurement, and the Grabb, Mapstone, Oakes method [Batzdorf et al., 2015; NINDS Common Data Elements, 2016]. The Clivo-axial angle (CXA) is the angle formed between the posterior aspect of the lower clivus and the posterior axial line. The CXA has a normal range of 145° to 160°, but an angle of less than 135° is pathological [Henderson et al., 1993; Henderson et al., 2010a; Batzdorf et al., 2015]. Increasing kyphosis of clivo-axial angle (i.e., a more acute CXA) creates a fulcrum by which the odontoid deforms the brainstem [Menezes, 2012]. The medulla becomes kinked as the CXA becomes more kyphotic.

The second radiologic metric, the horizontal Harris measurement, is the distance from the basion to the posterior axial line (PAL) [Harris et al., 1994]. Instability is present when the basion to the PAL exceeds 12 mm. This measurement, used in conjunction with dynamic flexion and extension images of the cervical spine, can also be used to measure the dynamic translation between the basion and the odontoid [Batzdorf et al., 2015; NINDS Common Data Elements, 2016]. In the normal individual, there should be no measurable translatory movement

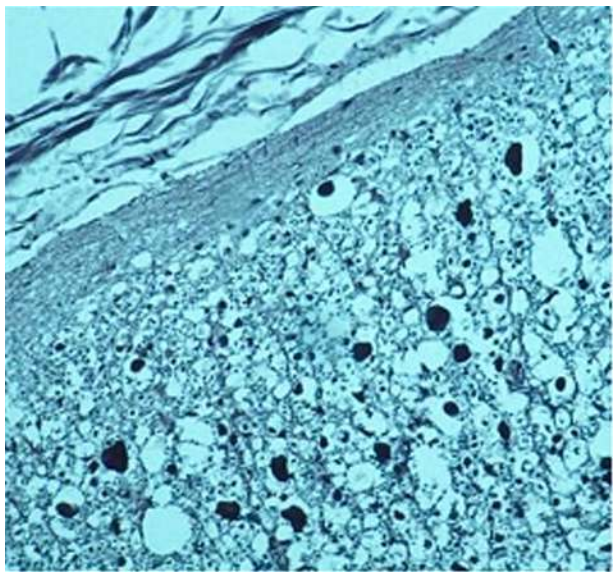

Figure 2. Axon retraction bulbs in the upper spinal cord, from cadaveric studies of subjects with basilar invagination (Microscopic photograph (×500), axial section of the dorsal column at the C2 level. Silver stain).

(sliding movement). Translation of greater than 1 mm between the basion and odontoid reflects craniovertebral instability, and may warrant stabilization (Fig. 3) [Wiesel and Rothman, 1979; White and Panjabi, 1990].

The third metric, the Grabb, Mapstone, and Oakes measurement predicts risk of ventral brainstem compression, and has been statistically correlated with clinical outcome [Grabb et al., 1999; Henderson et al., 2010b]. A measurement >9 mm suggests high risk of ventral brainstem compression [Grabb et al., 1999].

There is a relatively nascent recognition of the importance of dynamic imaging of the CCJ. For example, the brainstem may appear normal on routine magnetic resonance imaging in the supine position, but show pathological ventral brainstem compression in the flexion view sitting upright [Klimo Jr et al., 2008; Henderson et al., 2010b; Milhorat et al., 2010]. "Functional" dynamic studies in flexion and extension are important to determine whether there is pathological hypermobility at the craniocervical junction [Klekamp, 2012].

Treatment

Indications for surgery include severe headache, symptoms which constitute the cervical medullary syndrome, neurological deficits referable to the brainstem and upper spinal cord, radiological findings of CCI, and

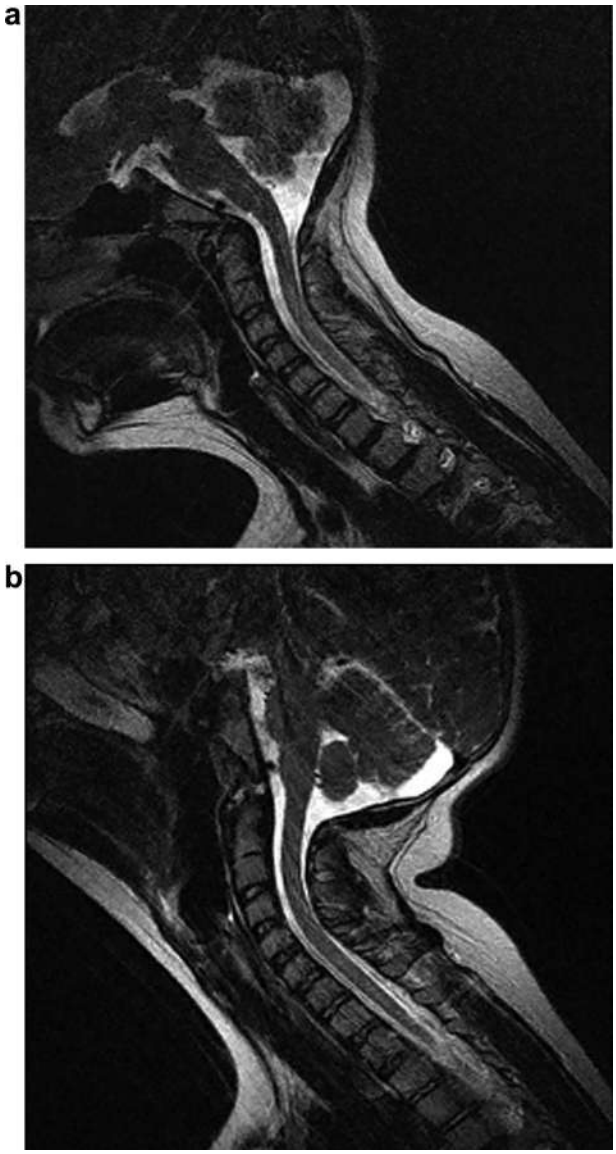

Figure 3. **a**: The craniocervical junction in flexion, showing a forward slide of the basion with respect to the odontoid (Sagittal view, T2 weighted MRI of the cervical spine in flexion). **b**: In extension, the basion lies along the posterior edge of the odontoid process, demonstrating a translation of 6 mm from flexion to extension (Sagittal view, T2 weighted MRI cervical spine).

failure of a reasonable course of non-operative therapy. Though there are no established criteria for treatment of CCI in EDS, there is abundant literature addressing the diagnosis of CCI [White and Panjabi, 1990; Harris et al., 1994; Batzdorf et al., 2015], and the treatment of CCI with craniocervical stabilization in various congenital or degenerative connective tissue disorders [Nagashima et al., 1981; Goel and Sharma, 2005; Henderson et al., 2010b; Milhorat et al., 2010; Tubbs et al., 2011a; Klekamp, 2012; Yoshizumi et al., 2014].

Areas Needing Investigation

(1) Prevalence and natural history of axial ligamentous instability in EDS.
(2) Validation of radiological metrics for determining CCI in the EDS population.
(3) Development of an international data registry using the NINDS Common Data Elements [2016] to facilitate therapeutic trials for CCI in EDS.

SEGMENTAL KYPHOSIS AND INSTABILITY

Epidemiology

The prevalence of cervical and thoracic segmental instability in the population of patients with hypermobility syndromes has not been well established. However, discopathy and early degenerative spondylotic disease in hEDS and classical type EDS is well established. EDS is characterized by segmental instability, kyphosis, and scoliosis. Spondylosis, defined by the presence of non-inflammatory disc degeneration, is usually preceded by mild segmental instability [Shedid and Benzel, 2007]. As a consequence of cervical and thoracic instability, and discopathy in EDS, there is loss of the normal cervical lordosis and an increasing kyphosis, rendering EDS patients prone to progressive myelopathy, and mechanical neck and chest pain.

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Etiology

Ligamentous laxity is an important determinant in the development of spinal instability other connective disorders such as rheumatoid arthritis, Down syndrome and osteogenesis imperfecta, but there have been no series to demonstrate this linkage in EDS. The importance of ligamentous laxity is increasingly appreciated among clinicians [Tredwell et al., 1990; Steilen et al., 2014].

The pathophysiology of segmental instability is well described: during flexion, there is deformation of the lateral and ventral columns of the spinal cord, directly related to the strain on the cord [Henderson et al., 2005; Shedid and Benzel, 2007]. Extension more often results in compression of the cord by buckling of the ligamentum flavum, resulting in myelopathic symptoms [Muhle et al., 1998]. The cervical spinal cord can be physiologically tethered in the sagittal plane, such that normal cord elongation in flexion is exaggerated by the kyphosis; this results in increased deformity and anatomic stretching of the cord. This "sagittal bowstring effect" underlies a physiological tethering effect, with resulting neurological deficits [Shedid and Benzel, 2007]. Others have recognized the importance of the dentate ligaments in applying stressors to the spinal cord, with the subsequent result of focal myelopathy [Cusick et al., 1977].

Clinical and Diagnostic Findings

Clinical findings include pain and disability, as well as sensory, motor, and reflex changes. Radiculo-myelopathy may manifest in an acute, subacute, or chronic manner as radicular and dermatomal or non-radicular myelopathic hypoesthesia, hyperesthesia, or paresthesia, and less often weakness. Over time, there may be ascending numbness, spasticity, Lhermitte's sign, and eventually leg weakness, altered gait, clumsiness, and long tract findings. There is often marked tenderness to palpation over unstable motion segments.

Clinical differential diagnoses in the EDS population should be kept in mind: instability at the atlanto-occipital and atlantoaxial joints, shoulder, clavicular and rib subluxations, brachial plexopathy, vascular anomalies, dissection or venous insufficiency, peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, myelopathy due to drugs—such as statins, colchicine, steroids- vitamin deficiency, especially B12 and B3, mitochondrial dysfunction, stroke, and psychological disorders.

Though CT scans and MRI remain the standard for most practitioners, radiological findings do not always correlate well with clinical findings or surgical outcome [Arnasson et al., 1987]. Dynamic instability is unlikely to be demonstrated in a resting supine subject, and pathological instability will often become manifest only when the ligaments are placed under stress. Though not yet validated, dynamic MRI in the upright position subjects the vertebral spine to physiological loading, and can be performed in the flexed and extended positions to demonstrate instability (Fig. 4) [Milhorat et al., 2010; Klekamp, 2012].

White and Panjabi [1990] have defined the reference ranges for flexion, extension, lateral tilt, and rotation

at each level of the spine. Radiological findings of segmental instability may include evidence of spinal cord compression or deformity, hyper-angulation at one or more segmental levels (>11.5° angulation between adjacent vertebra, subluxation >3 mm), and the presence of pathological longitudinal stretching.

Treatment

Initial management includes neck bracing and physical therapy with therapists who are knowledgeable regarding ligamentous laxity including EDS, attainment of a good sagittal balance, and avoidance of certain activities. Rest will often improve symptoms. If symptoms are refractory to conservative management, fusion, and stabilization of unstable levels may be indicated.

The rate of adjacent segment degeneration (the tendency for increased degeneration of discs adjacent to fused motion segments) has not been determined in the EDS population, but should be considered in surgical planning;

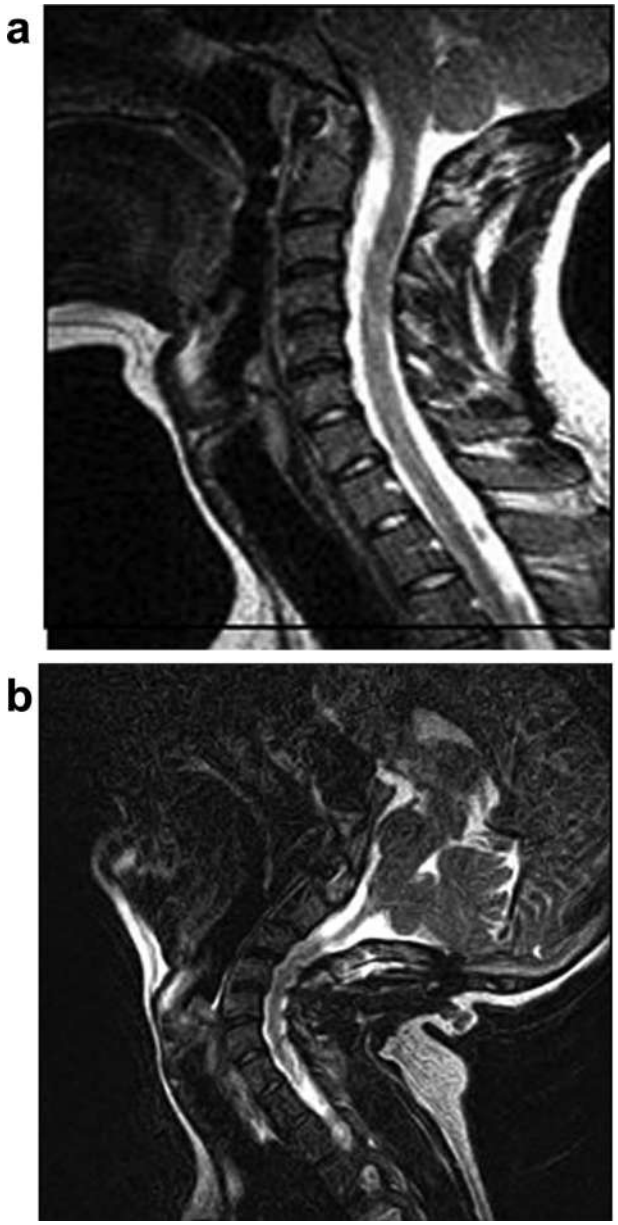

Figure 4. **a**: Segmental cervical instability, showing widespread degenerative disc disease characteristic of EDS-HT, but no spinal cord compression on neutral view (Sagittal view, T2 weighted MRI of the cervical spine in the neutral position). **b**: Dynamic instability evident upon extension of the neck, showing postero-listhesis of C4 on C5, causing spinal cord compression (MRI sagittal view of the cervical spine, T2 weighted).

motion-sparing technology may be an important option in this population, though there is yet no published literature in the EDS population.

Areas Needing Further Investigation

(1) Definition, prevalence and natural history of segmental instability in the EDS population.
(2) Clinical history of segmental instability after stabilization, including rates of adjacent segment degeneration in different types of EDS.
(3) Studies to improve diagnostic efficacy of segmental instability utilizing upright MRI.

TETHERED CORD SYNDROME

Tethered cord syndrome (TCS) in EDS is most often associated with a structurally abnormal filum terminale, and usually characterized by low back pain and the clinical triad of neurogenic bladder, lower extremity weakness and sensory loss, and musculoskeletal abnormalities.

Epidemiology

The incidence of the specific diagnosis of TCS is unclear, both within the general and EDS populations in the United States [Bui et al., 2007]. The prevalence of TCS in a diverse sample of Turkish school children was 0.1% [Bademci et al., 2006]. In a cohort of 2,987 consecutively evaluated patients with diagnoses of CMI or "low lying" cerebellar tonsils (LLCT, tonsillar descent 0–4 mm), Milhorat et al. [2009] found TCS, using a definition that allowed for normal position of the conus medullaris on MRI (i.e., at or above, the L1 vertebra), in 14% of the CMI patients they examined and in 63% of the LLCT cohort.

Etiology

The filum comprises a fibrous, collagenous, and elastic band that connects the conus medullaris with the dural sac at the S2 level. The filum contains neural, glial, and ependymal remnants that stem from embryonic spinal cord which begin to regress at 9–10 weeks of gestation [Jang et al., 2016]. The presence of fatty tissue, "nerve twigs" (dysplastic axons), fat and vascular lacunes, and suspicion of "congested" veins, are usually seen in the abnormal fila specimens obtained from patients with TCS [Thompson et al., 2014] Stretching of the spinal cord by the structurally abnormal filum is the presumed mechanism of TCS. Symptoms may become more apparent as a child grows. Forcible flexion and stretching is often deemed responsible for adult onset of TCS [Aufschnaiter et al., 2008]. Poor blood flow and oxidative stress in the spinal cord have also been implicated in animal models as mechanisms of neuronal injury [Yamada et al., 2007].

Clinical and Diagnostic Findings

TCS is characterized by aching/burning pain in the low back, legs and feet, and sensori-motor findings in lower extremities: weakness is common, with heaviness, stiffness, and tightness of legs and cramps; paresthesias in the pelvic area or legs and hypoesthesia to pinprick in the lumbar and sacral dermatomes is often observed. Findings are often asymmetric. A history of toe-walking may be elicited. Urological findings include urinary hesitancy, frequency, urgency, retention/incomplete emptying, nocturia, irregular urinary stream, sensory loss of the bladder, frequent urinary tract infections, and incontinence.

There is often enuresis into late childhood. There may be fecal incontinence, constipation, or sexual dysfunction. As TCS results in a combination of upper and lower motor neuron injury, there is often hyperreflexia in the lower extremities, but normal reflexes in the arms. The legs are usually weak, with normal upper extremity strength. Sensory loss is usually prominent in the lumbar and sacral dermatomes, but normal in the arms and trunk. Orthopedic deformities include scoliosis, kyphosis, functional ankle and foot deformities (ankle pronation with physical strain), and pes planus or pes cavus [Hoffman et al., 1976; Pang and Wilberger, 1982].

Urodynamic testing is important in the diagnosis of TCS. Neurogenic bladder manifestations may range from urinary retention and detrusor underactivity to urinary incontinence, overactivity of the detrusor, and sphincter dysfunction [Tu and Steinbok, 2013]. While formal urodynamic criteria have not been established for TCS, detrusor sphincter dysynergia, large post void residual, and very large bladder capacity (>800 ml) are good urodynamic indicators of a neurogenic bladder. Urodynamics can help to differentiate the neurogenic bladder of TCS from that due to diabetes or bladder obstruction from prostatic hypertrophy.

MRI of the cervical, thoracic, and lumbar spine is required to rule out other causes of leg weakness and low back pain, such as disc herniation, spondylolisthesis, stenosis, neoplasm, or intrinsic lesions of the spinal cord—such as multiple sclerosis or signs of trauma. The MRI may show low lying conus (below the mid L2 level), fatty infiltration, a stretched or thickened filum, a syrinx in the lower spinal cord, scoliosis or spina bifida occulta. The term "occult tethered cord" (OTCS) refers to where the MRI shows a normal position of the conus [Tu and Steinbok, 2013]. A large diameter of the filum terminale in axial T2 studies is a positive indicator that favors untethering in the presence of TCS [Fabiano et al., 2009].

Controversy exists over whether it is necessary to radiologically demonstrate a "low lying conus medullaris," that is, a conus ending at the lower L2 level or below. There has been the intuitive presumption that a low-lying conus represents a spinal cord under tension. However, this presumption has not been verified, and indeed, there are no epidemiological studies which allow the definition of a specific imaging finding to establish the diagnosis of TCS. Nor are there epidemiological studies in the normal population that demonstrate specific findings that

exclude TCS. On the other hand, there is a growing body of evidence that supports the clinical diagnosis of TCS with or without the radiological demonstration of a low-lying conus medullaris, which justifies surgical intervention when the clinical criteria are met [Tu and Steinbok, 2013].

Treatment of TCS

There is no standard technique in the surgical treatment of TCS. Generally, the lamina is removed, anywhere from L2 to S1, a durotomy is made, and electrical stimulation is used to confirm the absence of any nerve roots which may be associated with the filum. Finally, a microsurgical resection of the filum terminale (usually a 10 mm segment for pathology) is performed (Fig. 5). The filum tends to be taut, and to briskly retract upon sectioning. However, findings are variable, and there is no evidence to suggest that the intraoperative findings predict or correlate with the surgical outcome and severity of the TCS [Pang and Wilberger, 1982; Milhorat et al., 2009]. In some cases, it may be necessary to perform a lumbar stabilization across the motion segment in which the filum was sectioned. The resected filum should be sent for histopathological evaluation.

Areas Needing Research

(1) Prospectively and retrospectively evaluate specific clinical features and radiological metrics for predictive accuracy, to establish validated inclusion and exclusion criteria for future studies regarding TCS.
(2) Determine the incidence of TCS in EDS patients.
(3) Determine epidemiologically whether TCS is a co-morbid feature of CMI in EDS.
(4) Validate outcome measures by which to determine the surgical outcomes.
(5) Establish complication rates for TCS surgery in the EDS population.

DYSTONIAS AND OTHER MOVEMENT DISORDERS

Epidemiology

Movement disorders can be broadly divided into hyperkinetic disorders (too much movement) or hypokinetic movement occurring in the conscious state. The hyperkinetic movement disorders—including dystonia, tremor, chorea, myoclonus, and tic disorders—are observed in the EDS population according to anecdotal reports from large series of patients, but have not been documented in the peer-reviewed literature.

Etiology

Pain and trauma are frequent components of EDS, and there is a significant body of literature suggesting movement disorders may arise from extracranial trauma. Post-traumatic dystonia may develop in a limb following trauma to that limb [van Rooijen et al., 2011]. This may be one mechanism that establishes a link between EDS and movement disorders. However, while several of the authors have strong clinical suspicion of a connection, there are no published studies that confirm that movement disorders are a co-morbidity of hEDS [Rubio-Agusti et al., 2012].

While dystonia in joint hypermobility syndromes (JHS) have been observed, causality has not been demonstrated. In one large series, one third of patients with "fixed dystonia" were found to have JHS [Kassavetis et al., 2012]. The authors suggested that movement avoidance may have been adopted to avoid pain, and in time resulted in fixed dystonia. The etiology of the fixed dystonia has also been variously attributed to peripheral injury [van Rooijen et al., 2011], and psychogenic movement disorder [Hallett, 2016].

Clinical and Diagnostic Findings

Neurological evaluation and EEG to rule out seizure should be performed.

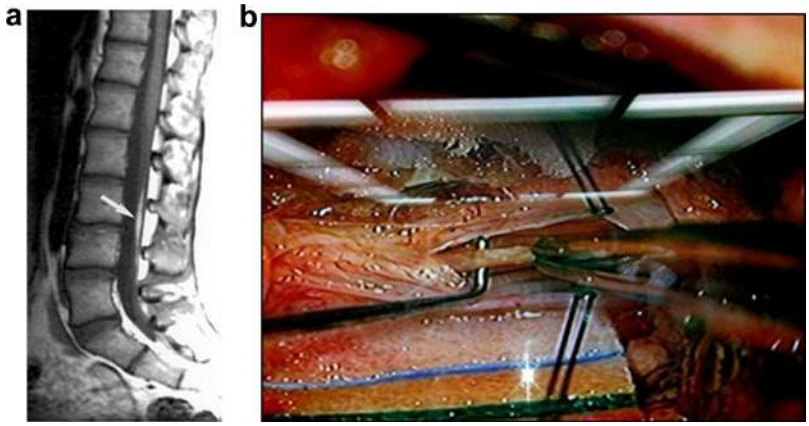

Figure 5. **a**: Tethered cord syndrome: conus at the normal level (L1), fatty filum suggestive of tethered cord syndrome (Sagittal view lumbar spine, T1 weighted MRI). **b**: Tethered cord syndrome: the thickened filum terminale at the L2 level, just before division. (Intraoperative photograph of the lumbar spine thecal sac and the durotomy).

The diagnosis of psychogenic movement disorder has been met with some skepticism [Palmer et al., 2016], but is distinguished from malingering, and thought to result from psychological causes [Hallett, 2016]; it is characterized by involuntary, disabling movements, abrupt in onset, a waxing/waning course, changes in the nature of the movement over time, worsening with stress, anxiety or depression, and improvement with distraction; they are difficult to diagnose and treat. Prognosis for improvement is better in patients with a shorter duration of illness [Lang, 2006].

Treatment

There is no established treatment algorithm for movement disorders in patients with EDS.

Areas Needing Research

(1) Establish studies to determine the epidemiology and etiology of movement disorders in EDS, and to demonstrate whether there is a comorbid relationship.
(2) Develop evidence-based treatment strategies for movement disorders in the EDS population.

NEUROMUSCULAR FEATURES OF EHLERS-DANLOS SYNDROME

Epidemiology

EDS, especially hEDS, is associated with high prevalence of myalgia, nocturnal muscle cramps involving the calves, hypotonia, progressive muscle weakness, poorly developed musculature, and scapular winging, which to some extent may be the result of avoidance of exercise due to hypermobility and instability of joints [Banerjee et al., 1988; Palmeri et al., 2003].

Musculoskeletal pain starts early, is chronic and debilitating [Voermans et al., 2010]. Neuromuscular disease manifests symptomatically with muscle weakness, myalgia, easy fatigability, and limited walking distance; physical findings include muscle weakness, reduction of vibration sense, and mild impairment of mobility and daily activities [Voermans et al., 2009b].

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Brachial and/or lumbosacral plexus neuropathies and other compression mono-neuropathies are not uncommon in EDS [Voermans et al., 2006; van Rooijen et al., 2011]. The presence of radiculopathy or small-fiber neuropathy probably explains a higher prevalence of neuropathic symptoms (paresthesias/numbness in hands or feet) than registered on neurophysiological or ultrasound testing. There is a high prevalence of ulnar nerve luxation at the elbow detected on dynamic ultrasound [Granata et al., 2013].

Etiology

Some pathophysiologic studies are available on the relationship between tenascin-x(TNX) deficient EDS and neuromuscular complications. Human and murine studies suggest a correlation between TNX levels and degree of neuromuscular involvement, and a corresponding role of the extracellular matrix defect in muscle and peripheral nerve dysfunction in EDS [Huijing et al., 2010; Voermans et al., 2011]. However, TNX deficiency accounts for only a very small percentage of patients with hEDS. Reduced quantitative muscle function appears to be secondary to muscle dysfunction rather than reduced muscle mass [Rombaut et al., 2012]. Abnormal myo-tendinous junctions in the muscle belly [Penisson-Besnier et al., 2013], mild to moderate myopathy and/or neuropathy, and defects of the extracellular matrix of the connective tissue investing muscle and peripheral nerve may increase muscle dysfunction [Voermans et al., 2009b, 2012; Syx et al., 2015].

The pathophysiological mechanism of peripheral neuropathy in hEDS appears, in part, to result from abnormal stretching and pressure upon peripheral nerves that results from joint subluxation. The connective tissue of peripheral nerves might fail to resist excessive mechanical stress: increased vulnerability is linked to underlying genetic defects in TNXB, collagens I, III, or V deficient epi-, peri-, and endoneurium [Voermans et al., 2009b; Granata et al., 2013]. This defect might also relate to the occurrence of axonal polyneuropathy in various types of EDS [Muellbacher et al., 1998].

Abnormal extracellular matrix in generalized connective tissue structure suggests molecular overlap between inherited connective tissue disorders and certain congenital myopathies, awareness of which may be helpful in recognition of these rare disorders [Voermans et al., 2008; Donkervoort et al., 2015].

Clinical and Diagnostic Features

The approach to neuromuscular symptoms and signs, and helpful ancillary investigations has been thoroughly reviewed [Merrison and Hanna, 2009], and supplemented by the WUSTL database on neuromuscular disorders.

Treatment

A recent study on medical consumption and outcome reported the impact of pain upon daily functioning in hEDS.

Most patients (92%) used pain medications; 52% underwent physical therapy—including neuromuscular exercises, massage, and electrotherapy—of whom two thirds reported a positive outcome. The study concluded that the impaired functional status of hEDS patients strongly determined the high rate of treatment consumption, which underscores the importance of development of evidence-based guidelines for treatment [Rombaut et al., 2011]. There is increasing evidence that treatment should consist of a multidisciplinary program. One study demonstrated success combining physical therapy, cognitive behavioral therapy, and group therapy, followed by individual home exercises and weekly guidance by physiotherapist for three months, then readmission for reevaluation and further training advice. Patients reported improved performance of daily activities, muscle strength and endurance, reduced kinesiophobia, and increased participation in daily life [Bathen et al., 2013].

Areas Needing Research

(1) The contributions of the various causative factors to muscle dysfunction in EDS, including increased compliance of the series-elastic component of muscle tissue, failure of maximal voluntary muscle activation, and impaired proprioception.
(2) Clinical trials of physical training and cognitive behavioral therapy on muscle strength and endurance in EDS patients.
(3) The development of evidence-based guidelines to improve muscle strength.

TARLOV CYST SYNDROME

Epidemiology

Tarlov cysts are perineurial cysts that may impose pressure upon adjacent neural structures. Numerous small surgical series describe the spectrum of pathology, but there is significant confusion in the reported literature with other cystic structures: the sacral meningocele and dural ectasia. The sacral meningocele principally affects males, fills the sacrum, and typically involves all of the sacral roots. Dural ectasia may present with large intra-abdominal cysts associated with connective disorders [Nabors et al., 1988; Stern, 1988].

There is a general presumption that these cystic abnormalities, including Tarlov cysts, are incidental findings. However, the belief that all Tarlov cysts are asymptomatic has no support in the literature. An unpublished review at Johns Hopkins on 756 patients with symptomatic spinal cysts, found 18 with large sacral internal meningoceles with dramatic associated sacral erosion, of whom 16 were women with Marfan disease or EDS. The remainder had typical Tarlov cysts, with a female to male ratio of seven to one, usually on sacral nerve roots. A small number existed on the lumbar, thoracic or cervical roots. Delay in treatment resulted because most patients had been told that the cysts were asymptomatic and did not need to be treated, or that no satisfactory treatment existed, or that treatment was too dangerous to contemplate. Rarely, there may be massive dilatation of the lumbar and sacral thecal sac, with extensions of the subarachnoid space along nerve roots and into abdomen and pelvis.

Etiology

The finding of inflammatory cells in the walls of symptomatic Tarlov cysts [Voyadzis et al., 2001] begs comparison with the recent findings inflammatory cells in the fila terminale of EDS patients with TCS [Klinge, 2015].

Clinical and Diagnostic Findings

Tarlov cysts are a radiological diagnosis. The Tarlov cysts appear primarily in the sacrum, at the level of the root ganglia, causing erosion of the surrounding bone (Fig. 6). Cervical and thoracic Tarlov cysts may produce pain and neurological symptoms or deficits in the distribution of the involved nerve root, or myelopathic from an extradural or subarachnoid cyst in the high thoracic region, or symptomatic from a mediastinal cystic extension behind the trachea.

The most common syndrome, occurring in approximately 70% of symptomatic patients, is comprised of sacral pain, worse when sitting and standing, and improved when lying down; pain in the S2–S5 dermatomes in the pelvis and perineum, sciatica in the Sl and S2 dermatomes, and less commonly L5 root dermatome. Bowel and bladder dysfunction are common. One third of patients have bowel and bladder dysfunction, and sensory complaints related to nerve roots S2, S3, S4 without sciatica. A small group of patients have bowel and bladder dysfunction and sacral root sensory loss without pain.

Treatment

Of patients undergoing surgical obliteration of the Tarlov cysts, successful outcomes are reported in 80–88% of patients, with few complications [Voyadzis et al., 2001; Feigenbaum and Henderson, 2006]. Alternatively, patients may undergo aspiration of the cyst and injection of the cysts with fibrin glue, although the results are less satisfactory [Patel et al., 1997].

Areas Needing Research

(1) Determine the prevalence of Tarlov cysts in the general population and the hEDS and classic type EDS populations.
(2) Define the ratio of symptomatic versus asymptomatic patients, and the factors that appear to trigger pain.
(3) Compare the pathophysiology of Tarlov cysts in the general population versus the EDS population.
(4) A prospective randomized trial to compare treatments: surgical resection versus aspiration and injection of fibrin glue.
(5) Longitudinal studies of natural and clinical history of Tarlov cysts in EDS.
(6) Utility of urodynamic studies as opposed to patient report for symptoms of neurogenic bladder.

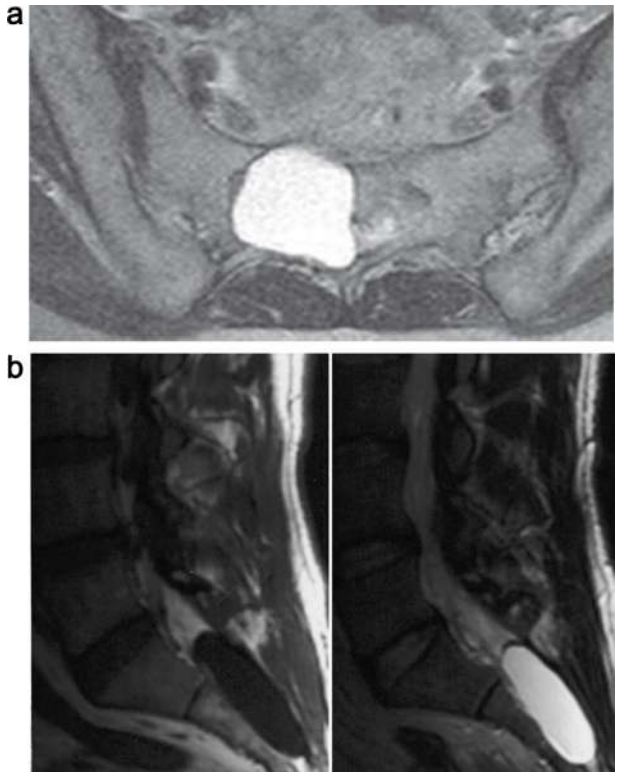

Figure 6. **a**: Tarlov cyst, with substantial bone erosion and compression of the right S2 nerve to the wall of the cyst in 9 o'clock position (T2 weighted MRI, axial view through sacrum). **b**: Large S2/S3 Tarlov cyst, T1 weighted view, Tarlov cyst on T2 weighted view (Sagittal MRI views through the sacrum).

CONCLUSION

Incompetent connective tissue results in lax ligaments within the axial skeleton, peripheral nerve sheaths, and possibly the architecture of the myoneural and muscular endplates. Ligamentous laxity of the axial skeleton in particular, subjects the central and radicular nervous system to entrapment, deformation, and biophysical deformative stresses. Biophysical stress is increasingly recognized in the alteration of gene expression, cellular function, and ultimately phenotypic expression. Clinical practice guidelines, based upon stronger epidemiological and pathophysiological evidence, are needed for the diagnosis and treatment of the various neurological and spinal manifestations of EDS.

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RESEARCH REVIEW

Pain Management in the Ehlers–Danlos Syndromes

PRADEEP CHOPRA,* BRAD TINKLE, CLAUDE HAMONET, ISABELLE BROCK, ANNE GOMPEL, ANTONIO BULBENA, AND CLAIR FRANCOMANO

Chronic pain in the Ehlers–Danlos syndromes (EDS) is common and may be severe. According to one study, nearly 90% of patients report some form of chronic pain. Pain, which is often one of the first symptoms to occur, may be widespread or localized to one region such as an arm or a leg. Studies on treatment modalities are few and insufficient to guide management. The following is a discussion of the evidence regarding the underlying mechanisms of pain in EDS. The causes of pain in this condition are multifactorial and include joint subluxations and dislocations, previous surgery, muscle weakness, proprioceptive disorders, and vertebral instability. Affected persons may also present with generalized body pain, fatigue, headaches, gastrointestinal pain, temporomandibular joint pain, dysmenorrhea, and vulvodynia. Pain management strategies may be focused around treating the cause of the pain (e.g., dislocation of a joint, proprioceptive disorder) and minimizing the sensation of pain. Management strategies for chronic pain in EDS includes physical therapy, medications, as well as durable medical equipment such as cushions, compressive garments, and braces. The different modalities are discussed in this paper. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Ehlers–Danlos syndrome; hypermobility; pain; proprioception; neuropathic; joint pain; pelvic pain

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INTRODUCTION

Pain is common in Ehlers–Danlos syndrome (EDS) and may correlate with hypermobility, frequency of subluxations and dislocations, soft tissue injury, history of previous surgery, myalgias, and may become chronic [Sacheti et al., 1997; Mulvey et al., 2013]. Pain may be musculoskeletal or widespread. It may be acute and/or chronic. The pain may interfere with socialization and activities of daily living. It can often affect sleep quality (which is common in EDS), which in turn contributes to functional impairment, independent of the level of fatigue [Voermans et al., 2009].

Pradeep Chopra, M.D., is a Pain Medicine specialist with a special interest in complex pain conditions such as Ehlers Danlos Syndrome and Complex Regional Pain Syndrome in adults and children. He has authored multiple publications and articles on the subject of complex chronic pain. He is the Director, Pain Management Center, Providence, Rhode Island.

Brad Tinkle is a clinical geneticist with interests in connective tissue disorders and is Division Head of Clinical Genetics at the Advocate Children's Hospital.

Professor Hamonet is a physician specialist in Rehabilitation Medicine, Ph.D. in Social Anthropology. He works at the Hotel-Dieu hospital (Paris, France) and specializes in Ehlers Danlos Syndrome. He has done extensive research in EDS, rehabilitation medicine. He created the department of Physical and Rehabilitation Medicine with a special focus on EDS.

Isabelle Brock, M.D., has been working as a clinical research physician studying treatment options for EDS and is currently the clinical research project manager for GERSED (study and research group for EDS) in Paris, France.

Professor Anne Gompel is an expert and member of the committee at the Regulatory Agencies for drugs in France. Involved in National Academic tasks as the General Secretary of the "National College of Professors of medical Gynecology," She has a special interest in gynecology and EDS.

Professor Antonio Bulbena, M.D., M.Sc, Ph.D., is the Chair of the Department of Psychiatry at the Autonoma University of Barcelona with clinical, academic, and administrative contributions particularly in the area of psychosomatic medicine and anxiety disorders, dementia, chocolate and carbohydrates, clinical measurement in psychiatry, phobias, seasonality, and biometeorology. Has recently developed the neuroconnective phenotype and has published numerous books, book chapters, and scientific articles in peer-reviewed journals.

Clair Francomano, M.D., is a clinical geneticist with a long interest in the hereditary disorders of connective tissue. Her professional work in the last 10 years has centered on Ehlers-Danlos Syndrome. She is Director of Adult Genetics and of the Ehlers-Danlos Society Center for Clinical Care and Research at the Harvey Institute for Human Genetics, and Associate Professor of Medicine at Johns Hopkins University School of Medicine. She serves on the Executive Board and the Medical and Scientific Board of the Ehlers-Danlos Society.

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*Correspondence to: Pradeep Chopra, MD, Assistant Professor (Clinical), Alpert School of Brown Medicine, Department of Biology and Medicine, 102 Smithfield Avenue, Pawtucket, RI 02860. E-mail: painri@yahoo.com

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Overall, pain impacts health-related quality of life.

Pain is common in Ehlers–Danlos syndrome (EDS) and may correlate with hypermobility, frequency of subluxations and dislocations, soft tissue injury, history of previous surgery, myalgias, and may become chronic. Pain may be musculoskeletal or widespread.

Multiple pathologies likely contribute to pain in EDS since it is a disease of connective tissue, which is found in virtually every organ system (Table I). The following is a literature review and discussion of the evidence of the underlying mechanisms contributing to pain in this complex disorder with management considerations.

METHODS

An international group of physicians with experience in treating pain in EDS formed a working group under the auspices of the International Consortium on the Ehlers–Danlos Syndromes. The working group conferenced by telephone approximately twice a month starting mid-2015. The working group then met in Paris, France, and again in New York in 2016 to hone the description, management, and future directions.

A detailed literature search was done on PubMed with the following keywords: "Hypermobility," "Ehlers–Danlos Syndrome," connective tissue, collagen, and pain. Papers selected were case series, case controlled studies and reviews. Case reports were not formally included but were scanned for any additional information.

LITERATURE REVIEW

Sacheti et al. [1997] interviewed 51 patients with EDS of which 28 (55%) were diagnosed with EDS hypermobile type (hEDS). They reported that the incidence of pain in hEDS was 28 out of 28 (100%). In this population, the mean score on the Numerical Rating Scale was 8 out of 10 for all types of EDS. Out of the 28 patients with hEDS, 24 (85.7%) reported progressively worsening pain. The authors concluded that moderate to severe pain is common in hEDS, starts early in life and progresses and evolves over time but that it is often complex and varied, frequently reporting pain at multiple locations.

In a more recent study of 273 patients with EDS by Voermans et al. [2009], 246 (90%) patients reported pain. Of the 246 patients who reported pain, 230 (93%) of them reported joint hypermobility, 193 (78%) had a history of dislocations, 236 (96%) reported dermal features, 227 (92%) had previous surgery, and muscle weakness was reported by 196 (80%). The hEDS was diagnosed in the majority (59%), of which, 95% were females.

Pain is often initially more localized to joints or limbs initially. Musculoskeletal pain in EDS is influenced by external factors such as lifestyle, sport activities, trauma, surgery, and various co-morbidities. Many patients report their very first painful sensations acutely, in relation to joint traumas such as dislocations and sprains as well as "growing pains" mostly localized to the knees/thighs [Castori et al., 2013]. Approximately 30% of children with hEDS reported arthralgias, back pain, and myalgias. This rate increases to >80% in patients over 40 years of age [Castori et al., 2011]. It is inversely correlated to generalized joint hypermobility, as assessed by the Beighton score, as those over the age of 33 years, often have a "negative" Beighton score but yet pain symptomatology in all aspects continues and, in most cases, increases.

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Children are often not believed by practitioners about their pain much less their joint hypermobility [Gazit et al., 2016]. While it may be acute and musculoskeletal, many also present with more recurring or chronic pain [Cattalini et al., 2015; Stern et al., 2016]. Such chronic pain issues, especially abdominal pain, are often misdiagnosed as a behavioral condition or Munchausen by proxy in children and young adults [Fikree et al., 2016]. Children may also present with recurrent, unexplained bruising or multiple joint subluxations and dislocations whereby parents are accused of child abuse [Castori, 2015].

One study found that pain was most frequently localized in the neck, shoulders, hips, forearms, and legs in 40 EDS patients [Voermans et al., 2009]. Neck pain is a common feature of hEDS and is frequently associated with headaches. It is often difficult to segregate the two conditions. Loose ligaments in the cranio-cervical junction and cervical spine may manifest as occipital-atlanto and/or atlanto-axial instability [Menezes and Van Gilder, 1988; Menezes et al., 2001]. This is compounded by ligamentous laxity of the cervical spine [Da Silva et al., 1992; Henderson et al., 2005a] and may present as cervical-medullary syndrome, with other presenting symptoms including difficulty swallowing, speech difficulty,

TABLE I. Review of Literature of Types of Pain in hEDS

Manifestations	Number of patients studied	Incidence (%)	References
Generalized body pain	>800 (cumulative)	90	Jerosch and Prymka [1996]; Camerota et al. [2011]; Hamonet et al. [2012, 2014]; Hamonet and Brock [2015]; Scheper et al. [2015]; Voermans and Knoop, 2011
Soft-tissue pain	>800 (cumulative)	90	Hudson et al. [1998]; Hamonet et al. [2012, 2014]; Scheper et al. [2015]
Dislocations	>800 (cumulative)	78	Voermans et al. [2010]; Hamonet et al. [2012, 2014]
Joint pain	28* 232# 644^	Elbow (43)* Shoulders (80)* Hands (75)* Knees (71)* Spine (67)*	Moore et al. [1985]; Aktas et al. [1989]*; Sacheti et al. [1997]; Tubiana [2000]; Berglund et al. [2005]; McCulloch and Redmond [2010]; Hamonet et al. [2012]^; Hamonet et al. [2014]; Hamonet and Brock, 2015#]; Christopherson and Adams [2014]; Scheper et al. [2015]
Fatigue	644 [cumulative] 11 [cumulative]	95 6 (55)*	Gulbahar et al. [2006]; Voermans et al. [2009, 2010]; *Celletti et al. [2012]; Hamonet et al. [2012]
Bone loss	23	16 (70)	Gulbahar et al. [2006]
Neuropathic pain	29*	68*	DeGraaf [1973]; Kass and Kayed [1979]; Stoler and Oaklander [2006]*; Camerota et al. [2011]; Voermans et al. [2011]
Loss of proprioception	18*, 32#, 22^	Significant *P*-value	Helliwell [1994]*; Ferrell et al. [2004]; Fatoye et al. [2009]; #Rombaut et al. [2010]; Zarate et al. [2010]; Celletti et al. [2011]; Galli et al. [2011]; ^Clayton et al. [2013]; Smith et al. [2013]; Deparcy [2016]
Headaches	28*	75*	Sansur et al. [2003]; Schievink et al. [2004]; DeCoster et al. [2005]; Henderson et al. [2005a]; Gulbahar et al. [2006]; Milhorat et al. [2007]*; Bendik et al. [2011]; Rozen [2014]; Hamonet and Brock [2015]
Gastrointestinal pain	21*	85.7*	Douglas and Douglas [1973]; Petros and Swash [2008]; Castori et al. [2010]*; Zarate et al. [2010]; Dordoni et al. [2015]; Hamonet and Brock [2015]; Mohammed et al., 2010
Temporomandibular joint pain	42*	71.4*	*DeCoster et al. [2004, 2005]; Hagberg et al. [2004]
Menorrhagia	387	77.57	Gompel [2016]
Dysmenorrhea		73.1	
Vulvodynia/ dyspareunia	387	42	Gompel [2016]

dysautonomia, gait changes, weakness, spasticity, and sensory alteration [Henderson et al., 2005b; Hamonet et al., 2012]. See also "Neurological and Spinal Features of Ehlers-Danlos Syndrome," this issue [Henderson et al., 2017].

Bendik et al. [2011] reported multiple headache types among 28 hEDS female patients in an interview-style case-control study. Headaches, in particular migraine, was higher in prevalence and more often more disabling than the control population (N = 232). Castori et al. [2015] reported the incidence of headaches in no less than 1/3 of patients with EDS with migraines as the most common headaches. Other possible causes of headaches include tension-type headache, new daily persistent headache, temporomandibular joint dysfunction (TMD), Chiari malformation, cervicogenic, neck–tongue syndrome, and medication related [Neilson and Martin, 2014].

Other major cause of headaches in EDS patients includes TMD [Milhorat et al., 1999]. TMD may be present in more than 70% of patients with EDS [DeCoster et al., 2004, 2005]. See also "Oral and Mandibular Manifestations in the Ehlers-Danlos Syndromes," this issue [Mitakides and Tinkle, 2017]. Cervicogenic and new daily persistent headache have also been reported to be associated with cervical spine hypermobility in a small series of EDS patients [Rozen, 2014]. Tension-type is very common as well predominantly among those with neck and shoulder dysfunction and pain.

Many joints have involvement in EDS. Patients with hEDS present commonly with pain in their hands and wrists, especially those with repetitive use [Quarrier, 2011]. They report increased pain to the forearm from the constant muscle strain. The thumb basilar joint is a particularly common joint involved in hEDS because it relies, in large part, on ligaments for stability [Christophersen and Adams, 2014]. A

study of 55 patients with EDS showed a highly significant correlation between the presence of electrophysiologically proven carpal tunnel syndrome and the occurrence of hEDS [Aktas et al., 2008]. As is often seen in many other musculoskeletal chronic pain conditions, the pain is most often at the insertion site. See also "Role of Orthopedic Management in the Ehlers-Danlos Syndromes," this issue [Ericson and Wolman, 2017].

CHRONIC PAIN

Chronic pain is one of the major symptoms presented by patients with hEDS [Sacheti et al., 1997; Voermans et al., 2010]. It often presents as diffuse body pain affecting almost every part of the body. It is common and may be severe [Voermans et al., 2009]. In one study, the prevalence of chronic pain was 90% in patients with various types of EDS, with the highest scores on severity of pain found in hEDS [Voermans et al., 2009].

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Loss of proprioception in hEDS has been reported in the medical literature and is considered to be an important factor in hEDS-related chronic pain [Helliwell, 1994; Ferrell et al., 2004; Fatoye et al., 2009; Clayton et al., 2013; Smith et al., 2013]. Proprioception, also known as joint position sense, is the ability of a joint to determine its position, detect movement, and sense of resistance to force [Rombaut et al., 2010]. Proprioception is essential for maintaining the balance of the human body, detecting movement, and coordination of normal activities. It helps protect the joints from hyperextending and damaging ligaments [Stillman, 2002].

Several different hypotheses have been brought forward to explain poor proprioception in hEDS [Smith et al., 2013]. Two such hypotheses are that the excessive joint mobility may damage proprioceptive receptors in the joints [Fatoye et al., 2009] or that the sensation of pain in the joint may diminish proprioception [Felson et al., 2009]. Exercises to enhance proprioception demonstrated an improvement in pain [Ferrell et al., 2004]. Improvement of proprioception may be effective for ameliorating both the functional status, including balance, and chronic pain [Clayton et al., 2013]. Chronic pain is associated with motor and proprioceptive disturbances; it is not clear if this is due to disturbances in position sense, muscle spindle function, or central representations of the body [Tsay et al., 2015].

Often, hEDS may be misdiagnosed as fibromyalgia because of diffuse pain with a strong myofascial component. These are to be considered as two distinct conditions with very specific diagnostic criteria. They may co-exist as two separate conditions but have different etiologies. The 2010 classification of fibromyalgia which has a sensitivity of 88% only has many overlapping features with EDS [Wolfe et al., 2010].

Often, hEDS may be misdiagnosed as fibromyalgia because of diffuse pain with a strong myofascial component. These are to be considered as two distinct conditions with very specific diagnostic criteria. They may co-exist as two separate conditions but have different etiologies.

The evidence to show the precise mechanisms of pain in hEDS is weak. Many of the proposed mechanisms have been drawn from other chronic pain conditions. Studies to distinguish both pathologies are very necessary. Pain and fatigue have a high prevalence in EDS, frequently manifesting as the predominant symptoms and as the most disabling features [Rombaut et al., 2011]. Clinical examination, pain questionnaires, quantitative sensory testing, and neurophysiological responses disclosed no somatosensory nervous system damage. Conversely, quantitative sensory testing, documented hyperalgesia to cold and heat stimuli, and an increased wind up ratio implied central sensitization [Rombaut et al., 2015; Scheper et al., 2016]. This suggests that the pain related to EDS probably shares mechanisms with those underlying fibromyalgia [Di Stefano et al., 2016]. In a study of 206 female patients with EDS, the impact of pain and functional impairment was similar to fibromyalgia but worse than that of rheumatoid arthritis [Rombaut et al., 2011].

Any form of pain be it nociceptive or neuropathic may be a secondary or even tertiary effect of underlying causes. It is those underlying causes that need to be treated. Pain management should be as diverse as its presentation and treated from all angles [Ferrell et al., 2004; Gulbahar et al., 2006; Felson et al., 2009; Voermans et al., 2009; Camerota et al., 2011; Galli et al., 2011; Castori et al., 2012; Hamonet et al., 2012; Gompel, 2016; Scheper et al., 2015; Deparcy, 2016; Hugon-Rodin et al., 2016].

MANAGEMENT

Management of chronic pain in hEDS is hindered by lack of evidence based studies that clearly demonstrate effectiveness of different modalities. The way to manage pain in hEDS would be to adapt and alter options that are used in the non-EDS population. Chronic pain

is a symptom but is also a disease entity by itself with demonstrated changes in the nervous system. Chronic pain maybe nociceptive (pain resulting from tissue injury), or neuropathic (pain generated ectopically and abnormally by either the peripheral or central nervous system) [Pappagallo, 2005; Pappagallo and Werner, 2008]. Most cases of chronic pain are an uneven mix of nociceptive and neuropathic pain. Pain management strategies may be focused around treating the cause of the pain (e.g., dislocation of a joint) and minimizing the sensation of pain.

1. Successful management of chronic pain requires a multidisciplinary approach.
2. Physiotherapy: available evidence suggests that patients who receive exercise intervention improve over time [Palmera et al., 2014]. Physical rehabilitation consists of core stabilizing and joint stabilizing and proprioception enhancing exercise coupled with general fitness program [Grahame, 2009; Rozen, 2014]. Stretching exercises should be limited to gentle stretching to avoid any risks of subluxations or dislocations. Techniques that have been used in treating hEDS pain include manual therapy for overactive muscles, trunk stabilization, posture re-education, joint awareness using biofeedback, joint mobilization with muscle release [Simmonds and Keer, 2008]. See also "The evidence-based rational for physical therapy treatment of children, adolescents and adults diagnosed with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobile type," this issue [Engelbert et al., 2017].
3. Cognitive behavioral therapy: this approach is applicable to all patients especially those whose pain is intractable, life dominating and unresponsive to analgesics or other physical interventions [Grahame, 2009]. To date there have been no clinical trials to demonstrate its efficacy in EDS.
4. Pharmacological choices:

(a) Non-steroidal anti-inflammatory drugs (NSAIDs): May be helpful if the pain is of inflammatory origin. Chronic use of NSAIDs is frequently associated with gastrointestinal, renal, and hematologic consequences [Sacheti et al., 1997]. They may also worsen symptoms of MCAS (mast cell activation syndrome) which may be a co-morbidity in hEDS. See also "Mast Cell Disorders in the Ehlers-Danlos Syndromes," this issue [Seneviratne et al., 2017].

(b) Opioids: for acute, severe pain, opioids may be an option, but only for a short duration. There is good evidence that long-term treatment with opiates is not a viable option and may lead to central pain sensitization. A trial of tramadol may be a valuable alternative for some patients with hEDS [Sunshine et al., 1992; Brown and Stinson, 2004]. The specific risk of using opioids in hEDS is centered on worsening gastrointestinal issues such as constipation and nausea as well as increasing symptoms of MCAS.

(c) Options for neuropathic pain include low dose tricyclic anti-depressants, anti-convulsants, and selective norepinephrine reuptake inhibitors. They have been shown to be effective to treat neuropathic pain in non-EDS patients; however, no trials have been done in hEDS to show their efficacy. There is concern in hEDS that if given to treat pain they might worsen other symptoms such as dysautonomia.

(d) Acetaminophen, to avoid hematologic consequences that could be associated with NSAIDs.

(e) Topical lidocaine for localized pain after subluxations as well as painful gingival tissue [Hamonet and Brock, 2015].

(f) Nefopam is a non-morphine derived potent analgesic [Hamonet and Brock, 2015].

(g) For musculocutaneous pain: injections with 1% lidocaine into trigger points [Hamonet et al., 2014; Hamonet and Brock, 2015].

(h) For dyspareunia: lubricants and/or topical estrogens (twice a week) combined with hyaluronic acid and benzydamine. In the most severe cases, lidocaine gel just before intercourse [Gompel, 2016; Hugon-Rodin et al., 2016].

(i) Dysmenorrhea can be treated with NSAIDs as it is often time-limited [Gompel, 2016; Hugon-Rodin et al., 2016].

(j) Women with dysmenorrhea and whose overall symptoms worsen during the peri-menstrual period may be aided by hormonal control with anti-gonadotropic, hypoestrogenic progestins [Gompel, 2016; Hugon-Rodin et al., 2016]. This might be due to the fact that proprioceptive accuracy decreases during menses [Fouladi et al., 2012].

(k) Transcutaneous neuro stimulator (TENS) to block pain signals via gate control theory [Hamonet and Brock, 2015].

(l) Anti-decubitus cushions and mattresses can be used for pain and discomfort when sitting/working and to improve sleep [Hamonet and Brock, 2015].

(m) Treating the underlying proprioceptive disorder with compressive, that is, tight clothing, physiotherapy, and proprioceptive shoe inserts [Hamonet et al., 2010; Hamonet and Brock, 2015].

(n) Dystonia has been described in 54% of EDS patients in a cohort study of 626 patients. Treatment with Levodopa/carbidopa or Levodopa 50 mg/benserazide 12.5 may improve dystonia, pain, and fatigue [Hamonet et al., 2016a].

(o) Fatigue and pain are linked when it comes to disability issues. They both diminish the quality of life and need to be addressed. Treating the fatigue treats the pain and vice versa. Dysautonomia is a common factor in EDS and when treated may alleviate both fatigue and pain [Bravo, 2010].

FUTURE DIRECTIONS

The management of the often severe, changing, debilitating pain in patients with hEDS is currently insufficient. Traditional pain medications do not seem to adequately treat most patients probably because the underlying cause is different to most other pain. It is, therefore, our understanding that studies not only into pain management itself are

necessary to decrease the pain but also into the management of fatigue, dystonia, energy consumption, and the treatment of the impaired proprioception among others.

It is our opinion that studies into the following subjects are urgently needed:

- Studies to differentiate between fibromyalgia and hEDS are needed as the cause of pain in hEDS may be different to that of fibromyalgia and require different treatment. Many patients are being (mis)diagnosed with fibromyalgia and thus not treated for all the other symptomatology and co-morbidities that might occur with hEDS.
- Earlier diagnosis might lead to better preventive measures. Prospective studies that look at the outcome of proprioceptive treatment on pain, fatigue, and other symptoms are necessary to evaluate if early intervention can decrease symptom progression. It is thus necessary to study tools for diagnosing EDS in children [Deparcy, 2016].
- Research on the use of NSAIDs including the differentiation between acute and chronic use in conjunction with the increased hemorrhagic tendency in hEDS.
- Oxygen therapy by face mask is already approved for cluster migraines. Oxygen therapy by face mask has been shown to decrease pain in EDS [Hamonet and Brock, 2015; Hamonet et al., 2016b]. Studies on oxygen therapy in the use against migraines and fatigue in hEDS are warranted.
- Studies into the treatment of proprioceptive impairment and its reduction of the different aspects of pain and fatigue.
- Gompel [2016] suggest that a systematic prospective study is needed to confirm the hypothesis on the role of hormonal modulation in pain management in this population.
- Studies on the treatment of dystonia, which seems to increase the occurrence of subluxations and thus pain, are necessary.
- Dysfunctions reported with oxidative phosphorylation, electron transport chain activity, and ATP production and recycling cause alterations in energy metabolism contributing to fatigue [Filler et al., 2014]. Studies considering a possible link of pain and fatigue in hEDS due to mitochondrial dysfunction are thus warranted.
- Low Dose Naltrexone (LDN) may be a good option for patients with neuropathic pain, mixed nociceptive and neuropathic pain, and pain secondary to autoimmune dysfunction in patients with hEDS. Naltrexone suppresses activation of microglia thus attenuating the production of proinflammatory cytokines. This effect is achieved by using very low doses of naltrexone [Chopra and Cooper, 2012]. Anecdotal reports of LDN in the management of chronic pain in hEDS have been promising.

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ARTICLE

Oral and Mandibular Manifestations in the Ehlers–Danlos Syndromes

JOHN MITAKIDES* AND BRAD T. TINKLE

The Ehlers–Danlos syndromes (EDS) are hereditary disorders that affect the connective tissue and collagen structures in the body. Several types of EDS have been identified. Oral and mandibular structures, which include oral soft tissue, dentition, facial and head pain, and the functioning of the temporomandibular joint (TMJ), are variably affected in the various types of EDS. These various manifestations of EDS have been noted for many years, but newer diagnostic techniques and studies are shedding additional light on the challenges faced by EDS patients in the area of oral and mandibular disorders. Further, the impact of temporomandibular disorder (TMD) on musculoskeletal dysfunction and vice versa, make this an important feature to recognize. Oral and mandibular hypermobility of the TMJ with associated consequences of EDS are noted. These features, diagnostic parameters and treatment procedures are presented.

KEY WORDS: Ehlers-Danlos syndrome; temporomandibular dysfunction; temporomandibular joint; oral manifestations; hypermobility

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INTRODUCTION

Oral and mandibular manifestations have been observed in all types of EDS patients. Collagen defects compromise oral health including vascularity, bone, teeth, gum tissue, nerve tissue, as well as the tendons and ligaments that retain maxillofacial structures in position in addition to the temporomandibular joint (TMJ) [Norton and Assael, 1997; Abel and Carrasco, 2006]. These oromandibular manifestations in EDS are often poorly recognized by healthcare providers but are commonly reported by patients and impact pain, functionality as well as quality of life [Conti et al., 2012]. Here, we describe the oral and mandibular manifestations of EDS, diagnostic techniques, and treatment modalities.

ORAL SOFT TISSUE MANIFESTATIONS

The structural collagen(s) and its function is altered in all types of EDS. The mucosal tissue is often thin [Ferré et al., 2012]. Mucosal fragility is also commonplace [Nelson and Assael, 1997]. Easy wounding occurs with oral appliances. Poor wound healing and excessive hemorrhaging is common with incidental injury as well as dental procedures.

Early onset periodontitis is seen in a variety of EDS patients, especially type VIII, the periodontal type [Reinstein et al., 2013]. The structural defects in collagen or collagen-related proteins as part of the innate immune system may increase susceptibility to degradation by bacterial pathogens. Functional consequences of altered collagen could also affect oxygen and nutrient delivery to the tissue affecting the overall health but this may also be affected in a pro-inflammatory state. Alterations of the extracellular matrix would also likely affect diffusion of not only nutrients but other small molecules and may be an important aspect of the observation resistance to local anesthesia [Hakim et al., 2005].

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John Mitakides, D.D.S., D.A.A.C.P., is the founder of The TMJ Treatment Center. He is a Diplomate of the American Academy of Craniofacial Pain, licensed to practice in Ohio, Texas, and Maryland. He is on staff at the Ehlers-Danlos Center at Greater Baltimore Medical Center, Cincinnati Children's Hospital Medical Center, and Kettering Memorial Hospital.

Brad Tinkle, M.D., Ph.D., is a clinical geneticist with interests in connective tissue disorders and is Division Head of Clinical Genetics at the Advocate Children's Hospital.

*Correspondence to: John Mitakides, D.D.S., D.A.A.C.P., The TMJ Treatment Center, 2141 North Fairfield Road, Beavercreek 45431, OH. E-mail: john@mitakides.com

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system may increase susceptibility to degradation by bacterial pathogens.

The lack of lingual and inferior labial frenula has been noted in several studies. De Felice et al. [2001] studied 12 patients with EDS, 4 of whom were classified as classic EDS and the remaining eight as hypermobile (hEDS). All patients were clinically characterized and included "significant" skin hyperlaxity. All 12 patients had an absent inferior labial frenulum (between the lower lip and gum line) whereas only nine also had absence of the (sub)lingual frenulum. Although a small sample size, both sites were significantly distinct from the appropriate control group. However, such observations were not reproduced in two subsequent studies [Bohm et al., 2001; Shankar et al., 2006].

Machet et al. [2010] evaluated patients of classic (n = 4), hypermobile (n = 19), and vascular (n = 20) types of EDS. As a subgroup (classic and hypermobile), the sensitivities of the absence of the inferior labial frenulum was 42% and 53.5% for the lingual frenulum with specificities of 99% and 98%, respectively. In vascular EDS, sensitivity was 65% with 97% specificity with an odds ratio of 72. Celletti et al. [2011] evaluated 32 patients with clinically characterized hEDS. Using a variation of assessment, the investigators did not find complete absence of the lower labial frenulum in any subject. However, the lingual frenulum was not visualized in 23 patients and 13 controls by one method but only four patients and one control by another method. Both methods produced significant results but demonstrated that the methodology could widely change the prevalence of and therefore usefulness of such a sign. It has also been noted that up to 50% of EDS patients are able to touch their tongue to their nose (Gorlin sign) but it is unclear if the absence of the lingual frenulum has an impact on the presence of this sign [Tanwar et al., 2014; Awal et al., 2015].

BONE STRUCTURE AND DENTITION

In the EDS patient tooth mobility has been noted which may accelerate the periodontal recession [Norton and Assael, 1997; Abel and Carrasco, 2006]. Orthodontia therapy is rapid due to accelerated tooth movement in the EDS patient and is usually accomplished in 1 year or less. Unfortunately, rapid but mild relapses and tooth movement are noted usually by 18 months. Tooth retention will be a lifelong necessity [Fridrich et al., 1990].

Several tooth abnormalities have been noted among EDS patients in one study [Table I; Norton and Assael, 1997]. Posterior teeth are reported to have high cusps and deep fissures. The roots may be abnormally shaped, fused and/or elongated. Pulp stones are seen in some. Congenital absence of teeth and microdontia have been also noted [Norton and Assael, 1997; Létourneau et al., 2001].

THE TEMPOROMANDIBULAR JOINT

The anatomy of the TMJ is complex. The joint is classified as a ginglymoarthrodial joint and may be better described as a sliding ball and socket joint. The muscles of mastication allow function and motion of the TMJ and mandible. Bilaterally, they are the temporalis (anterior, middle, and posterior), the masseter (superficial and deep), the internal pterygoid, and the external pterygoid muscles. Muscles of the inferior border of the mandible, anterior and posterior neck, and suboccipital triangles can also be affected by temporomandibular dysfunction (TMD). Included are the anterior belly of digastric, superior pharyngeal constrictor, middle pharyngeal constrictor, and the omohyoid muscles. It should also be noted that the TMJ and its muscles and functions are intimately associated with cervical and pharyngeal functions of the head and neck. Therefore, the general anatomy of the head and neck well beyond the TMJ must also be considered.

TMJ hypermobility and TMD have been linked to systemic joint hypermobility in several studies [Harinstein et al., 1988; Buckingham et al., 1991; Westling and Mattiasson, 1991; Westling, 1992; De Coster et al., 2005; Kavuncu et al., 2006; Hirsch et al., 2008] with fewer linking to hEDS [Diep et al., 2016]. Much like any joint in EDS, the TMJ often is hypermobile, subluxes and can dislocate [Norton and Assael, 1997; Wincour et al., 2000; Pasinato et al., 2011]. TMJ dislocation is noted to occur more often in women in the general population which mirrors that of EDS

TABLE I. Dental Manifestations of EDS

Soft tissue
• Fragile oral mucosa
• Early onset of periodontal defects
Dentition
• High cusps and deep fissures on the crowns of teeth
• Higher incidence of enamel and dental fractures
• Stunted roots or dilacerations
• Coronal pulp stones
• Aberrant dentinal tubules
• Pulpal vascular lesions and denticles
• Ready movement of teeth in response to orthodontic forces
• Easier accomplishment of orthodontic retention
Temporomandibular joint
• Hypermobile TMJ with high incidence of subluxation/dislocation
• TMD

[Nosouhian et al., 2015]. The TMJ can relocate once hyperextended but cause the cartilaginous disc to stay dislocated resulting in pain, bony destruction, and limited mobility. The muscles of mastication can be overused, spasm, and cause referred face, head, and neck pain thus resulting in decrease functionality and quality of life [Hagberg et al., 2004; Berglund and Björck, 2012].

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EXAMINATION AND DIAGNOSIS OF TMD

The tracking of opening and chewing motions can be diagnostic of TMD. Common symptoms of TMD include: (i) deflection of the jaw to the affected side; (ii) limitation of opening; (iii) inability to chew; (iv) pain in front of the ear; (v) headaches in the temples or lateral side of the jaw; (vi) tooth pain; (vii) inability to turn the head and/or neck; (viii) inability to get the posterior teeth together; (ix) fullness, itching or pain in the ear(s); (x) "popping" or crepitus with movement of the TMJ.

The mouth opening for the first 33 mm is unstressed pure rotation. Opening beyond the 33 mm involves translation of the condyle and the meniscus down the articular surface. The meniscus should remain interposed between surfaces. If it becomes dislodged anteriorly, the motion of translation is blocked and mouth opening is limited to approximately 33 mm or less. If the meniscus is dislodged posteriorly, the patient will not be able to close their mouth, occlude their teeth, or chew on the affected side. Patients with hypermobile TMJ will often display increased maximal mouth opening often well-beyond the normal range of 40–55 mm [Norton and Assael, 1997; Hirsch et al., 2008].

It is not uncommon that the hypermobile patient suddenly dislocates within the TMJ and thereafter has a limited mouth opening of 20–33 mm. This may be due to injury or stress such as: (i) prolonged opening of the mouth (i.e., dental work or intubation); (ii) blow to the head, face, or jaw; (iii) "whiplash" type injury; (iv) hyperopening; (v) hypermobile joints with increase range of motion; (vi) degenerative breakdown of TMJ articular surfaces; (vii) unbalanced occlusion; (viii) habits such as nail biting or gum chewing; (ix) bruxing or clenching the teeth and jaws. Of all of these possible causes, the most common is the bruxing of the teeth and/or clenching of the jaws. When these habits are combined with EDS or other hypermobility syndromes, the effects are substantially amplified, particularly in craniocervical instability patients [Inês et al., 2008].

In an initial examination for TMD, it is important to observe the typical tissues of the oral cavity and the head and the neck, but also the function of the TMJ, cervical, pharyngeal, and tonsillar areas. Excessive translation of the mandible may be associated with pharyngeal collapse which could be related to sleep-disordered breathing in EDS patients [Guilleminault et al., 2013].

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Muscles of mastication positions, action, tenor (especially spasms), and health should be noted. The muscles of mastication are the temporalis, masseter, internal pterygoid, and external pterygoid muscles. Palpation of these muscles will delineate fasciculation and tender areas that generate myofascial pain referral patterns. Traditionally the temporalis muscle refers pain to the upper teeth, and the masseter refers pain to the lower molars. It is not uncommon, however, to have all of the teeth in a quadrant be percussive; teeth may be sensitive to biting pressure and/or produce an aberrant vitality test. Nociceptive pain may also be present.

THE RELATIONSHIP AND UNDERLYING CAUSES OF THE TMD IN EDS

Several studies have addressed TMJ hypermobility, generalized joint hypermobility, and TMD with various conclusions. The studies reported between 40% in one study and up to 100% in another, of patients presenting with multiple types of headache and/or unilateral or bilateral TMJ pain [Castori and Voermans, 2014].

In a recent study of 114 EDS patients comprising several types with an equal number of controls, a higher proportion of the EDS patients experienced hypermobile joints during extreme mouth opening, poor mouth opening ability when biting into thick food, clicking, crepitation, and permanent locking of the jaw open and closed. Many of the EDS patents reported decreased hypermobility of the joint with age [Abel and Carrasco, 2006].

Understanding the relationship between the head, neck, and mandible structures ultimately provides a key to pain management. The classic TMD headache has been deemed to be caused by muscle spasms triggered by stress, clenching of the jaws, ischemia, osteoclastic and compression degeneration, and/or neurological input to the trigeminal nerve, which is a potential TMD input source of migrainous head pain [Shankland, 1998]. Inflammation of TMJ structures also occurs due to meniscal displacement and/or condylar displacement. Muscle spasticity and postural disorders also impact TMD [Ciancaglini et al., 1999]. An additional, less widely recognized significant trigger

of TMD pain is displacement of the cervical vertebrae [De Laat et al., 1998; von Piekartz and Lüdtke, 2011].

CRANIOCERVICAL INSTABILITY, CERVICAL SPINE DISORDERS, AND TMD

As early as 1934, researchers noted the relationship between craniocervical instability (CCI), craniomandibular disorder, and headaches [Costen, 1997]. De Laat et al. [1998] found 71% of cervical spine disorders (CSD) in the TMD group with 40% in the non-TMD group. Similar findings had been described previously by de Wijer et al. [1996], abeit using a smaller group. More recently, Inês et al. [2008] examined the effect of TMD and positioning of the skull over the cervical region. The authors found that 90% of the patients with cervical pain had TMD, and, thus, concluded that the position of the cervical spine (postural) impacted TMJ function. As the neck and especially the upper cervical spine are often involved in EDS patients, the interaction, recognition, and potential co-management should be considered.

MANAGEMENT

Soft Tissue

Dental visits should be minimal in length to avoid causing problems related to the TMJs. All injections should be given with care to preclude hematomas especially the inferior alveolar nerves. An orthodontic appliance for a patient with EDS should be smooth and relatively simple in spring design, so that the tongue and buccal mucosa are not abraded.

The periodontal ligaments are fragile which requires the orthodontic forces to be less than usual. The teeth will move rapidly due to the fragility of the periodontal ligament and relapse quickly. Longer periods of tooth retention is recommended. Dental and oral surgeries should be avoided if possible. If surgery is necessary, blood coagulation tests should be evaluated before proceeding. Suturing should be done with extreme care due to the fragility of the tissues and oral mucosa.

TREATMENT OF TMD

Years of study of TMD, as well as advanced imaging techniques, have led to a deeper understanding of the syndrome, its causes, and treatment. Yet, while proper diagnosis and precise treatment of TMD is always complex, it is far more so in the EDS patient. Even practitioners highly trained in the area of TMD can face unexpected challenges in diagnosing and treating an EDS patient if they do not have an in-depth understanding of EDS. Some symptoms are obvious to the practitioner familiar with the disorder, and some are very subtle.

Yet, while proper diagnosis and precise treatment of TMD is always complex, it is far more so in the EDS patient. Even practitioners highly trained in the area of TMD can face unexpected challenges in diagnosing and treating an EDS patient if they do not have an in-depth understanding of EDS.

Assuming TMJ hypermobility and generalized joint hypermobility increases the prevalence of TMD, all EDS patients should be treated prophylactically. Prevention of TMJ injury should be paramount. Postural alignment as well as upper back and cervical issues need to be addressed. Lifestyle changes can include alteration of chewing patterns, diet, stress reduction techniques, and management of physical activities.

Multiple treatments are available for management of pain and TMD-associated problems, depending on the source and type of symptoms. Because all musculature in the body is susceptible to spasm and contracture, eliminating or minimizing muscle spasms is often the first step in reducing pain, and offers conservative treatment options which are appropriate for the EDS patient. With the multiple manifestations of EDS, it is important that TMD care be conservative, focused and highly informed. The following techniques are helpful:

- Deep heat has the ability to relax muscle fibers and decrease spasms. The usual protocol is 10-3-10: 10 min of warm, followed by 3 min of cold, and 10 min of warm.
- Cold laser (Superpulsed Low Level Laser Therapy) has been shown to be effective in pain management of TMD [Marini et al., 2010].
- Friction muscle massage stretches and relaxes the muscle fibers. A muscle is relaxed when it is a full length.
- Custom splints to stabilize the TMD have proven effective over time. Such appliances, when carefully created to target appropriate anterior repositioning, provide stabilization, limit joint injury, and help maintain physiological posture.
- Prolotherapy, also called regenerative injection therapy, is a non-surgical alternative medicine treatment for ligament and tendon reconstruction. Injections of a combination of dextrose and local anesthetic have proven promising [Hakala, 2005].
- Medications offer a variety of options, such as muscle relaxants, mood elevators, anti-inflammatories, and pain medications. In the EDS patient, care must be taken to consider other medications and possible additional effects of any medication.
- Botulinum toxin to relax muscle or at trigger points can provide almost immediate relief for some patients. Botulinum toxin is injected into specific trigger points, particularly for the purposes of relieving migraines, muscle spasms, involuntary positional motions, and structural physicality.
- Physical therapy can assist with muscle integrity, posture, and can maintain

ranges of motion and physiological structural position for function. It is vital that the physical therapist understand the special needs of the EDS patient, including the attendant increased fragility.

- Surgical options should be limited to extreme cases, such as physical damage to the TMJ. EDS patients in particular face unique surgical challenges, making them less than ideal candidates for surgical TMJ stabilization. Surgical repairs heal slowly and often with unpredictable results.

FUTURE DIRECTIONS

Oral mandibular manifestations are commonly encountered in the EDS patient but their true prevalence and significance should be studied to establish the relationship between EDS and TMD. Additional study could also be informative regarding diagnosis and treatment, particularly in the area of craniofacial pain. Most importantly, the relationship of cervical spine disorders to TMD in EDS patients requires further study. While the "mechanics" of a malfunctioning TMJ are well established, the question remains: in addition to obvious factors such as trauma or bruxism, what causes malfunctioning of the joint? Could cervical spine disorders and craniocervical instability be an underlying causative factors?

The increased fragility and friability of the oral tissues are an indication of the friability of other mucosal-based tissues in the body. The presence of the concerning signs of EDS should be an indication to the practitioner to consider further consultations including rheumatology, dermatology, and/or genetics to confirm and establish the potential type of EDS.

EDS patients face a variety of quality of life issues, often including sleep disturbances related to chronic pain [Voermans et al., 2010]. It is important that practitioners not overlook additional issues that could affect sleep. The previously discussed relationship between head, neck, and mandibular structures, in combination with EDS-type changes in soft tissue and cartilaginous structures, might also be a contributing factor for sleep-disruptive manifestations. EDS tissue laxity and lack of tonicity may cause constriction and in some cases, collapse of the nasal and pharyngeal spaces. Mandibular structure, function, and motion all dictate the position of the actions of the origins and insertions of the musculature that allow pharyngeal structure and function in the action of breathing.

Recent studies have suggested a link between sleep-disordered breathing (SBD) and EDS, "which is commonly unrecognized, and is responsible for daytime fatigue and poor sleep," [Guilleminault et al., 2013]. Additionally, the study concluded, "ED[S] patients are at particular risk for SDB due to genetically related cartilage defects causing these patients to develop facial structures known to cause SDB."

While the relationship between bruxism, including sleep-related bruxism, and TMJ remains unclear [Manfredini and Lobbezoo, 2010] given the prevalence of TMJ disorders and soft tissue impairment in the EDS patient, practitioners should be cognizant of the possibility of an affected airway, which can best be determined by a formal sleep study. The subject of sleep-disordered breathing in the Ehlers–Danlos patient is one that requires additional study.

Additionally, further studies to document the prevalence of the absence/hypoplasia of the oral frenula in the various types of EDS with specific emphasis on consistency of the evaluation. Further studies on the prevalence of Gorlin sign in the various EDS types and the relationship to the lingual frenulum could prove helpful to dental practitioners in the recognition of EDS.

SUMMARY

Research has confirmed a variety of oral and mandibular manifestations associated with EDS. TMD and pain resulting from a malfunctioning oral and mandibular structure appear to be highly prevalent in the EDS patient population. This relationship is logical given the nature of EDS and its effects on the multiple oral structures and collagen. The exact nature of this relationship merits further study. Additionally, the relationship between TMD, myofascial pain, and CCI presents an opportunity for meaningful research, with the goal of providing more effective treatment.

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RESEARCH REVIEW

Mast Cell Disorders in Ehlers–Danlos Syndrome

SURANJITH L. SENEVIRATNE, ANNE MAITLAND ,* AND LAWRENCE AFRIN

Well known for their role in allergic disorders, mast cells (MCs) play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury, with an array of chemical mediators. After being recruited to connective tissues, resident MCs progenitors undergo further differentiation, under the influence of signals from surrounding microenvironment. It is the differential tissue homing and local maturation factors which result in a diverse population of resident MC phenotypes. An abundance of MC reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts). Situated near nerve fibers, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, MCs can modulate the function of local and distant structures (e.g., other immune cell populations, fibroblasts, angiogenesis), and MC dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs). This report reviews basic biology of mast cells and mast cell activation as well as recent research efforts, which implicate a role of MC dysregulation beyond atopic disorders and in a cluster of Ehlers–Danlos Syndromes, non-IGE mediated hypersensitivity disorders, and dysautonomia. © 2017 Wiley Periodicals, Inc.

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INTRODUCTION: MAST CELLS AND THEIR PROPERTIES

In the late 19th century, Paul Ehrlich named a granule-dense cell, "mast-zellen," situated near blood vessels in the mucosa and connective tissue. He theorized these cells were providing nourishment to the local tissue environment. Using commercial dyes such as dahlia, toluidine blue, methylene blue, and neutral red, he noted metachromatically staining mature mast cells (MCs) in the connective tissue of several organs.

MCs develop from multipotent hemopoietic progenitors in the bone marrow [Moon et al., 2010]. Stem cell factor (KIT ligand) binds to homodimeric KIT (a transmembrane tyrosine kinase receptor) and influences MC differentiation, growth, survival, migration, and effector functions. MCs acquire a tissue specific phenotype depending on signals they receive from the local tissue environment. Several factors such as interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-9 (IL-9), and transforming growth factor β1 (TGFβ1) have been shown to influence the number and mediator content of MCs [Galli et al., 2011].

Under non-pathological states, mature differentiated MCs are found exclusively within tissues, compared to other innate immune cells, such as basophils, neutrophils, and eosinophils. Within tissues, MCs congregate around nerves, blood vessels, and lymphatic vessels. Based on their location (connective tissue or mucosal) and content of their granules, two types of MCs have been described. MCs residing in connective tissue, skin, and the peritoneal cavity contain tryptase (MC_T) in their granules and express interleukin-5 (IL-5) and interleukin-6 (IL-6). MCs homing to the gut and respiratory mucosa contain tryptase and chymase (MC_{TC}), and express IL-4 [Sigal, 2011]. When fully differentiated, MCs exhibit a wide range of biological properties including phagocytosis, antigen presentation, cytokine and chemokine production, and the immediate release of vasoactive substances. They have a role in local tissue homeostasis (tissue repair, angiogenesis) and co-ordination of immune responses to a myriad of pathogens, recognized through evolutionarily conserved surface receptors like toll-like receptors, complement receptors, and receptors for adenosine phosphate, oestrogen, and immunoglobulins), physical stimuli (pressure, temperature), and toxins. As yet, no animal model or disease state has

Suranjith L. Seneviratne, Institute of Immunity and Transplantation, Royal Free Hospital and University College London, United Kingdom; Faculty of Medicine, Department of Surgery, University of Colombo, Colombo, Sri Lanka.
Anne Maitland, Division of Clinical Immunology, Department of Medicine, Mount Sinai Hospital, New York, New York.
Lawrence Afrin, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.
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*Correspondence to: Anne Maitland, MD, PhD, Division of Clinical Immunology, Department of Medicine, Mount Sinai Hospital, Box 1089, 1 Gustave L. Levy Place, New York, NY 10028. E-mail: anne.maitland@mssm.edu
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been identified where there is a complete lack of MCs [Metcalfe et al., 1997]. When activated, MCs produce a range of preformed and newly synthesised mediators (Fig. 1) [Louisias et al., 2013]. Within minutes of activation, preformed mediators (histamine and proteases) are released. This is followed by de novo synthesis of membrane-derived lipid mediators (prostaglandins and leukotrienes) and a range of pro- and anti-inflammatory cytokines and chemokines.

MCs residing in connective tissue, skin, and the peritoneal cavity contain tryptase (MC_T) in their granules and express interleukin-5 (IL-5) and interleukin-6 (IL-6).

MCs are best known for their role in immediate IgE-mediated, allergic responses in anaphylaxis, food allergy, venom allergy, and asthma. Recent reports have also implicated MCs in nonallergic disorders, including headache syndromes, irritable bowel syndrome, non-celiac gluten enteropathy, osteoporosis, autoimmune syndromes, neuropsychiatric disorders, and interstitial cystitis [Theoharides et al., 2015].

MAST CELLS AND CONNECTIVE TISSUE

Different components of the extracellular matrix affect the migration and differentiation of MC progenitors, MC activation, and pattern of mediator release. Human MCs express laminin receptors and can adhere to fibronectin and vitronectin.

The hypermobile type of Ehlers–Danlos Syndrome (hEDS) is the dominant form of EDS. A subpopulation of hEDS patients have been found to have MCAD (more often MCAS than SM). Several reports have described of co-morbid clinical manifestations in patients with CTDs, including EDS, functional gastrointestinal disorders [Fikree et al., 2015]; eosinophilic gastrointestinal disorders [Abonia et al., 2013]; an increased prevalence of asthma [Morgan et al., 2007], neuropsychiatric conditions [Sinibaldi et al., 2015], and osteoporosis [Deodhar and Woolf, 1994]; and orthostatic intolerance [Garland et al., 2015]. Luzgina et al. [2011] found an increased number of chymase-positive MCs in the eyelid skin of patients with CTDs (joint hypermobility, skin hyper-elasticity, spinal deformities, thumb and wrist sign, vascular, fragility, varicose veins, and telangiectasias).

Several reports have described of co-morbid clinical manifestations in patients with CTDs, including

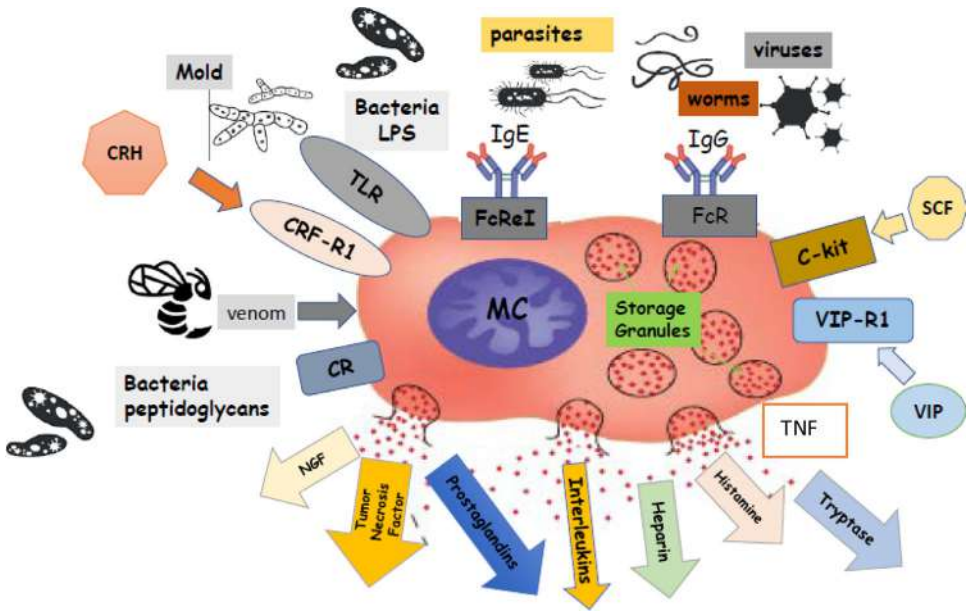

Figure 1. MC activate and release bioactive substances, responding to a variety of mechanical, biological, or chemical stimuli. MCs release preformed mediators in granules (histamine, heparin, serotonin, and enzymes) and newly synthesized (cytokines, growth factors, and lipid metabolites). C-kit, transmembrane tyrosine kinase receptor; CR, complement receptor; CRF-R1, corticotropin releasing factor receptor 1; CRH, corticotropin releasing hormone; FcεRI, Fc epsilon receptor I; FcγRI, Fc gamma receptor I; LPS, lipopolysaccharide; MC, mast cell; NGF, nerve growth factor; SCF, stem cell factor; TLR, Toll-like receptor; TNF, tumor necrosis factor-α; VIP, vasoactive intestinal peptide; VIP-R1, vasoactive intestinal peptide receptor 1. Adapted from the following references: [Afrin, 2013; Cardet et al., 2013; Theoharides et al., 2015] and arranged using images from shutterstock.com.

EDS, functional gastrointestinal disorders; eosinophilic gastrointestinal disorders; an increased prevalence of asthma, neuropsychiatric conditions, and osteoporosis; and orthostatic intolerance.

Several investigators have noted a possible link between EDS and MCAD, primarily patients with the hypermobility type of EDS. Immunohistochemisty analysis identified an increased content of chymase positive MCs in undamaged skin of patients with signs suggestive of CTDs (hyperelasticity of the skin, joint hypermobility, spine and thorax deformities, thumb sign, wrist sign, vascular fragility, varicose veins, and telangiectasias) [Luzgina et al., 2011]. Louisias et al. [2013] described symptoms compatible with a non-IgE mediated MC disorder in patients with the joint hypermobility syndrome: most reported naso-ocular symptoms, asthma, and history of anaphylaxis and describe a positive response to classical MC/MC mediator antagonists. Plasma histamine and serum tryptase levels were normal and prostaglandin measurements were not undertaken. Cheung and Vadas [2015] suggested a possible new disease cluster: Mast Cell Activation Syndrome (MCAS), Postural Orthostatic Tachycardia Syndrome (POTS), and EDS. Patients having a diagnosis of POTS and EDS were given a screening questionnaire to look for symptoms consistent with MCAS, and 66% of the respondents reported such symptoms. Recently, Milner et al. identified families with an elevated, baseline serum tryptase, which was associated with the triad of dysautonomia, MCAD, and joint hypermobility [Lyons et al., 2016]. The elevated tryptase level was not consistent with SM. Instead, increased copy numbers of the *TPSAB* gene, that encodes alpha tryptase, were detected. Moreover, these observations highlight the role of MCA, impacting the structure and function of connective tissue, as described in inflammatory arthritis [Nigrovic and Lee, 2005].

MAST CELL ACTIVATION DISORDERS

Mast cell activation disorder (MCAD) refers to an increased number of MCs, increased activity of MCs, or both. Akin et al. [2010] classified diseases associated with MC activation as primary, secondary, and idiopathic groups (Table I). The conditions may be associated with (1) "an expansion of clonal MCs," and/or (2) by increased, aberrant MC mediator release. Monoclonal MC activation syndrome (MMCAS) was included within the primary group; non-clonal MC activation syndrome (MCAS) was included within the idiopathic group.

Consensus diagnostic criteria have been established for most of the forms of mastocytosis (e.g., the WHO 2008 criteria define the approach to systemic mastocytosis (SM) [Horny et al., 2008]. However, as MCAS is so recently recognized, no consensus definition has yet been established. There are two proposals for diagnostic criteria for MCAS [Molderings et al., 2011; Valent et al., 2012] (Table II). The presence of EDS (of any form) in the patient's history is not known to affect the approach to diagnostic evaluation for MCAD.

The most well-known form of MCAD, MC disorders proven to be primary/clonal are rare, with an estimated prevalence of one case per 10,000–100,000 persons. Primary, clonal MC disorders include mastocytosis and MMCAS. Reported secondary causes of MC disorders include comorbid immune disorders, including classic atopic syndromes ("allergies"/IgE-Fcε receptor-mediated MC activation); autoimmune disorders (autoimmune chronic urticaria, multiple sclerosis, rheumatoid arthritis) [Benoist and Mathis, 2002]; and chronic infections, of which some likely occur in the context of primary immune deficiency disorders [Cardet et al., 2013].

Allergic disorders are a well-recognized cause of MC activation (MCA). Here, allergens cross link IgE molecules on the surface of MCs, leading to MCA,

TABLE I. Classification of Diseases Associated With Mast Cell Activation (Adapted From [Akin, 2014; Theoharides et al., 2015])

Primary	Mastocytosis
	Monoclonal Mast Cell Activation Syndrome
Secondary	Allergic/atopic (IgE mediated) disorders
	Mast cell activation associated with chronic inflammatory or neoplastic disorders
	Physical urticarias
	Chronic autoimmune urticaria
Idiopathic	Anaphylaxis
	Angioedema
	Urticaria
	Mast cell activation syndrome

TABLE II. Diagnostic Criteria for Systemic Mastocytosis and Mast Cell Activation Syndrome (Adapted From Afrin, World Journal of Haematology, 2014)

WHO 2008 diagnostic criteria for systemic mastocytosis
Major criterion
Multifocal dense aggregates of MCs (15 or more) in sections of bone marrow or other extra-cutaneous tissues and confirmed with tryptase immunochemistry or other special stains
Minor criteria
Atypical or spindled appearance of at least 25% of the MCs in the diagnostic biopsy
Expression of CD2 and/or CD25 by MCs in marrow, blood, or extra-cutaneous organs
KIT codon 816 mutation in marrow, blood, or extra-cutaneous organs
Persistent elevation of serum total tryptase >20 ng/ml
Diagnosis of SM made by either (1) major criterion + any one or more minor criteria or (2) any three minor criteria
Proposed diagnostic criterion for MCAS: Valent et al. [2012] criteria
Chronic/recurrent symptoms (flushing, pruritus, urticaria, angioedema, nasal congestion or pruritus, wheezing, throat swelling, headache, hypotension, and/or diarrhea) consistent with aberrant MC mediator release
Absence of any other known disorder that can better account for these symptoms
Increase in serum total tryptase of 20% above baseline plus 2 ng/ml during or within 4 hr after a symptomatic period
Response of symptoms to histamine H_1 and/or H_2 receptor antagonists or other "MC-targeting" agents such as cromolyn
Proposed diagnostic criteria for MCAS: Molderings et al. [2011] criteria
Major criteria
Multifocal MC aggregates as per WHO major criterion for SM
Clinical history consistent with chronic/recurrent aberrant MC mediator release
Minor criteria
Abnormal MC morphology as per WHO SM minor criterion 1
CD2 and/or CD25 expression as per WHO SM minor criterion 2
Detection of known constitutively activating mutations in MCs in blood, marrow, or extracutaneous organs
Elevation in serum tryptase or chromogranin A, plasma heparin or histamine, urinary N-methylhistamine, and/or other MC-specific mediators such as (but not limited to) relevant leukotrienes (B4, C4, D4, E4) or PGD2 or its metabolite 11-β-PGF2α

TABLE III. Diagnosis of MCAS Made by Either (1) Both Major Criteria, or (2) the Second Major Criterion Plus Any One of the Minor Criteria, or (3) Any Three Minor Criteria

A: Clinical signs & symptoms of mastocytosis patients. Adapted from [Alvarez-Twose et al., 2010]	
Sign/symptom	%
Skin lesions	90
Pruritus	82
Flushing	56
Diarrhoea	35
Abdominal cramping	30
Neuropsychiatric symptoms	23
Anaphylactic	23
Peptic symptoms	20
Osteoporosis	18
Hepatomegaly	12
Splenomegaly	08

B: Clinical signs & symptoms of "Non-clonal" mast cell activation disorder. Adapted from [Hamilton et al., 2011]	
Sign/symptom	%
Abdominal pain	94
Dermatographism	89
Flushing	89
Headache	83
Neuropsychiatric symptoms	67
Diarrhoea	67
Rhinitis	39
Asthma	39
Anaphylaxis	17

releasing a range of mediators and producing the well-known range of allergic manifestations. Physical MC triggers constitute common, non-IGE MCADs, such as those affected by physical urticarias, including cholinergic and cold-induced urticaria [Simons, 2010]. Research efforts are now describing mechanisms of non-IGE mediated MCA. Oxidative mechanical stress has been shown to induce MC mediator release [Briganti et al., 2001]. Boyden et al. [2016] described a missense variant in *ADGRE2* associated with vibratory urticaria. Recently, in subjects with an inherited, elevated baseline of serum tryptase, Milner et al. described a dominant inheritance of increased copy number of *TPSAB1* gene, which encodes alpha tryptase. Clinical manifestations of hypertryptasemia include dysautonomia, joint hypermobility, and MC activation [Lyons et al., 2016]. Active research is also exploring the neurohormonal activation of MCs [Theoharides et al., 2015]. If a clonal MC disorder is not detected nor a secondary cause identified, as detailed above, then children and adults with clinical symptomology and with evidence of aberrant MC mediator release are deemed to have idiopathic MCAD [Cardet et al., 2013; Picard et al., 2013; Theoharides et al., 2015].

CLINICAL FEATURES OF MCAD

The clinical presentation of MCAD tends to be very heterogeneous. Clinicians need to be aware of this so as to suspect the condition and carry out appropriate testing. Mutational heterogeneity in the affected MC subsets may contribute to the heterogeneity of clinical expression. Common presenting symptoms and signs of mastocytosis and MCAS are given in Table III [Alvarez-Twose et al., 2010; Hamilton et al., 2011]. Conditions that need to be considered in the differential diagnosis of MCAD include: cardiovascular, endocrine, gastrointestinal and neurological disorders, infections, and medication-induced side effects.

The following criteria have been proposed for diagnosing MCAD:

(1) Typical signs and symptoms of MC mediator release (affecting at least two organ systems)
(2) [Akin, 2014; Theoharides et al., 2015]

Skin	Flushing, pruritis, urticaria, angioedema
Cardiovascular	Hypotension
Respiratory	Asthma: cough, wheezing; throat swelling
Gastrointestinal	Diarrhea, bloating, cramping
Naso-ocular	Rhinitis, pruritis
Anaphylaxis	Stinging insect allergy, peri-operative anaphylaxis

(3) Objective evidence of MC-derived mediator release or chronically activated MCs [Afrin, 2013; Cardet et al., 2013]

Tryptase**	Baseline elevated level; Elevated serum tryptase, following a suspected MC activation event: 20% + 2 ng/ml above baseline
Histamine	Elevated 24-hr urinary histamine metabolite (N-methylhistamine)
Prostaglandin	Elevated 24-hr urinary prostaglandin D_2; 11-β-prostaglandin-$F_{2\alpha}$
Tissue Biopsy	CD117 + cells that are clustered and/or, spindle-shaped; co-expression of CD25 and CD2 on CD117 + Cells (MCs)
Heparin	Increased blood level
Chromogranin A	Increased blood level (note confounders of cardiac or renal failure, proton pump inhibitor use, or neuroendocrine cancer)

**Although all MCs contain tryptase, there is evidence indicating that tryptase is not always secreted following engagement of different MC activation pathways [Marshall, 2004].

(4) Response to therapy that directly or indirectly blocks MC mediator activity [Cardet et al., 2013; Akin, 2014]

Histamine H_1 and H_2 receptor blockade
Ketotifen
Cromolyn sodium
Aspirin
Leukotriene receptor antagonists
Omalizumab

A diagnostic algorithm for MCAD is shown in Figure 2 [Picard et al., 2013].

LABORATORY ASSESSMENT OF MCAD

Diagnostic pursuit of MCAS typically focuses on probing blood and urine for elevated levels of mediators relatively specific to the MC [Afrin and Molderings, 2014]. However, at present, of the over 100 mediators produced by activated MCs, only handful can be measured within commercial laboratories. Assays certified for clinical use are not available for most MC mediators, and even for those MC mediators which can be tested in the clinical laboratory, most have an unfavorable level of specificity for the MC, leaving relatively few mediators to be tested. Furthermore, many of the diagnostic tests are not widely available to the clinician or are cost-prohibitive. Ideally, serum tryptase and chromogranin A, plasma histamine, prostaglandin (PG)D_2, and heparin, as well as urinary (random and 24-hr) histamine, *N*-methylhistamine (NMH), PGD_2, 11-β-$PGF_{2\alpha}$, and leukotriene (LT) E4 should be assessed. Whether to pursue such tests in parallel or sequentially depends on the balance between diagnostic expediency versus containment of testing costs.

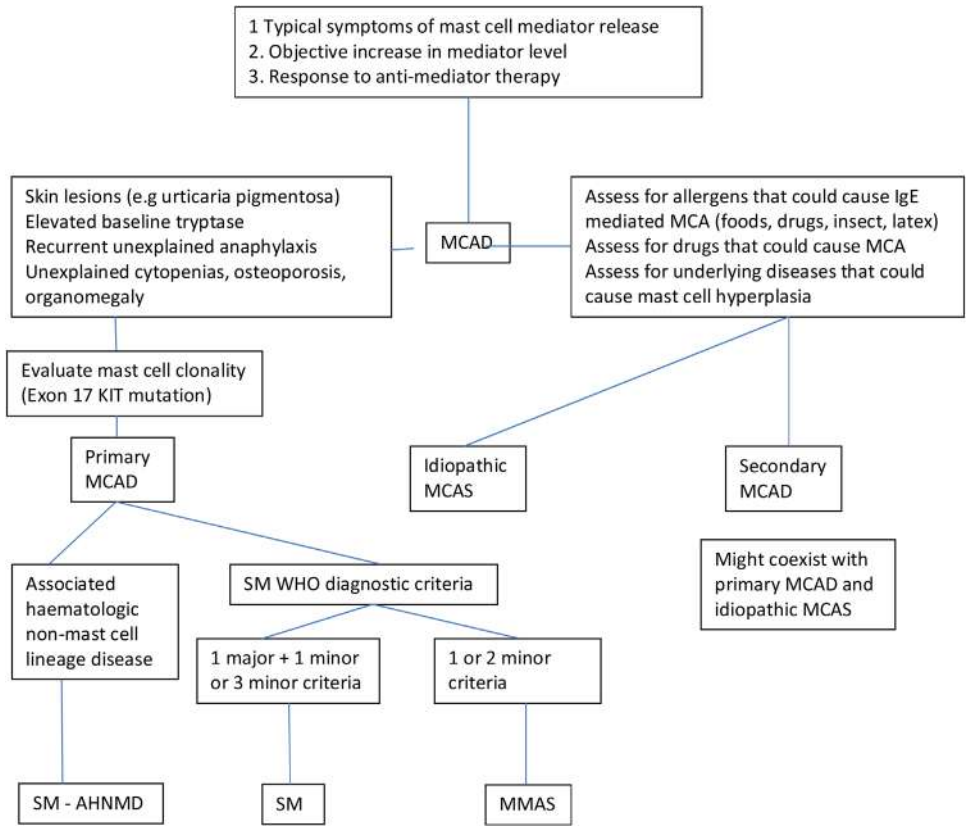

Figure 2. Diagnostic algorithm for mast cell activation disorders. Permission to reprint from Dr. Mariana Castells, [Picard et al., 2013]. KIT, a transmembrane type III tyrosine kinase receptor; AHNMD, associated hematologic non-mast cell lineage disease; MCA, mast cell activation; MCAD, mast cell activation disorder; MCAS, mast cell activation syndrome; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis.

Some metabolites have longer half-lives (e.g., tryptase, histamine) and are thermostabile than others (e.g., heparin, the prostaglandins). It is prudent to continuously chill all specimens throughout collection and handling (including centrifugation). The authors recommend identifying at least two elevated MC mediator levels (either the same mediator, or different mediators), and preferably across two different time points (in keeping with the chronic clinical nature of the disease), before diagnosing MCAS in a patient with a history consistent with chronic/recurrent aberrant MC mediator release and absence of any other evident disease better accounting for the full range and chronicity of all the symptoms and findings in the past.

The technical and logistical challenges in MC mediator testing need to be acknowledged. If mediator testing is negative in a patient whose clinical history strongly suggests MC activation, repeat testing should be done at a timepoint when the patient is particularly symptomatic. Upper and/or lower gastrointestinal tract mucosal biopsies stained for MCs (CD117 at a minimum) looking for increased numbers of or constitutively active MCs also can be helpful.

Serum Tryptase Levels. Tryptase is the most abundant protein in MCs and is heat stable. The amount found in basophils is about 300 times lower than in MCs. The human tryptase gene is located on chromosome 16, and codes for five isoenzymes: alpha, beta, gamma, delta, and epsilon. Beta tryptase is the predominant form stored in the MC granule. It is found as a tetramer and is stabilized by proteoglycans such as heparin. The isoforms are continuously released from MCs into the bloodstream and basal levels are a reflection of total MC numbers [Schwartz, 2006]. The ImmunoCAP® Tryptase assay measures total tryptase levels (that is all inactive proforms of alpha-tryptase and beta-tryptase, as well as the enzymatically active mature beta-tryptase). The conditions/disorders that cause an elevated basal serum tryptase level are given in Table IV.

Basal serum tryptase levels of 20 ng/ml are considered as a decision point in several MC diagnostic criteria. For example, a basal serum tryptase level greater than 20 ng/ml is a minor diagnostic criterion for SM. Valent et al. [2012] suggested a rise in serum total tryptase of 20% above baseline, plus 2 ng/ml, within 4 hr of the onset of an acute flare of symptoms as a

TABLE IV. Conditions/Disorders That Could Cause Elevated Basal Serum Tryptase Levels Adapted From the Following References [Cardet et al., 2013; Picard et al., 2013]

Condition/disease	Source of tryptase
SM	Neoplastic MCs
MCAS	Activated MCs (monoclonal or polyclonal)
Allergic/atopic disorders	Activated MCs and/or activated basophils
End stage kidney disease	Normal MCs
Helminth infection	Reactive MCs
Myelodysplastic syndromes	Neoplastic MCs or/and basophils or/and blast cells
Acute myeloid leukaemia	Myeloblasts
Chronic myeloid leukaemia	Immature leukaemic basophils (rarely MCs)
Chronic eosinophilic leukaemia	Neoplastic MCs
Idiopathic	Unknown

Some haemodialysis patients may present with elevated tryptase levels, due to reduced excretion.
MC, mast cell; MCAS, mast cell activation syndrome; SM,systemic mastocytosis.

significant rise. However, as yet there has not been clinical validation of this formula as a discriminating tool for diagnosing MCAS.

It needs to be stressed that a normal serum tryptase level does not exclude MCAS. Furthermore, levels above 20 ng/ml do not exclude MCAS, and levels below 20 ng/ml do not exclude SM. Persistence of the serum tryptase level above 20 ng/ml makes SM more likely, necessitating marrow examination to exclude mastocytosis. Even if the serum tryptase level is persistently below 20 ng/ml, consideration of SM may need to made if the patient's history of illness is more consistent with SM (i.e., sudden onset of symptoms in middle or older age in contrast to MCAS's usual history of symptoms dating back to adolescence or childhood).

Urinary or Plasma Histamine and Histamine Metabolites

Levels are measured in a 24 hr urine collection, a spot urine sample and plasma sample. Sample chilling is important and special care needs to be taken with sample collection and storage. The levels are best measured during an attack or soon thereafter and should be undertaken within a laboratory with experience in their measurement.

Prostaglandins and leukotrienes in urine or plasma: Prostaglandin (PGD2), 11-β-prostaglandin-$F_{2\alpha}$, or leukotriene (LTE4) are measured in plasma or a 24-hr urine sample [Schäfer et al., 2014]. The patient needs to take care in keeping the sample chilled when collecting a 24 hr urine sample. PG interpretation is confounded by recent use of non-steroidal anti-inflammatory drugs (NSAIDs). When NSAIDs have not been recently used, the finding of PG levels below the lower limit of normal may point toward the loss of the sample's thermal integrity while en route to the reference laboratory.

Histopathological Examination of Bone Marrow

A bone marrow biopsy needs to be considered when the baseline tryptase level is >20 ng/ml or those who have syncopal or pre-syncopal events as part of their symptoms (irrespective of the tryptase levels) [Akin, 2014]. Such an examination may need to be bilateral to increase the chances of finding the typically patchily distributed aggregates of abnormal MCs [Butterfield and Li, 2004].

In addition to evaluating the number of MCs, changes in morphology or distribution and evidence of degranulation should be looked for. Antibodies against KIT (i.e., CD117), CD25, tryptase, and chymase should be used. Flow cytometric assessment for co-expression of CD117 together with CD25 and/or CD2, CD30, and mutational assessment for mutations in KIT (in particular, the *KIT* D816V mutation at a minimum) should be done. CD25 expression in MCs is a minor diagnostic criterion in SM. When MCAS seems more likely than SM, marrow examination is usually unhelpful. Even if MMCAS is found on flow cytometric or mutational testing, at present there are no known differences in prognosis of, or the therapeutic approach toward, MMCAS versus MCAS.

Histopathological Examination of Other Tissues

If mediator testing is unrevealing, the Molderings diagnostic criteria (REF) provide an alternative path to diagnosis of MCAS, namely, finding increased MCs in extracutaneous tissue, most commonly gastrointestinal (GI) or genitourinary (GU) tract mucosal biopsies. Biopsy specimens obtained from the gastrointestinal tract, urinary bladder, and skin should be stained for mast cells. A cut-off of >20 MCs per high power field has been considered by several groups when interpreting the tissue biopsy findings. Traditionally, staining of tissue biopsies for MC disease has employed stains targeting MC granules or their contents, for example, tryptase, Giemsa, toluidine blue, Alcian blue, etc.

However, more recently, it has become clear that CD117 (the dominant MC regulatory element brightly present on virtually all MCs) more reliably reveals MCs [Feyerabend et al., 2005; Leclere et al., 2006]. Given that the essence of MCAD is inappropriate MCA and thus inappropriate MC degranulation, relying on granule-targeting stains may increase the false negative rate. MCs in SM are found in abnormal aggregates but remain normally dispersed in MCAS. Furthermore, the MCs in SM typically are of aberrant morphology (most commonly spindled) while in MCAS they retain their normal round to ovoid shape. Again, CD117 co-expression with CD25 and/or CD2 is uncommonly found on flow cytometry in MCAS (whether in marrow or other tissue), and *KIT* codon 816 mutations, too, are rarely found in MCAS.

Gene Mutation Analysis

Although *KIT* D816V mutation testing by routine PCR analysis in the blood of SM patients is often positive (but far from perfect), this testing is virtually always negative in the far more prevalent setting of MCAS. Real-time quantitative PCR testing for *KIT* D816V is far more sensitive and has been shown in at least one study to be positive in 100% of SM patients [Kristensen et al., 2011]. There have been no reports that investigated this technique in the MCAS population.

Molderings [2015] have published two studies showing that on "full sequencing" of MC *KIT*, although one or more mutations are found in almost every MCAS patient, codon 816 mutations (whether D816V or any other) are virtually never found in MCAS. Clearly, codon 816 mutations have consequences that strongly influence the development of MCAD toward the mastocytosis phenotype. Without codon 816 mutations, it is far more likely MCAD will develop toward the MCAS phenotype. Although testing for this mutation on a bone marrow sample is more appropriate in SM, some patients do not wish to undergo the more invasive procedure.

Chromogranin A (CgA)

CgA is a heat-stable, 439-amino acid protein, and a member of the granin family of proteins. Granins are widespread in endocrine, neuroendocrine, peripheral, and central nervous tissues, where they are found in secretory granules. CgA is also secreted by MCs. It is known to be elevated in heart and renal failure, neuroendocrine cancer, and when proton pump inhibitors (PPIs) are being used. PPI therapy should be omitted for at least 5 days prior to measurement of baseline levels.

Plasma Heparin

Heparin may be the single best performing diagnostic marker for MC activation [Vysniauskaite et al., 2015]. However, the level of endogenous plasma heparin found normally and even in most cases of MCAS is below the lower limits of detection of most clinical assays for this metabolite (typically 0.10–0.30 anti-Factor Xa units/ml). Standard clinical assays are engineered to assist with monitoring of heparin therapy, which produces far higher levels of heparin than found normally or in MCAS. Thus, although an occasional MCAS patient may present a level detectable by one of the commonly used assays, typically a more sensitive assay is needed. As the half-life of heparin is approximately 1 min (similar to PGD_2), sample chilling is important.

TREATMENT OF MCAD

MCAD is presently incurable (except for the rare instance of a solid mastocytoma) and therapy, is therefore, symptomatic except when cytoreduction is additionally required in advanced mastocytosis. MCAD therapy should always include maneuvers aimed at controlling MC mediator production, release, and end-organ effects.

Many cases of childhood cutaneous mastocytosis (CM) seem to spontaneously regress in adolescence. However, it seems that MCAS emerges in at least some such patients within several years after regression of CM (personal observation, LBA). Only in the relatively rare forms of SM which either are aggressive malignancies themselves (e.g., aggressive SM or MC leukemia) or are associated with significant malignancies (e.g., SM with associated clonal hematologic non-MC-lineage disease, or SM-AHNMD in the WHO 2008 classification) are cytotoxic/chemotherapeutic and cellular therapies considered. Such therapies have been extensively discussed elsewhere in the literature and are beyond the scope of this paper.

In general, co-morbidity of EDS (any form) is not known to affect the approach to treatment of MCAD, except to note that chronic glucocorticoid therapy (a poor choice anyway in MCAD given the treatment's chronic toxicities, including in connective tissues) may be an even poorer choice in MCAD patients also featuring EDS. Desensitization therapy can be considered. It is important that patients identify potential triggers for their symptoms (dietary, chemicals, medications, allergens), and environmental modifications, to reduce exposures. Common MC triggers are given in Table V. MCAD patients have many physical sensitivities (e.g., heat, cold, ultraviolet radiation, exertion, etc.) and antigenic sensitivities (e.g.,pollen, mold, etc.). There is a core group of foods (tending to be patient-specific) that many patients find difficult to consume without developing adverse symptoms.

In general, co-morbidity of EDS (any form) is not known to affect the approach to treatment of MCAD, except to note that chronic glucocorticoid therapy (a poor choice anyway in MCAD given the treatment's chronic toxicities, including in connective tissues) may be an even poorer choice in MCAD patients also featuring EDS.

TABLE V. Triggers of Mast Cell Activation Adapted From the Following References [Cardet et al., 2013; Picard et al., 2013]

Alcohol
Heat
Drugs: antibiotics, NSAIDs (nonsteroidal anti-inflammatory drugs), Narcotics, Neuromuscular blocking agents
Radiocontrast media
Invasive procedures (e.g., general anaesthesia, biopsy, endoscopy)
Hymenoptera stings
Fever or infection
Exercise
Physical stimuli (e.g., pressure, friction)
Emotions/stress

Patients and clinicians should be alert to the propensity of MCAD patients to react to medication excipients. The emergence of adverse reaction within the first few doses of an ordinarily well tolerated medication should prompt (1) a review of the formulation's ingredient list to try to identify a particular offending excipient; and (2) identification of alternative formulations to be tried, containing as few of the excipients in the offending formulation as possible. Sometimes MCAD patients benefit from custom-compounded formulations of their medications.

Some MCAS patients are highly reactive to a range of foodstuffs. Elimination diets such as described for the eosinophilic esophagitis population are helpful in some patients but not others. As with medication trials, diet trials typically need to last only 1–2 months to determine if they are going to be significantly beneficial. The implementation of more than one change around the same time (e.g., a dietary change around the same time as a medication change) can be greatly confounding and should be avoided.

In spite of the substantial fatigue and malaise that many MCAD patients experience, they should be strongly encouraged to exercise regularly. This should only be to the usual individual limit of tolerance that each patient has likely learned from experience. This is because overexertion could trigger a flare of MC activation in some patients. Since both physical and psychological stress have long been known to activate MCs, interventions aimed at stress reduction (e.g., psychotherapy) can be helpful.

In spite of the substantial fatigue and malaise that many MCAD patients experience, they should be strongly encouraged to exercise regularly. This should only be to the usual individual limit of tolerance that each patient has likely learned from experience.

An effective "primary" physician—whether a primary care physician or specialist—is critically important for successful management of most complex diseases, including MCAD. The absence of a local "physician/partner" who can reliably help the patient access local health care resources as needed and remote resources could lead to the MCAD patient facing difficulty in gaining and then maintaining control over their disease.

Drug treatment needs to be tailored to the individual patient as their tolerance and the symptomatic benefit they receive tends to vary. Commonly used medications include H_1 and H_2 antihistamines, sodium cromoglicate, ketotifen, omlaizumab, and the leukotriene receptor blockers. Medications should usually be added one at a time, with an adequate time interval between the additions of successive drugs. Some patients need to begin medications at a lower dose and then gradually escalate to a standard dose. Patients need to be told that the time for noticing an initial symptomatic response may be a few weeks [Cardet et al., 2013; Akin, 2014; Zhang et al., 2016].

Many agents have been shown to significantly help various MCAD patients, but at present therapeutic response profiles appear highly individualized. There are no biomarkers predictive of response in general or of which symptoms will respond to any given agent in a given patient.

H_1 and H_2 Antihistamines

These medications block the H_1 and H_2 receptors present on many end organs and on MCs themselves, too. They have been in use for many years and most doctors are aware of their beneficial effects and potential adverse effects. Longer acting, generally non-sedating second generation H_1 antihistamines (e.g., cetirizine, fexofenadine, loratadine) have been used in preference to the older, sedating H_1 antihistamines. Most patients need a higher dose (between two to four times) the dose

used for treatment of mild hay fever symptoms. Many patients find a 2–3 times daily dosing to be more helpful than a once daily dosing regimen. The H_2 antihistamines (e.g., ranitidine, famotidine) are helpful for abdominal symptoms and sometimes benefit extra-gastrointestinal symptoms, too. Antihistamines need to be taken for an adequate length of time. Patients should be discouraged in making frequent changes to the doses they take.

Sodium Cromoglicate

Many patients add the MC-stabilising drug sodium cromoglicate to their H_1/H_2 antihistamines, with a view to getting additional symptomatic benefit. It is important that mediator measurements are done prior to this medication been added. Some patients experience a flare of symptoms during the initial few days of taking this drug. Oral, liquid, inhaled, and ophthalmic formulations are available. Although the drug is poorly absorbed and undergoes little systemic circulation, there is a systemic (IV) formulation in development.

Ketotifen

This has both MC-stabilising and antihistamine effects. A few patients are not able to tolerate this because of drowsiness. Tablet, liquid, and eye drop formulations are available. Oral ketotifen is an inexpensive drug, but its availability in the United States only in compounded form increases its expense there.

Leukotriene Receptor Blockers (e.g., Montelukast)

This is a widely used medication in asthma and spontaneous chronic urticaria patients. It is generally well tolerated. Administration twice daily may benefit MCAD patients more than once daily.

Steroids

The long-term use of oral steroids at any dose is discouraged due to well-known toxicities. In addition to its many adverse effects, its effect on bone density would not be helpful in patients with a disorder of connective tissue such as EDS. However, the use of a short course of steroids may be needed if there is acute onset of skin or airway reactivity. Low dose inhaled steroids may be needed if airway hyper-reactivity is present.

Self-Injectable Epinephrine Devices

All patients with systemic MC activation or susceptible to anaphylaxis should be prescribed two self-injectable epinephrine devices and taught how and when this should be used. A glucagon autoinjector may be needed instead if the patient requires beta adrenergic receptor blockade.

Other Medications

From the few reports available, non-steroidal immunosuppressants such as cyclophosphamide, cyclosporine, azathioprine, and monoclonal antibodies such as omalizumab [Zhang et al., 2016] and alemtuzumab are only occasionally helpful [Afrin, 2013]. Several patients find a range of other preparations (such as vitamin C, aspirin, flavone analogues, cannabinoids, etc.) to help their symptoms. Low-dose hydroxyurea helps some MCAD patients and is safely used for years to decades—indeed, life-long—in certain other diseases. A wide range of supportive medications are used by the MCAD population including decongestants, bronchodilators, antiemetics, proton pump inhibitors, anti-depressants of various classes (e.g. tricyclic agents), bowel motility agents, micronutrient supplements, pancreatic enzyme supplements, bone-strengthening agents such as bisphosphonates, tumor necrosis factor (TNF) alpha antagonists, etc.

Next to fatigue, pain is one of the most common symptoms of MCAD. NSAIDs help some patients but are triggers (potentially to anaphylactic extent) in others and must be initiated cautiously when no history of NSAID tolerance is known. Narcotics, too, commonly are triggers; fentanyl, tramadol, and hydromorphone tend to be better tolerated than other narcotics in MCAD patients. Sometimes other classes of MC-targeted agents typically without analgesic effect nevertheless prove analgesic (e.g., antihistamines may relieve chronic migraine headaches in some MCAS patients).

Given the rarity of SM, together with how recently MCAS has come to be recognized, there are no large controlled studies of any intervention for MCAD. Few clinical trials in SM have been performed, and there have been no clinical trials yet in MCAS. Patient and treating clinician alike must take a methodical approach in stepping through trials of the many therapies shown helpful in various MCAD patients, limiting to one change at a time in the regimen whenever possible. Most such treatment trials need last only 1–2 months, typically starting at low doses and escalating step-wise as tolerated to identify maximal effective dosing. Clearly significantly effective treatments are retained, while others not meeting that high bar are stopped lest unmanageable polypharmacy develop. In the absence of a more scientifically informed strategy at present, proceeding in order of treatment cost often is the most reasonable approach.

The most inexpensive and sustainable therapy for MCAD includes the histamine H_1 and H_2 receptor blockers. Benzodiazepines, NSAIDs including aspirin (in patients that can tolerate them), flavonoids (such as quercetin and luteolin), alpha lipoic acid, N-acetylcysteine, and Vitamin C are also inexpensive interventions. Leukotriene receptor blockers and synthesis inhibitors are somewhat more expensive, as are sodium cromoglicate, pentosan, and cannabinoids. Emergency and perioperative management of severe flares of mast cell disease has been amply discussed in the literature and is available publicly [Akin, 2014]. In general, histamine H_1 and H_2 receptor antagonists, glucocorticoids, and benzodiazepines form the core of the therapeutic attack at such a problem.

The clinical (and suspected underlying mutational) heterogeneity of MCAD ensure each therapy found helpful in certain patients will fail in others. Thus, failure of any given therapy (even antihistamines) should not be taken as a sign of

either misdiagnosis or "refractory" disease. With sufficient persistence at trying various interventions, most patients with non-malignant MCAD can eventually identify a regimen that helps them achieve the presently subjective goal of feeling significantly better than the pre-treatment baseline the majority of the time.

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ARTICLE

Psychiatric and Psychological Aspects in the Ehlers–Danlos Syndromes

ANTONIO BULBENA,* CAROLINA BAEZA-VELASCO, ANDREA BULBENA-CABRÉ, GUILLEM PAILHEZ, HUGO CRITCHLEY, PRADEEP CHOPRA, NURIA MALLORQUÍ-BAGUÉ, CHARISSA FRANK, AND STEPHEN PORGES

There is increasing amount of evidence pointing toward a high prevalence of psychiatric conditions among individuals with hypermobile type of Ehlers–Danlos syndrome (JHS/hEDS). A literature review confirms a strong association between anxiety disorders and JHSh/hEDS, and there is also limited but growing evidence that JHSh/hEDS is also associated with depression, eating, and neuro-developmental disorders as well as alcohol and tobacco misuse. The underlying mechanisms behind this association include genetic risks, autonomic nervous system dysfunction, increased exteroceptive and interoceptive mechanisms and decreased proprioception. Recent neuroimaging studies have also shown an increase response in emotion processing brain areas which could explain the high affective reactivity seen in JHS/hEDS. Management of these patients should include psychiatric and psychological approaches, not only to relieve the clinical conditions but also to improve abilities to cope through proper drug treatment, psychotherapy, and psychological rehabilitation adequately coupled with modern physiotherapy. A multidimensional approach to this "neuroconnective phenotype" should be implemented to ensure proper assessment and to guide for more specific treatments. Future lines of research should further explore the full dimension of the psychopathology associated with JHS/hEDS to define the nature of the relationship. © 2017 Wiley Periodicals, Inc.

KEY WORDS: joint hypermobility; anxiety; psychopathology; neuroconnective phenotype; hypermobile Ehlers–Danlos syndrome

Professor Antonio Bulbena, M.D., M.Sc, Ph.D., is the Chair of the Department of Psychiatry at the Autonoma University of Barcelona with clinical, academic, and administrative contributions particularly in the area of psychosomatic medicine and anxiety disorders, dementia, chocolate and carbohydrates, clinical measurement in psychiatry, phobias, seasonality, and biometeorology. Has recently developed the Neuroconnective Phenotype and has published numerous books, book chapters, and scientific articles in peer-reviewed journals.

Carolina Baeza-Velasco, Ph.D., is a clinical psychology at the Paris Descartes University, with important contributions in the area of psychological assessment and treatment of patients with comorbid anxiety disorders and joint hypermobility among other conditions. Has published several articles about the psychological factors of EDS and related conditions.

Andrea Bulbena-Cabre, M.D., M.Sc., is a Psychiatry Research Fellow at the Icahn School of Medicine at Mount Sinai/J. J. Peters Bronx VA Hospital. She has specialized in psychosomatic medicine and is currently studying the anxiety-joint hypermobility phenomena in bipolar and psychotic spectrum disorders. Other research interests include substance abuse, especially in synthetic cannabis and psychosis.

Guillem Pailhez, M.D., Ph.D., is an Assistant Professor at the Department of Psychiatry at the Autonoma University of Barcelona, has devoted his career in the study of the interactions between mind and body with special emphasis in anxiety disorders and the somatic conditions appearing in patients suffering from anxiety disorders.

Professor Hugo Critchley, M.D., is the chair of Psychiatry Department at the University of Sussex and has specialized in interoceptive awareness, dissociative symptoms such as derealization and depersonalization in psychosis, epilepsy, and anxiety. Has recently worked in autonomic phenotypes and has published several book chapters and scientific articles in peer-reviewed journals.

Pradeep Chopra, M.D., is a Clinical Assistant Professor of Medicine in the Warren Alpert Medical School of Brown University. His area of expertise includes pain management, low back pain, migraines, neuropathic pain, post-herpetic neuralgia, and myofascial pain. He also has an active interest in critical care medicine and has also published numerous book chapters and scientific articles in peer-reviewed journals.

Nuria Mallorqui-Bagué, Ph.D., is a Clinical Psychologist at the Department of Psychiatry Hospital Bellvitge IDIBELL in Barcelona, Spain. She is an expert in CBT and mindfulness based cognitive therapy for ADHD, hypochondriasis, and OCD spectrum disorder and has made important contributions in neuroimaging and affective reactivity in EDS.

Charissa Frank is the president of the Flemish Patient Organization of Hereditary Collagen Disorders in Belgium, not only representing Ehlers–Danlos syndrome, but other disorders such as Marfan and Loeys-Dietz as well and provides an important supportive network for patients suffering from those conditions. After a successful international business career, she now focusses her attention on managing and leading the patient organization in Belgium.

Stephen Porges, Ph.D., is a "Distinguished University Scientist" at the Kinsey Institute, Indiana University Bloomington and Professor of psychiatry at the University of North Carolina in Chapel Hill in North Carolina. He has made important contributions in the area of neural regulation and proposed the polyvagal theory providing insight into the mechanism mediating symptoms observed in the brain, emphasizing the importance of physiological state and behavioral regulation.

*Correspondence to: Prof. Antonio Bulbena, M.D., M.Sc, Ph.D, Neuropsychiatry and Drug Addiction Institute (INAD), Mar Health Park, Passeig Marítim 25-29, 08003 Barcelona, Spain. E-mail: abulbena@gmail.com

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INTRODUCTION

The relationship between the JHS/hEDS and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona [Bulbena et al., 1988]. It really was a clinical observation rather than a pathophysiological reasoning and the reiterated coincidence of the two conditions prompted us to study this association in more detail. Prior to this study, there were some scattered observations in the literature pointing to this new direction. In 1957, rheumatologist Rotés-Querol and Argany [1957] observed a remarkable degree of nervous tension suffered by patients with hypermobility. To a certain extent, there were some indirect references about the relationship between "visceroptosis" and anxiety/phobias in the classical psychosomatic literature [Flanders Dunbar, 1955].

Literature uses indistinctly Joint Laxity (the original name), Joint Hypermobility (the given name) and Elher–Danlos Syndrome-Hypermobile type (hEDS). Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease. JHS/hEDS is multisystem condition associated with musculoskeletal dysfunctions, possibly resulting from a glycoprotein deficiency and genetic alterations affecting the formation of collagen, which would explain tissue looseness, prolapsed organs, visceroptoses, pneumotorax, and vulnerability to trauma in these patients.

There are several sets of criteria that show minimal variations from the originally proposed by Rotés, although new self-assessment questionnaires have been added to the assessment methods of JHS [Hakim and Grahame, 2003; Bulbena et al., 2014]. A review paper of all the available criteria showed a high degree of agreement among all of them [Bulbena et al., 1992] but a more comprehensive set of 10 criteria obtained by cluster analysis was also proposed. However, the most often used are the "Beighton criteria" converted to a 9-point clinical scale by which subjects with a score ≥ 4 are considered as having JHS. In 2000, Grahame et al. [2000] developed the Brighton criteria to replace the Beighton criteria for the joint hypermobility syndrome (JHS). According to these criteria, the syndrome diagnosis is made taking into account the Beighton score and also some other clinical manifestations associated with hypermobility. The clinical assessment of the JHS/hEDS is not difficult but examiners should be trained in order to ensure the reliability of the exam.

Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease.

In this article, we review the psychopathology associated with JHS/hEDS, as well as the possible explanations for such association, the controversies, management, and future lines of research.

METHODS

The working group was composed of well-respected international clinician-researchers in the area of psychopathology with special interests in Ehlers–Danlos syndromes as part of the International Consortium on the Ehlers–Danlos Syndromes. Literature searches were conducted using the main electronic databases including the Cochrane Library, Informit, PsycINFO, PubMed, and Scopus. The main search terms used were "joint hypermobility syndrome," "joint hyperlaxity," "anxiety," and each separate psychiatric diagnostic category. Studies were included if they were published until September 2016, either in English or Spanish, if they reported any psychiatric conditions associated with joint hypermobility. The consensus was obtained after all authors completed their contributions and reviewed the manuscript on three separate occasions to ensure general agreement by all the authors. A total of 66 articles were included in the review.

LITERATURE REVIEW

Psychopathology

Herein, the syndromes joint hypermobility syndrome (JHS) and the hypermobile type of Ehlers–Danlos are considered as single entity (JHS/hEDS) for the purposes of this discussion defined by the previous diagnostic criteria, Brighton and Villefranche, respectively, except where the distinction is considered pertinent. See "The 2017 International Classification of the Ehlers-Danlos Syndromes" by Malfait et al., this issue.

Anxiety disorders

The relationship between JHS/hEDS and anxiety disorders has been widely explored during the past 30 years and current literature supports a solid association between these two variables [Bulbena et al., 2015]. Bulbena et al. [1993] conducted the first empirical case-control study where a sample of rheumatologic outpatients with JHS/hEDS were assessed and ~70% of hypermobile patients had some type of anxiety disorder, as compared to 22% in the controls [Bulbena et al., 1988]. A second study [Martin-Santos et al., 1998] evaluated outpatients with new

diagnoses of panic disorder and/or agoraphobia and found that JHS/hEDS was present in ~70% of patients with anxiety disorders compared to 10% in the controls. Garcia Campayo et al. [2010] also found a high prevalence of JHS/hEDS (61.8%) among subjects suffering from panic disorders compared with 10.9% among healthy controls.

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Other studies in non-clinical populations showed that individuals with JHS/hEDS scored significantly higher in state/trait and social anxiety scales [Bulbena et al., 2004; Baeza-Velasco et al., 2011a]. A recent meta-analysis [Smith et al., 2014] revealed that people with JHS/hEDS experience significantly greater perception and fear intensity and have higher probability of agoraphobia and panic disorders. These authors pointed out that current evidence is derived from Mediterranean adult populations and highlighted that more research should be done to study this association in other populations.

The only incidence study that evaluated the relationship between JHS/hEDS and anxiety disorders was done in the general population with a 15 years follow-up [Bulbena et al., 2011]. Cumulative incidence of panic/agoraphobia disorder was significantly higher in the JHS/hEDS group (41.4%) with a relative risk of 22.3 (95% confidence interval [CI] 4.6–108.7, $P < 0.0001$). Incidence of social and simple phobia was also significantly higher in the JHS/hEDS group and anxiolytic drug use was nearly fourfold higher among JHS/hEDS group.

Mood disorders

Some studies examined the relationship between mood disorders and JHS/hEDS but the research on this area is significantly smaller compared to anxiety disorders. Two studies [Bair et al., 2003; Gurer et al., 2010] explored depressive disorders in JHS/hEDS subjects but no differences were found when comorbid anxiety was controlled for. In contrast, Pasquini et al. [2014] observed a higher rate of depressive symptoms in JHS/hEDS patients compared to controls. Other studies also revealed higher depressive symptoms in individuals with joint hypermobility (JH) without a known diagnosis of JHS/hEDS [Baeza-Velasco et al., 2011b; Murray et al., 2013]. The meta-analysis of Smith et al. [2014] concluded that people with JHS/hEDS commonly exhibit more anxiety and depressive symptoms. Hershenfeld et al. [2016] found 42.5% prevalence of psychiatric disorders (especially depression and anxiety) in a retrospective sample of JHS/hEDS subjects. Therefore, some preliminary evidence suggests higher rates of depressive symptoms among JHS/hEDS, especially when comorbid anxiety is present.

Personality disorders

The evidence in the field of personality disorder is very scarce and to date there is only one study published about it. Pasquini et al. [2014] observed that subjects with JHS/hEDS have a 5.8 relative risk of having a personality disorder, particularly anxious obsessive-compulsive personality disorder. Although this is in line with prior research studies that support a strong relationship between anxiety and JHS/hEDS, these results should interpreted with caution due to the lack of large, well-designed studies in this field.

Addictions

Most of the research about addiction in JHS/hEDS focused on substances (alcohol and tobacco mainly) and there are no studies about other dimensions of addiction such as behavioral addiction. Carlsson and Rundgren [1980] found significantly higher joint hypermobility scores among female alcoholic patients but did not diagnose hEDS in these same patients so the relevance is unclear. Interestingly, they proposed a link to hormonal dysregulation in chronic alcoholics to the increase in joint laxity. Lumley et al. [1994] reported that in a sample of EDS patients (N = 48; including adults and children and multiple types), 12% were found to have a history of alcohol or illicit drug use although the type of illicit substance was not specified. Since chronic pain was one of the major psychological stressors in that study, it would be interesting to know if there was a misuse of pain medications as well. Regarding tobacco addiction, Carbone et al. [2000] studied the bone density in JHS/hEDS and found that the control group smoked more tobacco and were taller compared to the JHS/hEDS group, which is not consistent with other findings that showed that patients with hEDS have a tendency towards the ectomorphic (thin and tall) phenotype and also that people with hEDS smoke more cigarettes. A longitudinal study found smokers had significantly higher JH scores [Baeza-Velasco et al., 2015a] which was consistent with prior studies. Coping with distress is frequently cited as a motive for the higher tobacco and alcohol use as both substances are known to reduce anxiety.

Eating disorders

Most studies seem to point toward a relationship between ectomorph somatotype (linear, thin, and usually tall) and JHS/hEDS [Bulbena et al., 2015], with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia. Some case reports described a co-occurrence of EDS and eating disorders such as anorexia nervosa (AN) [Al-Mufty and Bevan, 1977; Miles et al., 2007], although the type of EDS was not specified in the reports. Goh et al. [2013] hypothesized that since there is symptom overlap seen AN and JH such as gastrointestinal symptoms, orthostatic intolerance, and fatigue associated syndromes, JH is a possible

indicator of a familial disorder of connective tissue elasticity which potentially plays a causal role in the development of the eating disorder.

Most studies seem to point toward a relationship between ectomorph somatotype (linear, thin, and usually tall) and JHS/hEDS, with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia.

Recently, Baeza-Velasco et al. [2015b] proposed a model of eating disorders in JHS/hEDS that provided some light about this phenomenon. The authors hypothesized that both articular and extra-articular features play a role in developing and maintain these eating patterns (Fig. 1).

Psychosis

There are some articles addressing the relationship between JHS/hEDS and schizophrenia. Bulbena et al. [2005] studied 124 patients with schizophrenia with and without comorbid JHS/hEDS and found JHS/hEDS was markedly more frequent within the schizophrenic-panic/phobic cluster (62.1%) [OR: 9.35, CI: 3.85–22.73, $P < 0.0001$]. Similarly, Bulbena et al. [2007] found that individuals with comorbid schizophrenia JHS/hEDS had higher rates of phobia/panic anxiety and more positive symptoms as well, and postulated that JH could be a clinical marker for this phenotype in schizophrenia. In a third case control study (schizophrenic patients vs. healthy controls) done by the same group evaluating the somatotype in schizophrenia, JHS/hEDS had comparable rates between the groups but there was a tendency toward positive association between anxiety-joint hypermobility and anxiety-ectomorphism [Pailhez et al., 2009]. A case report by Sienaert et al. [2003] described a case where a patient with comorbid schizoaffective disorder and classical EDS received electroconvulsive therapy, although it is unclear if the patient met diagnostic criteria for classical EDS.

Neurodevelopmental disorders

This is a burgeoning area of research that has developed over the recent years which seems to indicate a degree of co-occurrence of JHS/hEDS and some neuro-developmental disorders including attention-deficit/hyperactivity disorders (ADHD), developmental coordination disorder (DCD), and autism spectrum disorder (ASD).

In the area of ADHD, Eccles et al. [2014] found that adults with ADHD had higher rates of JH and symptoms of autonomic dysfunction compared to healthy controls. Another study, done by Harris [1998] that was published as a letter to the editor, found that the great majority (99%) of children with ADHD in his sample had JH, although this results should be interpreted with caution as it is based on clinical observations with no methodology reported. Similarly, Hollertz [2012]

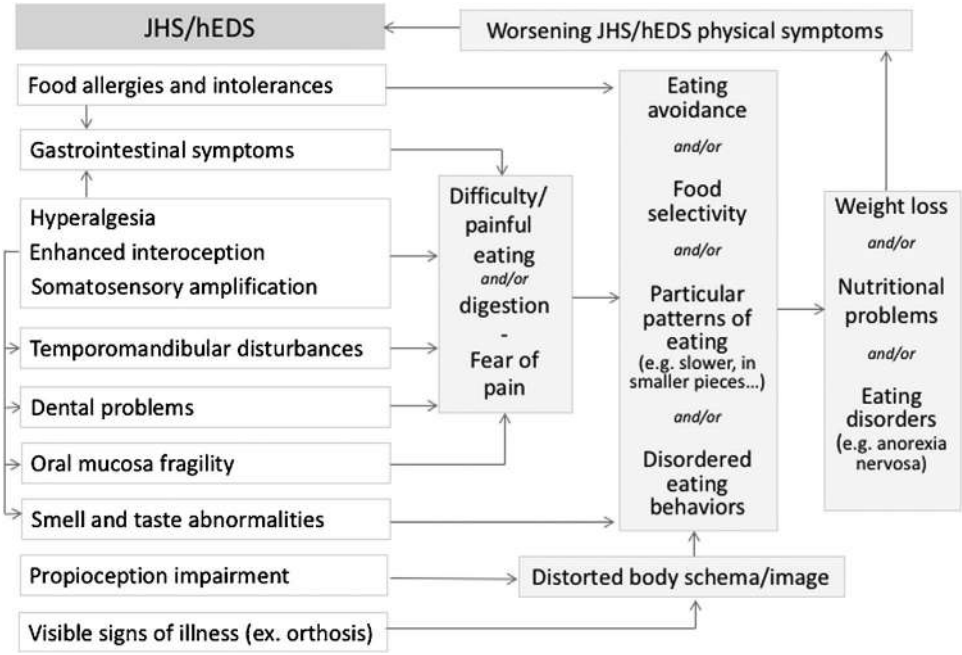

Figure 1. This figure reflects different extra-articular features such as gastrointestinal problems, temporomandibular disorders, and food intolerances that contribute to developing and maintaining disturbed eating behaviours and significant weight loss seen JHS/hEDS patients. See "Hypermobile Elhers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome type III and Ehlers-Danlos Syndrome Hypermobility Type): Clinical Description, and Natural History" by Tinkle et al., in this issue.

reported high co-occurrence of EDS and ADHD based on an observational study. Other authors such as Dogan et al. [2011] and Shiari et al. [2013] did matched case control studies and found that JH was significantly higher in the ADHD group as well as anxiety compared to healthy controls.

Concerning DCD, Kirby and Davies [2007] reported that children with DCD have more symptoms associated with JHS/hEDS including joint hypermobility, pain, and autonomic dysfunction compared to asymptomatic typically developing children. Jelsma et al. [2013] found a significantly higher mean score of JH in the DCD-group as compared to age-matched, typically developing children. Ghibellini et al. [2015] suggested that the relationship between JH and DCD may be due to poor proprioception in hypermobile children.

No articles are published regarding the relationship between ASD and JHS/hEDS but a few have looked at the prevalence of JH in ASD. Shetreat-Klein et al. [2014] did a matched case control study and found that ASD children have greater mobility of joints and more gait abnormalities compared to healthy controls. However, this study had a relatively small sample and excluded children with overt neurological problems, which may not be an accurate representation of the ASD population. Also, few case reports also highlighted the comorbidity ASD–JH [Tantam et al., 1990; Sieg, 1992; Takei et al., 2011], but further studies need to further explore the possible association of JHS/hEDS and ASD.

Psychiatric and Psychological Treatment for hEDS

Although no specific studies about psychopharmacologic treatment for hEDS have been published yet, there is significant evidence that JHS/hEDS patients take more anxiolytics than the counterpart. The overall use of psychotropic drugs was 41.4% in JHS/hEDS subjects compared to 13.9% in controls (OR: 4.38 CI 95% 1.8–10.9) [Bulbena et al., 2011].

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High levels of anxiety and depression are frequent in JHS/hEDS [Smith et al., 2014; Bulbena et al., 2015] and it has been shown that negative emotions may increase the experience of pain [Linton and Shaw, 2011]. Celletti et al. [2013] observed that patients with a JHS/hEDS had high scores of kinesiophobia. JHS/hEDS patients also have hyperalgesia [Castori, 2013], enhanced interoception [Mallorqui-Bague et al., 2014; Bulbena et al., 2015], and a tendency toward a somatosensory amplification [Baeza-Velasco et al., 2011b]. These aspects related to increased perception and/or reduced tolerance of pain [Feuerstein and Beattie, 1995; Pollatos et al., 2012], might influence the pain experience.

Dysfunctional coping strategies were also associated with JH [Baeza-Velasco et al., 2015a]. However, there are no studies exploring the coping strategies in JHS/hEDS and psychological aspects of pain perception merits more research to develop treatments programs. Some pilot cognitive behavioral therapy (CBT) experiences have been developed and suggested that CBT is valuable in the pain management of JHS/hEDS patients [Bathen et al., 2013].

Possible etiologies

Although it is possible that some psychiatric symptoms, risk or defensive behaviors, and personality traits can be a consequence of adaptation and difficulties in dealing with chronic illnesses, biological hypotheses have been considered to explain this association [Baeza-Velasco et al., 2015a]. The genetic link between anxiety and hyperlaxity should be further explored. In this sense, Gratacos et al. [2001] reported a cytogenetic anomaly (DUP-25) common to these two phenomena, although to date this study has not been replicated [Tabiner et al., 2003; Henrichsen et al., 2004]. Eccles et al. [2012] observed structural differences in areas of the brain implicated in emotion regulation in JHS.

Moreover, dysautonomia presents with symptoms that overlap with anxiety disorders. The perception/interpretation of physiological excitation play a role in anxiety disorders [Clark, 1986; Damasio, 1996; Craig, 2003] and JHS/hEDS patients have more intense interoception [Mallorqui-Bague et al., 2014] and are more likely to experience somatosensory amplification [Baeza-Velasco et al., 2011b]. Using multiple regression analysis, both JHS/hEDS and anxiety disorders were independently related to body perception and somatosensory amplification.

The Polyvagal Theory, proposed by Porges [2012], suggests that the evolution of the mammalian autonomic nervous system provides the neurophysiological substrates for adaptive behavioral strategies in both safe and dangerous environments. The theory provides a model to investigate the circuits that may be involved in dysautonomia and how atypical neural regulation of the autonomic nervous system that may function as a neural platform for several of the features observed in JHS/hEDS. Based on the Polyvagal theory [Porges and Furman, 2011], the Body Perception Questionnaire [Porges, 1993] has been applied to objectively quantify subjective reports of bodily reactions and states. The questionnaire identified atypical profiles in JHS/hEDS [Bulbena et al., 2014] and is being validated for clinical use.

In another study, trait anxiety scores did significantly correlate with both state anxiety and hypermobility

scores. Hypermobility scores were also associated with other key affective processing areas in the whole brain analysis [Mallorqui-Bague et al., 2014, 2015, 2016]. These findings increase our understanding of emotion processing in JHS/hEDS people and the mechanisms through which vulnerability to anxiety and somatic symptoms arises in this population.

Another physiological fact that may underlie this relationship is the strong value of the visceral afferent signals to the brain. This has been extensively studied by Critchley et al. [2013] who showed how different visceral inputs can influence thoughts, feelings, and behavior.

Considering the growing evidence of enhanced body awareness among JHS/hEDS along with the increased interception and somatosensory amplification, there might be an excess of alarming information which leads to psychological discomfort and psychiatric conditions.

Controversies

There are some controversies regarding the psychopathology associated with JHS/hEDS that should be addressed. First, patients with chronic pain and decreased functionality often display anxiety and depression [Bair et al., 2003], independently of the hEDS diagnosis. Another point is that hEDS is associated with multiple conditions like dysautonomia, which can cause a broad spectrum of physical complaints that can mimic anxiety-like symptoms. For instance, patients with dysautonomia experiencing intense heart rate fluctuations could be misdiagnosed with panic attacks. Another example could be the extreme fatigue caused by poor sleep architecture seen in these patients, that could be mistaken as depression. The key lies in being able to identify the cause of the anxiety and depression—if it is centrally mediated as a behavioral disorder or if it is the manifestation of associated conditions.

Another controversy in hEDS lies in diagnosing children or their parents with Conversion Disorder or Munchausen by Proxy respectively. These children often present with chronic pain, easy bruising, multiple joint dislocations, abdominal pain, dizziness, and fatigue that can be misdiagnosed as Conversion Disorder or Munchausen by Proxy. Barnum [2014] recently published a case of a child who had EDS but was misdiagnosed with conversion disorder and highlighted the stigmatizing consequences of making the wrong diagnosis in this population.

It is crucial that the physicians making the psychological assessment of hEDS patients are appropriately trained with the articular and extra-articular symptoms.

Management

The psychiatric and psychosocial issues have to be explored and properly evaluated in these patients. Pain, negative feelings, and poor emotion regulation are frequently associated with this condition. The consideration of all these aspects can help develop adapted protocols of evidence based psychiatric treatment and psychosocial interventions such as CBT (Table I).

Future lines of research

First, a comprehensive model of illness is needed; the single "medical specialty"

TABLE I. Roles of the Mental Health Professionals in the Management of JHS/hEDS

Objective/problem	Professional/intervention
Psychopathology (anxiety/mood disorders), Associated mental disorders (e.g., Addictions, sleep disorders, etc.)	Psychiatrist (diagnostic and treatment issues) Clinical/health psychologist (CBT) (psychotherapy with or without pharmacotherapy)
Management of chronic pain and negative emotions	Clinical/health psychologist (cognitive-behavioral approach: CBT). Psychiatrist Psychiatric nurse Occupational therapist
Improve knowledge about disease	Therapeutic patient education (pluridisciplinary)
Improve/develop competences to manage chronic disease (e.g., self-efficacy, coping strategies, etc.)	Clinical/health psychologist (CBT). Psychiatric nurse Occupational therapist
Neurodevelopmental disorders in childhood	Child/developmental psychiatrist Child/developmental psychologist (CBT)
Cognitive impairments (attention, memory, etc.)	Neuropsychologist
Support	Clinical psychologist (supportive therapy, different approaches) Psychiatric nurses, OT

This table defines the different r*oles of the mental health professionals in the management of* JHS/hEDS. The objective or problematic areas are introduced in the left column and the proposed intervention in the right column.

approach has to change for a multidisciplinary one. Models including both somatic and also psychiatric/psychological characteristics are required. A first approach was made through the ALPIM spectrum proposal, which is the acronym for anxiety and the domains of its most commonly occurring comorbidities: JHS/hEDS, pain disorders, immune disorders, and mood disorders [Coplan et al., 2015]. The authors of this study hypothesized that the ALPIM syndrome have predictable psychiatric and medical comorbidities and found that significant associations between joint hypermobility and bipolar III, headache with bipolar II, and bipolar II with chronic fatigue syndrome.

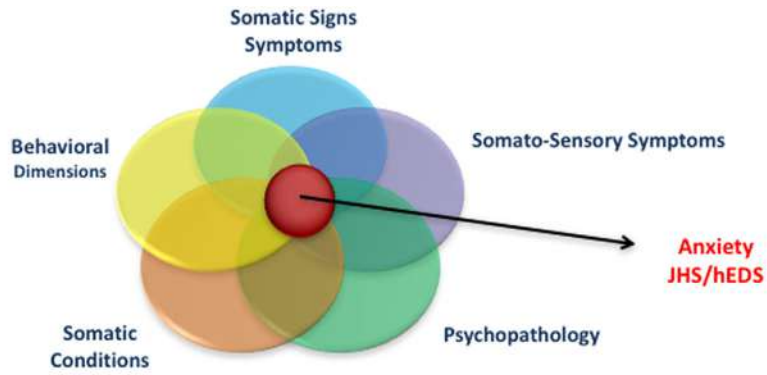
A more recent proposal is the "Neuroconnective phenotype" (Fig. 2), in which, around a common core Anxiety-hEDS, it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses.

Second, research on the underlying mechanisms is necessary, particularly to unmask the obvious but still occult genetic links. The DUP 25 in the chromosome 15 found among subjects suffering from both anxiety and JHS/hEDS [Gratacos et al., 2001], could not be replicated but it might be worthwhile to further investigate the possible genetic link with new genetic techniques such as whole genomic analyses. The psychophysiological circuits involved between the core features of JHS/hEDS (namely pain and body awareness) and their psychiatric correlates need to be uncovered. These neural correlates may also provide clues to unveil the emotional dysregulation found in JHS/hEDS.

Third, combined treatments tackling both somatic and psychological features should be developed and tested for better evidence based treatments. When talking about phenotypes in psychiatry, authors tend to include only behavioral and psychopathological traits, which again, represents a bias against somatic or body characteristics. Such restrictive view prevents the development of more comprehensive treatments. However, anxiety cases with JHS/hEDS tend to show more somatic features and therefore, it would be worthwhile exploring and developing more specific treatments for them.

Fourth, comprehensive models of care taking a multidisciplinary approach should be implemented. Several experiences, particularly in England, where there is the London Hypermobility Unit at the Hospital of St. John and St. Elizabeth, may be the prototypical model.

Fifth, considering the evidence of the increased risk associated with JHS/hEDS to develop anxiety disorders, preventive strategies particularly among children should be tested and implemented. This may help to guide for more specific treatments and to avoid undesirable outcomes in the adulthood. However, while the link between



- Behavioral Dimensions are patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis (i.e fight/flight, restriction (avoidance)/dependency
- Somatic symptoms include dysautonomia, asthenic somatotype, "blue " sclera*, "easy bruising", eczemas*, dyskinesia, dislocations, prolapses and hypertrophic scars*
- Somatic Conditions: irritable bowel syndrome, dysfunctional esophagus, chemical sensitivities, dizziness, fatigue, fibromyalgia, -dynias, hypothyroidism, asthma, migraines, temporomandibular dysfunction and food intolerances.
- Psychopathology: increased interoception, exteroception, decreased proprioception, anticipatory anxiety, high loss sensitivity, and high positive confrontation.
- Somato-sensory symptoms include increased olfactory sensitivity, eye-contact difficulty, selective photophobia, dyspnea, dysphagia, choking, palpitations, joint pain and enhances sensitivity to weather and chemicals

** These features have been previously described in the Neuroconnective phenotype*

Figure 2. The Neuroconnective phenotype. The Neuroconnective model is a proposal that may be useful for clinical practice disorders and of some psychosomatic conditions. It was described after the study and careful consideration of clinical and nonclinical data, pathophysiological mechanisms and the present anxiety nosological status. It is built around the core association of Anxiety-JHS/hEDS and it includes behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses dimensions. Each of the five dimensions includes features that may be present at different degrees and with individual variations and all dimensions incorporate patterns, clinical symptoms, signs and illnesses seen in these patients.

JHS/hEDS and anxiety disorders has been well established, there is limited evidence regarding the other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

CONCLUDING REMARKS

To conclude, patients with JHS/hEDS often suffer from anxiety disorder and the link between these two variables has been repeatedly found in the literature. There is limited literature about other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

In any case, a more careful psychiatric and psychological approach should be taken along other physical treatments to manage and treat this multisystem condition. A new model described as the Neuroconnective phenotype is proposed to evaluate the different dimensions of the pathology associated including behavioral patterns, clinical symptoms, and related illnesses

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