# Bleeding and bruising in patients with Ehlers–Danlos syndrome and other collagen vascular disorders

Anne De Paepe and Fransiska Malfait

*Centre for Medical Genetics, Ghent University Hospital, De Pintelaan 185, Ghent, Belgium*

## Summary

Easy bruising and bleeding are not only characteristic manifestations of clotting and platelet disorders, they are also prominent features in some heritable collagen disorders, such as the Ehlers–Danlos syndromes (EDS). The EDS comprise a heterogeneous group of connective tissue diseases sharing clinical manifestations in skin, ligaments and joints, blood vessels and internal organs. Most EDS subtypes are caused by mutations in genes encoding the fibrillar collagens type I, III and V, or in genes coding for enzymes involved in the post-translational modification of these collagens. Easy bruising is, to a variable degree, present in all subtypes of EDS, and is because of fragility of the capillaries and the perivascular connective tissues. Vascular fragility affecting medium-sized and large arteries and veins is typically observed in the vascular subtype of EDS, caused by a molecular defect in collagen type III, an important constituent of blood vessel walls and hollow organs. Extensive bruising, spontaneous arterial rupture, leading to severe internal bleeding or premature death, and rupture of hollow organs, such as the intestine or the gravid uterus are predominant features of this subtype. Haematological studies including evaluation of clotting factors, platelet aggregation and bleeding time are usually normal in patients with EDS, except for the Hess test (Rumple–Leede test), which may be abnormal, indicating capillary fragility. In some forms of EDS confirmation of the clinical diagnosis and subtype is possible with biochemical and molecular studies.

**Keywords:** arterial rupture, bleeding, collagen vascular disorders, easy bruising, Ehlers–Danlos syndrome.

Excessive bruising and an increased bleeding diathesis are important features of many disorders of coagulation and/or platelets, such as haemophilia A and B, and von Willebrand disease, and the many disorders of platelet number and function. They can, however, be prominently present in another group of diseases, the heritable collagen disorders, a heterogeneous group of genetic diseases that are caused by mutations in structural collagen genes or in genes coding for enzymes involved in their post-translational modification. Although individually rare disorders, together they represent an important category among the heritable disorders of connective tissue. Whereas the prototype collagen type I disorder Osteogenesis Imperfecta (OI) or 'brittle bone disease' mainly affects the hard connective tissues, the Ehlers–Danlos syndromes (EDS) typically affect soft connective tissues. The EDS comprise a clinically and genetically heterogeneous group of conditions of which the main features are skin hyperextensibility, joint hypermobility, easy bruising, and generalized connective tissue fragility (Steinman *et al*, 2002). Prominent bruising and bleeding is seen in all subtypes of EDS (Table I). There is, however, a wide range of severity in bleeding diathesis, comprising mild to severe bruising, subcutaneous haematomas, bleeding of the gums, and life-threatening internal bleeding because of arterial rupture. 'Easy bruising', which means the tendency to develop ecchymoses either spontaneously or upon minimal trauma, is seen in all subtypes of EDS, and can be explained by capillary fragility. Fragility of medium-sized and large arteries and veins is seen typically in the vascular subtype of EDS (EDS type IV) and occasionally in the rare kyphoscoliotic subtype (EDS type VI).

In children with EDS, excessive bruising is often the presenting complaint to the paediatrician. If pronounced, it can cause confusion with a haematological problem, a malignancy or even suspicion of child abuse. Careful evaluation of the medical and family history and rigorous clinical examination with special attention to subtle skin features that are characteristic for EDS are necessary to distinguish between a heritable connective tissue disorder and other causes of bruising. Laboratory investigation of clotting factors, platelet aggregation and bleeding time is usually normal in patients with a connective tissue disorder.

This review will focus on bleeding and bruising problems that are seen in different forms of EDS, particularly in the vascular EDS subtype. The clinical manifestations, the underlying biochemical and molecular defects, the differential diagnosis and management will be discussed. In order to understand the underlying mechanism of the gene defects that eventually lead to the different manifestations of EDS, a short

Correspondence: Dr A De Paepe, Centre for Medical Genetics, University Hospital, 0K5, De Pintelaan 185, B-9000 Ghent, Belgium. E-mail: anne.depaepe@ugent.be

Table I. Classification of the Ehlers–Danlos syndrome according to the Villefranche nosology (Beighton *et al*, 1998).

| Type | Inheritance pattern | Protein | Gene | Major (M) and minor (m) diagnostic criteria (Beighton *et al*, 1998) |
|------|---------------------|---------|------|----------------------------------------------------------------------|
| Classic type (EDS type I/II) | AD | Type V procollagen | *COL5A1/COL5A2* | M: skin hyperextensibility, widened atrophic scarring, joint hypermobility. m: easy bruising, smooth and velvety skin, molluscoid pseudotumors, subcutaneous spheroids, muscular hypotonia, complications of joint hypermobility, surgical complications, positive family history |
| Hypermobility type (EDS type III) | AD | Not known | Not known | M: generalized joint hypermobility, mild skin involvement. m: recurring joint dislocations, chronic joint pain, positive family history |
| Vascular type (EDS type IV) | AD | Type III procollagen | *COL3A1* | M: excessive bruising, thin and translucent skin, arterial/intestinal/uterine fragility or rupture, characteristic facial appearance. m: acrogeria, early-onset varicose veins, hypermobility of small joints, tendon and muscle rupture, arteriovenous or carotid-cavernous sinus fistula, pneumo(hemo)thorax, positive family history, sudden death in close relative(s) |
| Kyphoscoliotic type (EDS type VI) | AR | Lysyl hydroxylase1 | *PLOD1* | M: severe muscular hypotonia at birth, generalized joint laxity, kyphoscoliosis at birth, scleral fragility and rupture of the globe. m: tissue fragility, easy bruising, arterial rupture, marfanoid habitus, microcornea, osteopenia, family history |
| Arthrochalasis type (EDS type VIIA /VIIB) | AD | Type I procollagen | *COL1A1/COL1A2* Partial loss or complete skipping of exon 6 | M: severe generalized joint hypermobility with recurrent subluxations, congenital bilateral hip dislocation. m: skin hyperextensibility, tissue fragility, easy bruising, muscular hypotonia, kyphoscoliois, mild osteopenia, occasionally fractures |
| Dermatosparaxis type (EDS type VIIC) | AR | Procollagen-N-proteinase | *ADAMTS*-2 gene | M: severe skin fragility, sagging, redundant skin, excessive bruising. m: soft, doughy skin texture, premature rupture of membranes, large herniae |

AD, autosomal dominant; AR, autosomal recessive.

introduction on the classification and the biosynthesis of the collagens is provided.

## The collagens: classification, tissue distribution, function and biosynthesis

The collagens represent a large family of structurally related extracellular matrix (ECM) proteins. Amongst other functions, they are essential for development and organogenesis, cell attachment, platelet aggregation, and for providing tensile strength to the connective tissues in bone, skin, ligaments and tendon. The collagen proteins are homo- or heterotrimeric molecules that share unique triple-helical domains. Collagen molecules containing three identical polypeptide or α-chains are called homotrimers, whereas those composed of two or three different α-chains, are heterotrimers. The collagens are distinguished on the basis of their α-chain composition, molecular structure, supramolecular organization and tissue distribution. By convention the type of collagen is designated with a Roman number and the constituent α-chain with an Arabic number. The fibril-forming or fibrillar collagens represent the most widespread and abundant class of collagens (Table II). They include the collagen types I, II, III, V and XI. They are found in tissues as long, highly ordered fibrils with a characteristic banding pattern. Type I collagen is the major collagen type in the body and has a widespread tissue distribution. It is a heterotrimer of two α1-chains and one α2-chain, encoded by the *COL1A1* (chromosome 17) and the

**Table II.** Fibrillar collagen types, constituent chains, chromosomal localization of the genes, molecular structure and tissue distribution (Chu & Prockop, 2002; Kielty & Grant, 2002).

| Collagen type | chains | Gene locus | Chromosome location | Molecular structure | Tissue distribution |
|---|---|---|---|---|---|
| I | α1(I) | COL1A1 | 17q21·3-q22 | $[\alpha1(I)]2\alpha2(I)$ | Skin, bone tendon, ligament, dentine, cornea |
| | α2(I) | COL1A2 | 7q21·3-q22 | $[\alpha1(I)]_3$ | |
| II | α1(II) | COL2A1 | 12q14·3 | $[\alpha1(II)]_3$ | Hyaline cartilage, vitreous humour |
| III | α1(III) | COL3A1 | 2q32·2 | $[\alpha1(III)]_3$ | Skin, blood vessels, hollow organs |
| V | α1(V) | COL5A1 | 9q34·2-q34·3 | $[\alpha1(V)]_2\alpha2(V)$ | Skin, bone, fetal membranes, placenta |
| | α2(V) | COL5A2 | 2q24·3–31 | $[\alpha1(V)]_3$ | |
| | α3(V) | COL5A3 | 19p13·2 | $\alpha1(V)\alpha2(V)\alpha3(V)$ | |
| XI | α1(XI) | COL11A1 | 1p21 | $\alpha1(XI)\alpha2(XI)\alpha3(XI)$ where $\alpha3(XI) = \alpha1(II)$ | Hyaline cartilage, vitreous humour |
| | α2(XI) | COL11A2 | 6p21·3 | | |
| | α1(II) | COL2A1 | 12q14·3 | | |

*COL1A2* gene (chromosome 7) respectively. Type II and type XI collagen are predominantly found in cartilage. Type III collagen is a homotrimer consisting of three identical α1-chains, encoded by the *COL3A1* gene on chromosome 2 (Burgeson, 1988). It is an essential component of many connective tissues and is found in stretchable, tissues such as the blood vessel walls, the gastro-intestinal tractus, the uterus and the skin. Type V collagen is co-expressed with type I collagen in many connective tissues and is thought to play an important role in the fibrillogenesis of this collagen type (Birk, 2001).

Each fibrillar collagen has a central uninterrupted triple-helical domain with short non-helical domains at the carboxy- and the amino-terminal end. The presence of glycine, the smallest aminoacid, in every third position of each chain is a prerequisite for the formation of a stable collagen helix.

The biosynthesis of fibrillar collagens in the fibroblast is a complex process and starts with the synthesis of soluble precursor molecules, procollagens. The pro-α-chains contain globular amino- and carboxy-terminal propeptide extensions, called the N- and the C-propeptide. The intracellular association of three pro-α-chains occurs through interaction and disulphide bonding at the C-propeptide. In this way, correct alignment of the growing polypeptide chain is obtained as required for the formation and propagation of the triple-helix from the C- to the N-terminal end of the molecule. During helix propagation, the pro-α-chains undergo extensive enzymatic modifications (i.e. hydroxylation of prolyl and lysyl residues), which cease when the helix is formed. Completed triple-helical procollagen molecules are secreted into the extracellular environment where they are converted to collagen by removal of the N- and the C-propeptide by specific enzymes. Individual collagen molecules spontaneously assemble in a non-enzymatic process to form fibrils and fibres, which are stabilized by covalent cross-linking.

When the integrity of the vascular system is disturbed, platelets become exposed to components of the ECM present in the blood vessel wall and beyond. Platelets can interact directly or indirectly with several ECM proteins, of which type I and III collagen are of principal importance. Platelet interaction with collagens is a complex phenomenon. The platelets adhere to subendothelial collagens exposed at sites of blood vessel injury via the glycoprotein (GP) Ib-V-IX receptor complex, GPVI and the integrin α2β1. Initial entrapment of platelets on subenthothelial collagens requires the plasma protein von Willebrand factor (VWF), which binds simultaneously to collagen and GP Ib-V-IX under shear stress conditions. This unstable interaction facilitates transient tethering and rolling of the platelets. These interactions are followed by a more stable binding of collagen to platelet collagen receptors, principally integrin α2β1 and GPVI. These interactions stimulate platelet signalling, which results in shape change and spreading, and the secretion of multiple haemostatic factors (Gibbins, 2004).

## The Ehlers–Danlos syndrome

The EDS comprise a clinically and genetically heterogeneous group of connective tissue diseases of which the principle clinical features are skin hyperextensibility, delayed wound healing with atrophic scarring, joint hypermobility, easy bruising and generalized connective tissue fragility (Steinman *et al*, 2002). These clinical manifestations are present, to varying degrees, in each subtype of the condition.

Skin hyperextensibility should be tested at a neutral site, meaning a site not subjected to mechanical forces or scarring, such as the volar surface of the forearm. It is measured by pulling up the skin until resistance is felt. The skin is hyperelastic, which means that it extends easily and snaps back after release. Widened atrophic scarring is a manifestation of tissue fragility and occurs mainly over knees, elbows, shins, forehead, and chin. It is characterized by splitting of the skin following relatively mild trauma, and formation of 'cigarette–paper–scars', which are wide and thin scars. In areas of repetitive trauma, haemosiderin deposition may lead to dark and anaesthetic discoloration of the skin.

Joint hypermobility is often general, affecting both large and small joints and usually comes to attention when a child starts to walk. Joint hypermobility can be assessed using the Beighton scale (Beighton *et al*, 1973), which is the most widely accepted grading system for the objective semiquantification of joint hypermobility. The manoeuvres used in this scoring system are listed below:

1 passive dorsiflexion of the little fingers beyond 90° (one point for each hand);
2 passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb) (Fig 1);
3 hyperextension of the elbows beyond 10° (one point for each elbow);
4 hyperextension of the knees beyond 10° (one point for each knee);
5 forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (one point).

A score of 5/9 or greater defines joint hypermobility.

This joint hypermobility may lead to occasional or habitual dislocations of joints, such as the shoulder, the hip, the patella, and chronic musculoskeletal pain. This may lead to premature degenerative joint disease.

The latest classification of EDS, the Villefranche Nosology, recognizes six subtypes, based on the severity of the clinical symptoms, the pattern of inheritance and the underlying biochemical and molecular defect (Beighton *et al*, 1998). Several EDS subtypes are caused by mutations in the structural genes for type I (arthrochalasis type), type III (vascular type) or type V collagen (classic type) or in genes involved in the processing of type I collagen (kyphoscoliosis and dermatosparaxis type) (Table I).

The classic, hypermobile and vascular type of EDS are the most common, while the kyphoscoliosis, arthrochalasis and dermatosparaxis types represent very rare conditions. The Villefranche classification is important in helping the clinician to establish the accurate subtype of EDS, which is very important in terms of management and counselling to the patient and his or her family. For example, the severe vascular fragility in the vascular subtype of EDS may lead to premature death, and certain prophylactic measures should be advised.

Besides the recognized subtypes however, there are many unclassified EDS variants, in which the underlying molecular defect is not known.

## Ehlers–Danlos syndrome, vascular type

The vascular type of EDS, previously called EDS type IV or the arterial-ecchymotic type of Sack–Barabas (Sack, 1936; Barabas, 1967), is an autosomal dominant disorder that is caused by structural defects in the pro$\alpha$1(III) chain of type III collagen, encoded by the *COL3A1* gene. Of all EDS subtypes, it has the worst prognosis because of the risk of potentially fatal vascular and intestinal complications. Unlike in other types of EDS, the skin is not hyperelastic, but rather thin and translucent, showing a visible venous pattern over the chest, abdomen and extremities (Beighton, 1993; Steinman *et al*, 2002). Excessive bruising is the most common sign and is often the first presenting complaint. Bleeding from the gums following brushing of the teeth, or profuse bleeding after tooth extraction are also frequent signs. The bleeding tendency may lead to extensive haematological evaluation, with the usual result that no abnormality is identified. The Rumpel–Leede (or Hess) test may be positive, indicating capillary fragility (Barabas & Barabas, 1967; Anstey *et al*, 1991). Other early manifestations include obstetric problems, such as premature rupture of the membranes, congenital club foot or congenital hip dislocation. In childhood, inguinal hernia, pneumothorax, and recurrent joint dislocation or subluxation are common (Pepin *et al*, 1992). Patients with the vascular type of EDS often display a characteristic facial appearance, including prominent eyes (due to lack of subcutaneous adipose tissue around the eyes), a thin, pinched nose and small lips, hollow cheeks and lobeless ears (Fig 2). Hypermobility is usually limited to the small joints of the hands. Excessive wrinkling and thinness of the skin over hands and feet may produce an old-looking appearance, referred to as 'acrogeria' (Fig 3). Unusual cutaneous manifestations include elastosis perforans serpiginosa, keloid formation and Raynaud phenomenon.

The generalized vascular fragility largely dominates the clinical picture. Apart from excessive bruising and bleeding, it leads to precocious and severe varicosities and arterial rupture, which may potentially cause sudden death, usually in the third or the fourth decade of life. The vascular fragility affects large
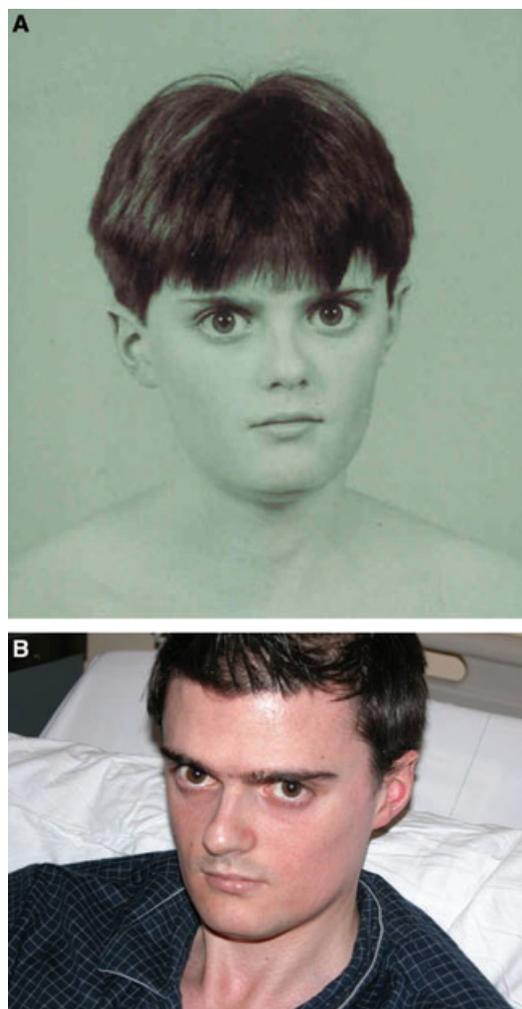


**Fig 1.** Joint hypermobility of the small joints; 'thumb-abduction test' or passive apposition of the thumbs to the flexor aspects of the forearm.

as well as small arteries, veins and capillaries, and bleeding may occur at every possible site in the body. It can present as acute abdominal pain, cerebral stroke, haemoptysis, haematemesis, renal colic and haematuria, retroperitoneal bleeding, muscular swelling, shock and sudden death. The most common locations of arterial bleeding are in the abdominal cavity and involve medium-sized arteries, such as the renal or splenic arteries, rather than the aorta itself. Acute myocardial infarction is a rare complication and is due to coronary dissection or rupture. In some individuals, there is evidence of aneurismal dilatation and dissection, or of arterio-venous fistulae, but in other patients ruptures occur at locations that appear completely normal by angiography (Steinman et al, 2002). Besides the vascular ruptures, dangerous internal complications, such as spontaneous rupture of the bowel (usually the colon, sometimes the intestine), the gravid uterus, and hemorrhagic pneumothorax may occur (Clark et al, 1980; Pope & Nicholls, 1983; Rudd et al, 1983; Peaceman & Cruikshank, 1987; Pepin et al, 2000). Although uncommon, EDS type IV is a cause of stroke in young adults. The mean age of intracranial aneurysmal rupture, spontaneous carotid-cavernous sinus fistula and cervical artery aneurysm is 28 years (North et al, 1995).

Obstetrical complications are not so rare and include vascular, intestinal or uterine rupture, vaginal lacerations, prolapse of uterus and bladder, and premature delivery because of cervical insufficiency or fragility of the membranes. Patients with a vascular EDS who are pregnant should be followed in a high-risk obstetrical programme.

The clinical appearance of patients with vascular EDS may, however, deviate from the typical picture, and especially the facial and cutaneous features, such as the acrogeria, may be very subtle or even absent. In the absence of a positive family history or a major vascular or intestinal complication, clinical diagnosis is difficult, especially in children.

## Biochemical and molecular defects in vascular EDS

The genetic defect underlying vascular EDS is a deficiency of type III collagen. The diagnosis of vascular EDS is based on compatible clinical findings and confirmed by biochemical testing. It is important to note that in virtually all clinically apparent cases of vascular EDS, the biochemical and molecular abnormality of type III collagen can be identified. Biochemical testing includes analysis by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) of radioactively labelled collagens extracted from skin fibroblast cultures. This analysis probably identifies more than 95% of individuals harbouring a defect of type III collagen. It enables the detection of quantitative (reduced amounts of collagen type III) or qualitative (structurally abnormal type III collagen with altered electrophoretic mobility) defects of type III collagen. For example, substitution of a glycine residue by a bulkier amino acid destabilizes and delays collagen triple-helix formation,



Fig 2. Characteristic appearance in a patient with vascular EDS at 12 (A) and at 22 (B) years. Note the large, prominent eyes, the fine nose, the small lips and the lobeless ears.



Fig 3. Typical acrogeric aspect of the hand of a 22-year old patient with vascular Ehlers–Danlos syndrome. The skin is thin and transparent with visible veins, an aged appearance of the skin and ecchymoses.

causing excessive post-translational modification and hence an altered electrophoretic pattern (De Paepe, 1994). Molecular genetic testing to identify mutations in the *COL3A1* gene is available to patients with a biochemically confirmed diagnosis of vascular EDS. To date, more than 250 *COL3A1* mutations have been identified (Dalgleish, 1998). Most mutations are point mutations leading to substitutions for glycine in the triple helical region of the collagen molecule, but other types of mutations have also been identified, such as splice site mutations, partial gene deletions, and, rarely mutations resulting in *COL3A1* haplo-insufficiency (Schwarze *et al*, 2001; Steinman *et al*, 2002). Vascular EDS is an autosomal dominant disorder, but parental somatic mosaicism for *COL3A1* mutations has been documented (Kontusaari *et al*, 1992; Richards *et al*, 1992; Milewicz *et al*, 1993; Palmeri *et al*, 2003). When the mutation is identified, prenatal and preimplantation diagnosis can be performed by direct demonstration of the mutation in the embryonic tissues.

Genotype–phenotype correlations have been extensively investigated in vascular EDS. Missense mutations located at the extreme carboxyl-terminal end of the molecule usually cause the so-called severe 'acrogeric' form of EDS, associated with severe vascular problems and early death. However, this relationship is not absolute and severe clinical phenotypes have been reported with more amino-terminal-located mutations as well. Interestingly, *COL3A1* haplo-insufficiency mutations lead to equally severe phenotypes as 'structural' *COL3A1* mutations, suggesting that depletion of normal type III collagen is the pivotal mechanism leading to vascular fragility.

## Bleeding and bruising in other subtypes of EDS and other diseases of connective tissue

Easy bruising is, to a variable degree, a common complaint in all subtypes of EDS (Table I).

In the *classic subtype* (EDS type I/II), bruising can vary from mild to moderate and it is accompanied by a very soft, fragile and hyperextensible skin, that splits easily after minor trauma. Wound healing is delayed and scars have a papyraceous or 'cigarette–paper–like' aspect. Due to repeated trauma, the scars, which are mainly present over pressure points such as elbows, knees, chins, and forehead, become hyperpigmented and wrinkled. Other features of classic EDS include generalized joint hypermobility with joints dislocations, molluscoid pseudotumors and subcutaneous spheroids, muscular hypotonia and other manifestations of tissue fragility, such as repetitive hernia. Mitral valve prolapse and, less frequently, tricuspid valve prolapse may occur and should be diagnosed by echocardiography, computed tomography or magnetic resonance imaging. In patients with severe classic EDS, prematurity due to premature rupture of the membranes is more frequent than in the general population. It is also in this severe group that aortic and bowel rupture may exceptionally occur. Mutations in the genes encoding type V collagen, *COL5A1* and *COL5A2*, are responsible for approximately 50% of patients with classic EDS (Malfait *et al*, 2004a). In rare instances, a *COL1A1* mutation causing the substitution of a non-glycine residue (R134C) in the proα1(I) collagen chain of type I collagen has been identified (Nuytinck *et al*, 2000). In a substantial proportion of patients with classic EDS, the molecular defect has not been identified yet. Recently, several interesting candidate genes have been identified by transgenic mouse studies, such as some genes encoding a group of ECM proteins, called 'small leucine-rich proteoglycans' (SLRP's) (Ameye & Young, 2002).

Easy bruising is also a prominent feature in a recently described autosomal recessive condition that shows great similarity to classic EDS, including hyperextensible skin and hypermobile joints, in the absence of delayed wound healing or atrophic scarring. This condition is caused by mutations in the gene encoding a non-collagenous protein, tenascin X (Schalkwijk *et al*, 2001).

The *kyphoscoliotic form* of EDS (EDS type VI) can be recognized by severe muscle hypotonia and joint hypermobility at birth. Usually, severe progressive kyphoscoliosis is observed in this condition. Ocular fragility may lead to retinal detachment, bleeding and rupture of the ocular globe, and microcornea is common. Easy bruising, which may be severe, and atrophic haemosiderotic scarring are part of the clinical picture. Patients often have a marfanoid habitus and there is a risk for arterial rupture (Wenstrup *et al*, 1989). Both aortic dilatation and dissection, and rupture of medium-sized arteries may occur. This is a rare autosomal recessive condition caused by deficient activity of the enzyme procollagen-lysine 2-oxoglutarate 5 dioxygenase-1 (lysyl hydroxylase-1, PLOD), a collagen-modifying enzyme.

In the *arthrochalasia type* of EDS (EDS type VIIA/B), severe generalized joint hypermobility with repetitive dislocations of different joints, and congenital bilateral hip dislocation are prominent features. The skin is moderately hyperextensible and atrophic and haemosiderotic scars, especially in adulthood, as well as mild to moderate bruising are seen (Giunta *et al*, 1999). This phenotype is strikingly different from the *dermatosparaxis type* of EDS (EDS type VIIC), where the predominant clinical features during childhood are severe bruising (Fig 4) and extreme fragility and laxity of the skin. Other characteristic features of the latter type include premature rupture of the membranes, large fontanels, umbilical hernia, short stature and characteristic facies with epicanthic folds, downslanting palpebral fissures, puffy eyelids, blue sclerae, and micrognathia (Nusgens *et al*, 1992; Petty *et al*, 1993; Fujimoto *et al*, 1997). Fragility of internal tissues is an important feature during childhood, as is illustrated by spontaneous bladder rupture at the age of 5 years in two children with the dermatosparaxis type of EDS (Malfait *et al*, 2004b). Both arthrochalasia and dermatosparaxis type are caused by a deficient processing of the N-propeptide of type I collagen. In the arthrochalasia type, this is due to a mutation in the *COL1A1* or the *COL1A2* gene, which results in the loss of the cleavage site for the procollagen-N-proteinase (Giunta

defect. This defect was correctable *in vitro* by the addition of normal human fibronectin. On the other hand, the patient's plasma failed to support the aggregation of gel-filtered platelets from controls in response to collagen. Since the measured levels of immunoreactive fibronectin were normal and immunohistochemical studies have shown fibronectin to be present in the platelets α-granules, the authors assumed a minor structural abnormality of the fibronectin molecule to be present. Of note, altered production, assembly and distribution of fibronectin have been observed in cultured fibroblasts from patients with several types of EDS (Cutolo *et al*, 1986; Barlati *et al*, 1991; Colombi *et al*, 1991). On the other hand, decreased levels of fibronectin with a normal electrophoretic mobility in eight members of a three-generation family, did not result in abnormalities of platelet aggregation or clinical signs of EDS (Shirakami *et al*, 1986).

Furthermore, many reports exist in which different forms of EDS have been associated with more or less well-characterized platelet or coagulation dysfunctions, including platelet aggregation dysfunction and prolonged bleeding time (Kashiwagi *et al*, 1965; Estes, 1968; Onel *et al*, 1973; Uden, 1982; Chouza *et al*, 1984; Anstey *et al*, 1991; Cunniff & Williamson-Kruse, 1995), platelet delta-storage pool disease (Espanol *et al*, 1998), deficiency of factor VIII (Clough *et al*, 1979; Bertin *et al*, 1989), factor IX (Gamba *et al*, 1986), factor XI (Anstey *et al*, 1991), factor XII (Fantl *et al*, 1961) and factor XIII (Anstey *et al*, 1991) and platelet sensitivity to aspirin (Grenko *et al*, 1993). These are, however, sporadic findings and are likely to be chance associations where the platelet or coagulation dysfunctions may have added to the bleeding tendency of an underlying EDS, thus prompting clinical investigation.

Easy bruising can occasionally be seen in other heritable collagen disorders, such as OI. This condition is characterized by a variable degree of bone fragility, with multiple fractures and sometimes bone deformities, short stature, blue sclerae and hearing impairment. It is caused by mutations in the *COL1A1* and *COL1A2* gene, encoding type I collagen. Rarely, individuals with OI may have vascular dissection (Mayer *et al*, 1996).

In patients presenting with an aortic dilatation or dissection, Marfan syndrome should be considered. This is an autosomal dominant connective tissue disorder, caused by mutations in fbrillin-1. The vascular type of EDS and Marfan syndrome can usually be distinguished easily on a clinical basis. The diagnosis of Marfan syndrome requires the presence of a combination of clinical manifestations in different organ systems, including the skeletal system, the eyes and the cardiovascular system. Patients with Marfan syndrome usually have a typical 'marfanoid habitus' with a long and slender build, mild joint hypermobility, scoliosis and/or pectus deformities and arachnodactyly. The major ocular abnormality is a bilateral lens dislocation. Most importantly, Marfan patients are at risk for developing mitral valve prolapse and/or dilatation and dissection of the aorta. There is no increased vascular fragility of capillaries or of small and middle-size arteries or veins,



**Fig 4.** Extensive bruising in a patient with the dermatosparaxis subtype of EDS.

*et al*, 1999), whereas in the dermatosparaxis type, this is caused by a defect of the enzyme itself (Colige *et al*, 1999).

*EDS type VIII* or *periodontic type* of EDS is a distinct entity that is characterized by severe early-onset periodontal disease in conjunction with the features of EDS, such as increased tendency to bruising on mild trauma, variable degree of skin hyperextensibility and fragility and mild to moderate joint hypermobility, especially of the digits. Discrete, chronically inflamed pretibial plaques, reminiscent of necrobiosis lipoidica, are often present (Stewart *et al*, 1977; Linch & Acton, 1979; Hartsfield & Kousseff, 1990). The existence of EDS type VIII as a distinct entity was uncertain, until a recent genome-wide linkage analysis established linkage of EDS type VIII to a region on chromosome 12q13 in a large Swedish family (Rahman *et al*, 2003).

Finally the existence of *EDS type X* as a distinct entity is questionable (Beighton *et al*, 1998). It was first described by Arneson *et al* (1980) in a family with a recessively inherited variant of EDS (joint hypermobility, thin skin with atrophic scarring, easy bruising, petechiae) and a platelet aggregation

although some patients with Marfan syndrome complain of easy bruising. This can be explained by the fact that patients with Marfan syndrome may have a thinner skin, and less subcutaneous fat, and hence less protective cushioning for minor traumata. Also, the joint laxity and poor visual acuity may contribute to a predisposition to contusions in some patients. Some patients with Marfan syndrome present mild hyperextensibility of the skin, reminiscent of EDS. However, the most common skin manifestation of Marfan syndrome are the striae atrophicae or stretch marks, which usually present on the back, the shoulders and the thighs.

## Guidelines for diagnosis and management

Laboratory investigation of clotting factors, platelet aggregation and bleeding time is usually normal in patients with a connective tissue disorder.

When the presence of EDS is suspected, additional morphological, biochemical and molecular analyses are available to confirm the diagnosis of some of the subtypes (Table I). In case of suspected vascular EDS, biochemical analysis of type III collagen extracted from cultures skin fibroblasts is mandatory to confirm the diagnosis.

No causal therapy is available for EDS, however, a series of 'preventive' guidelines are applicable to all forms of EDS. These guidelines, although not evaluated in large series of patients with EDS, are based on common sense and clinical experience, and are generally promoted by experts in the field of EDS.

Children with pronounced skin fragility should wear protective pads or bandages over the forehead, knees and shins, in order to avoid skin lacerations. Dermal wounds should be closed without tension, preferably in two layers. Deep stitches should be applied generously. Cutaneous stitches should be left in place twice as long as usual, and additional fixation of adjacent skin with adhesive tape can help prevent stretching of the scar.

Patients with pronounced bruising are advised to avoid contact sports and heavy exercise (Pepin & Byers, 2002). Protective pads and bandages can be useful also in the prevention of bruises and haematomas. Supplementation of ascorbic acid, a cofactor for cross-linking of collagen fibrils, can ameliorate the tendency towards bruising in some patients (Steinman *et al*, 2002). DDAVP (vasopressin) may be useful in EDS patients with chronic bruising or epistaxis, or perioperatively (e.g. for tooth extraction), in whom bleeding time is normalized by DDAVP (Stine & Becton, 1997).

In children with hypotonia and delayed motor development, a physiotherapeutic programme is important. Non-weight-bearing muscular exercise, such as swimming, is useful to promote muscular development and coordination. Sports with heavy joint strain, such as contact sports, are discouraged. Anti-inflammatory drugs may help in patients with joint pain.

Patients with mitral valve prolapse and regurgitation require antibiotic prophylaxis for bacterial endocarditis. A baseline echocardiogram with aortic diameter measurement is recommended prior to the age of 10 years with follow-up studies timed according to whether an abnormal measurement is found.

For the vascular type of EDS, some prophylactic measures are of special importance. Because of the pronounced vascular and tissue fragility, it is prudent for individuals with vascular EDS to avoid contact sports or isometric exercises (weightlifting) (Pepin & Byers, 2002), to refrain from drugs that interfere with platelet function, either alone (e.g. anti-inflammatory drugs, acetylsalicylic acid) or in combination (e.g. penicillins and cephalosporins) and from anti-coagulation therapy (Steinman *et al*, 2002). Invasive vascular procedures, such as arteriography and catheterization, should also be avoided because of the risk of vascular ruptures, which cause significant morbidity and may have fatal outcome (Cikrit *et al*, 1987; Freeman *et al*, 1996). They should rather be replaced by ultrasonography and/or subtraction angiography. Surgical interventions are generally discouraged because of increased vascular fragility and conservative therapy is recommended. If surgery is unavoidable, manipulation of vascular and other tissues should be performed with extreme care. Although no effective preventive treatment yet exists in vascular EDS, the use of β-blockers is now under study. This is done in analogy with the prophylactic efficacy of β-adrenergic blockade in slowing the rate of aortic dilatation and reducing the development of aortic complications in some patients with Marfan syndrome. (Shores *et al*, 1994).

Finally, emotional support and behavioural and psychological therapy may be indicated in all subtypes of EDS in order to accept and cope with the handicap. Patient support groups are available and can be beneficial.

## Acknowledgements

## References

Ameye, L. & Young, M.F. (2002) Mice deficient in small leucine-rich proteoglycans: novel in vivo models for osteoporosis, osteoarthritis, Ehlers–Danlos syndrome, muscular dystrophy, and corneal diseases. *Glycobiology*, **12**, 107R-116R.

Anstey, A., Mayne, K., Winter, M., Van de Pette, J. & Pope, F.M. (1991) Platelet and coagulation studies in Ehlers–Danlos syndrome. *British Journal of Dermatology*, **125**, 155–163.

Arneson, M.A., Hammerschmidt, D.E., Furcht, L.T. & King, R.A. (1980) A new form of Ehlers–Danlos syndrome. Fibronectin connects defective platelet function. *The Journal of the American Medical Association*, **244**, 144–147.

Barabas, A.P. (1967) Heterogeneity of the Ehlers–Danlos syndrome: description of three clinical types and a hypothesis to explain the basic defect(s). *British Medical Journal*, **2**, 612–613.

Barabas, G.M. & Barabas, A.P. (1967) The Ehlers–Danlos syndrome. A report of the oral and haematological findings in nine cases. *British Dental Journal*, **123**, 473–479.

Barlati, S., Moro, L., Gardella, R. & Colombi, M. (1991) Phenotypic correction of the defective fibronectin extracellular matrix of Ehlers–Danlos syndrome fibroblasts. *Cell Biology International Reports*, **15**, 1183–1194.

Beighton, P. (1993) The Ehlers–Danlos syndromes. In: *McKusick's Heritable Disorders of Connective Tissue* (ed. by P. Beighton), pp. 189–251, University of Cape Town Medical School, Cape Town, South Africa.

Beighton, P., Solomon, L. & Soskolne, C.L. (1973) Articular mobility in an African population. *Annals of the Rheumatic Diseases*, **32**, 413–418.

Beighton, P., De Paepe, A., Steinmann, B., Tsipouras, P. & Wenstrup, R.J. (1998) Ehlers–Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers–Danlos National Foundation (USA) and Ehlers–Danlos Support Group (UK). *American Journal of Medical Genetics*, **77**, 31–37.

Bertin, P., Treves, R., Julia, A., Gaillard, S. & Desproges-Gotteron, R. (1989) Ehlers–Danlos syndrome, clotting disorders and muscular dystrophy. *Annals of the Rheumatic Diseases*, **48**, 953–956.

Birk, D.E. (2001) Type V collagen: heterotypic type I/V collagen interactions in the regulation of fibril assembly. *Micron*, **32**, 223–237.

Burgeson, R.E. (1988) New collagens, new concepts. *Annual Review of Cell Biology*, **4**, 551–577.

Chouza, C., Caamano, J.L., De Medina, O., Bogacz, J., Oehninger, C., Vignale, R., De Anda, G., Novoa, E., De Bellis, R., Cardozo, H., Crispino, B., Romero, S., Correa, H. & Feres, S. (1984) Familial spastic ataxia associated with Ehlers–Danlos syndrome with platelet dysfunction. *Canadian Journal of Neurological Science*, **11**, 541–549.

Chu, M.-L. & Prockop, D.J. (2002) Collagen: gene structure. In: *Connective Tissue and its Heritable Disorders* (ed. by P. Royce & B. Steinmann), pp. 223–248. Wiley-Liss, Inc., New York.

Cikrit, D.F., Miles, J.H. & Silver, D. (1987) Spontaneous arterial perforation: the Ehlers–Danlos specter. *Journal of Vascular Surgery*, **5**, 248–255.

Clark, J.G., Kuhn, C. & Uitto, J. (1980) Lung collagen in type IV Ehlers–Danlos syndrome: ultrastructural and biochemical studies. *American Review of Respiratory Diseases*, **122**, 971–978.

Clough, V., MacFarlane, I.A., O'Connor, J. & Wood, J.K. (1979) Acquired von Willebrand's syndrome and Ehlers–Danlos syndrome presenting with gastro-intestinal bleeding. *Scandinavian Journal of Haematology*, **22**, 305–310.

Colige, A., Sieron, A.L., Li, S.W., Schwarze, U., Petty, E., Wertelecki, W., Wilcox, W., Krakow, D., Cohn, D.H., Reardon, W., Byers, P.H., Lapiere, C.M., Prockop, D.J. & Nusgens, B.V. (1999) Human Ehlers–Danlos syndrome type VII C and bovine dermatosparaxis are caused by mutations in the procollagen I N-proteinase gene. *American Journal of Human Genetics*, **65**, 308–317.

Colombi, M., Moro, L., Zoppi, N., Ghinelli, A. & Barlati, S. (1991) Altered fibronectin mRNA splicing in skin fibroblasts from Ehlers–Danlos syndrome patients: in situ hybridization analysis. *Cell Biology International Reports*, **15**, 1195–1206.

Cunniff, C. & Williamson-Kruse, L. (1995) Ehlers–Danlos syndrome, type VIII presenting with periodontitis and prolonged bleeding time. *Clinical Dysmorphology*, **4**, 145–149.

Cutolo, M., Castellani, P., Borsi, L. & Zardi, L. (1986) Altered fibronectin distribution in cultured fibroblasts from patients with Ehlers–Danlos syndrome. *Clinical and Experimental Rheumatology*, **4**, 125–128.

Dalgleish, R. (1998) The human collagen mutation database 1998. *Nucleic Acids Research*, **26**, 253–255.

De Paepe, A. (1994) Ehlers–Danlos syndrome type IV. Clinical and molecular aspects and guidelines for diagnosis and management. *Dermatology*, **189**(suppl. 2), 21–25.

Espanol, I., Hernandez, A., Pujol, R.M., Urrutia, T. & Pujol-Moix, N. (1998) Type IV Ehlers–Danlos syndrome with platelet delta-storage pool disease. *Annals of Hematology*, **77**, 47–50.

Estes, J.W. (1968) Platelet size and function in the heritable disorders of connective tissue. *Annals Internal Medicine*, **68**, 1237–1249.

Fantl, P., Morris, K.N. & Sawers, R.J. (1961) Repair of cardiac defect in patient with Ehlers–Danlos syndrome and deficiency of Hageman factor. *British Medical Journal*, **5234**, 1202–1204.

Freeman, R.K., Swegle, J. & Sise, M.J. (1996) The surgical complications of Ehlers–Danlos syndrome. *American Surgeon*, **62**, 869–873.

Fujimoto, A., Wilcox, W.R. & Cohn, D.H. (1997) Clinical, morphological, and biochemical phenotype of a new case of Ehlers–Danlos syndrome type VIIC. *American Journal of Medical Genetics*, **68**, 25–28.

Gamba, G., Gatti, V., Longoni, P., Grignani, G., Rizzo, S.C. & Cetta, G. (1986) Type IV Ehlers–Danlos syndrome and factor IX deficiency: a case report. *Haematologica*, **71**, 139–141.

Gibbins, J.M. (2004) Platelet adhesion signalling and the regulation of thrombus formation. *Journal of Cell Science*, **117**, 3415–3425.

Giunta, C., Superti-Furga, A., Spranger, S., Cole, W.G. & Steinmann, B. (1999) Ehlers–Danlos syndrome type VII: clinical features and molecular defects. *Journal of Bone and Joint Surgery*, **81**, 225–238.

Grenko, R.T., Burns, S.L., Golden, E.A., Byers, P.H. & Bovill, E.G. (1993) Type IV Ehlers–Danlos syndrome with aspirin sensitivity. A family study. *Archives of Pathology and Laboratory Medicine*, **117**, 989–992.

Hartsfield, J.K. Jr. & Kousseff, B.G. (1990) Phenotypic overlap of Ehlers–Danlos syndrome types IV and VIII. *American Journal of Medical Genetics*, **37**, 465–470.

Kashiwagi, H., Riddle, J.M., Abraham, J.P. & Frame, B. (1965) Functional and ultrastructural abnormalities of platelets in Ehlers–Danlos syndrome. *Annals of Internal Medicine*, **63**, 249–254.

Kielty, C. & Grant, M. (2002) The collagen family: structure, assembly, and organization in the extracellular matrix. In: *Connective Tissue and its Heritable Disorders* (ed. by P. Royce & B. Steinman), pp. 159–221. Wiley-Liss, Inc., New York.

Kontusaari, S., Tromp, G., Kuivaniemi, H., Stolle, C., Pope, F.M. & Prockop, D.J. (1992) Substitution of aspartate for glycine 1018 in the type III procollagen (COL3A1) gene causes type IV Ehlers–Danlos syndrome: the mutated allele is present in most blood leukocytes of the asymptomatic and mosaic mother. *American Journal of Human Genetics*, **51**, 497–507.

Linch, D.C. & Acton, C.H. (1979) Ehlers–Danlos syndrome presenting with juvenile destructive periodontitis. *British Dental Journal*, **147**, 95–96.

Malfait, F., Coucke, P., Symoens, S., Nuytinck, L., Loeys, B., De Paepe, A. (2004a) The molecular basis of classic Ehlers–Danlos syndrome. A comprehensive study of biochemical and molecular findings in 48 unrelated patients. *Human Mutation* (in press).

Malfait, F., De Coster, P., Hausser, I. & van Essen, A., Franck, A., Colige, A., Nusgens, B. & De Paepe, A. (2004b) Follow-up history and unusual oro-dental features of three patients with human dermatosparaxis (Ehlers–Danlos syndrome type VIIC). *American Journal of Medical Genetics* 7 September 2004 [Epub ahead of print].

Mayer, S.A., Rubin, B.S., Starman, B.J. & Byers, P.H. (1996) Spontaneous multivessel cervical artery dissection in a patient with a substitution of alanine for glycine (G13A) in the alpha 1 (I) chain of type I collagen. *Neurology*, **47,** 552–556.

Milewicz, D.M., Witz, A.M., Smith, A.C., Manchester, D.K., Waldstein, G. & Byers, P.H. (1993) Parental somatic and germ-line mosaicism for a multiexon deletion with unusual endpoints in a type III collagen (COL3A1) allele produces Ehlers–Danlos syndrome type IV in the heterozygous offspring. *American Journal of Human Genetics*, **53,** 62–70.

North, K.N., Whiteman, D.A., Pepin, M.G. & Byers, P.H. (1995) Cerebrovascular complications in Ehlers–Danlos syndrome type IV. *Annals of Neurology*, **38,** 960–964.

Nusgens, B.V., Verellen-Dumoulin, C., Hermanns-Le, T., De Paepe, A., Nuytinck, L., Pierard, G.E. & Lapiere, C.M. (1992) Evidence for a relationship between Ehlers–Danlos type VII C in humans and bovine dermatosparaxis. *Nature Genetics*, **1,** 214–217.

Nuytinck, L., Freund, M., Lagae, L., Pierard, G.E., Hermanns-Le, T. & De Paepe, A. (2000) Classical Ehlers–Danlos syndrome caused by a mutation in type I collagen. *American Journal of Human Genetics*, **66,** 1398–1402.

Onel, D., Ulutin, S.B. & Ulutin, O.N. (1973) Platelet defect in a case of Ehlers–Danlos syndrome. *Acta Haematologica*, **50,** 238–244.

Palmeri, S., Mari, F., Meloni, I., Malandrini, A., Ariani, F., Villanova, M., Pompilio, A., Schwarze, U., Byers, P.H. & Renieri, A. (2003) Neurological presentation of Ehlers–Danlos syndrome type IV in a family with parental mosaicism. *Clinical Genetics*, **63,** 510–515.

Peaceman, A.M. & Cruikshank, D.P. (1987) Ehlers–Danlos syndrome and pregnancy: association of type IV disease with maternal death. *Obstetrics & Gynecology*, **69,** 428–431.

Pepin, M & Byers, Ph. (2002) Ehlers–Danlos syndrome, Vascular type. WWW document. URL. http://www.geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=krgt8VI63hnXr&gry=&fcn=y&fw=EPnr&filename=/profiles/eds4/index.html.

Pepin, M., Superti-Furga, A. & Byers, PH. (1992) Natural history of Ehlers–Danlos syndrome type IV: a review of 137 cases. *American Journal of Human Genetics*, **51,** abstract A44.

Pepin, M., Schwarze, U., Superti-Furga, A. & Byers, P.H. (2000) Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. *New England Journal of Medicine*, **342,** 673–680.

Petty, E.M., Seashore, M.R., Braverman, I.M., Spiesel, S.Z., Smith, L.T. & Milstone, L.M. (1993) Dermatosparaxis in children. A case report and review of the newly recognized phenotype. *Archives of Dermatology*, **129,** 1310–1315.

Pope, F.M. & Nicholls, A.C. (1983) Pregnancy and Ehlers–Danlos syndrome type IV. *Lancet*, **1,** 249–250.

Rahman, N., Dunstan, M., Teare, M.D., Hanks, S., Douglas, J., Coleman, K., Bottomly, W.E., Campbell, M.E., Berglund, B., Nordenskjold, M., Forssell, B., Burrows, N., Lunt, P., Young, I., Williams, N., Bignell, G.R., Futreal, P.A. & Pope, F.M. (2003) Ehlers–Danlos syndrome with severe early-onset periodontal disease (EDS-VIII) is a distinct, heterogeneous disorder with one predisposition gene at chromosome 12p13. *American Journal of Human Genetics*, **73,** 198–204.

Richards, A.J., Ward, P.N., Narcisi, P., Nicholls, A.C., Lloyd, J.C. & Pope, F.M. (1992) A single base mutation in the gene for type III collagen (COL3A1) converts glycine 847 to glutamic acid in a family with Ehlers–Danlos syndrome type IV. An unaffected family member is mosaic for the mutation. *Human Genetics*, **89,** 414–418.

Rudd, N.L., Nimrod, C., Holbrook, K.A. & Byers, P.H. (1983) Pregnancy complications in type IV Ehlers–Danlos syndrome. *Lancet*, **1,** 50–53.

Sack, G. (1936) Status dysvascularis, ein Fall van besonderer Zerreislichkeit der blutgefässe. *Dtsch Arch Klin Med*, **178,** 663–669.

Schalkwijk, J., Zweers, M.C., Steijlen, P.M., Dean, W.B., Taylor, G., van Vlijmen, I.M., van Haren, B., Miller, W.L. & Bristow, J. (2001) A recessive form of the Ehlers–Danlos syndrome caused by tenascin-X deficiency. *New England Journal of Medicine*, **345,** 1167–1175.

Schwarze, U., Schievink, W.I., Petty, E., Jaff, M.R., Babovic-Vuksanovic, D., Cherry, K.J., Pepin, M. & Byers, P.H. (2001) Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers–Danlos syndrome, Ehlers–Danlos syndrome type IV. *American Journal of Human Genetics*, **69,** 989–1001.

Shirakami, A., Shigekiyo, T., Hirai, Y., Takeichi, T., Kawauchi, S., Saito, S. & Miyoshi, K. (1986) Plasma fibronectin deficiency in eight members of one family. *Lancet*, **1,** 473–474.

Shores, J., Berger, K.R., Murphy, E.A. & Pyeritz, R.E. (1994) Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *New England Journal of Medicine*, **330,** 1335–1341.

Steinman, B., Royce, P. & Superti-Furga, A. (2002) The Ehlers–Danlos syndrome. In: *Connective Tissue and its Heritable Disorders* (ed. by P. Royce & B. Steinmann), pp. 431–523. Wiley-Liss, Inc., New York.

Stewart, R.E., Hollister, D.W. & Rimoin, D.L. (1977) A new variant of Ehlers–Danlos syndrome: an autosomal dominant disorder of fragile skin, abnormal scarring, and generalized periodontitis. *Birth Defects Original Article Series*, **13,** 85–93.

Stine, K.C. & Becton, D.L. (1997) DDAVP therapy controls bleeding in Ehlers–Danlos syndrome. *Journal of Pediatric Hematology and Oncology*, **19,** 156–158.

Uden, A. (1982) Collagen and bleeding diathesis in Ehlers–Danlos syndrome. *Scandinavian Journal of Haematology*, **28,** 425–430.

Wenstrup, R.J., Murad, S. & Pinnell, S.R. (1989) Ehlers–Danlos syndrome type VI: clinical manifestations of collagen lysyl hydroxylase deficiency. *Journal of Pediatrics*, **115,** 405–409.