Pontine Tegmental Cap Dysplasia: The Severe End of the Clinical Spectrum

Authors C. Rauscher[1], A. Poretti[2], T. M. Neuhann[3], R. Forstner[4], G. Hahn[5], J. Koch[1], S. Tinschert[3], E. Boltshauser[2]

Affiliations Affiliation addresses are listed at the end of the article

Key words
- pontine hypoplasia
- vermis hypoplasia
- sensorineural deafness
- corneal anesthesia
- molar tooth sign

Abstract

Pontine tegmental cap dysplasia (PTCD) is a newly described hindbrain malformation with distinct neuroradiological findings. Only 12 cases of PTCD have been described so far, all sporadic. We report 2 further patients. Both children presented after birth with significant feeding problems due to impaired mouth opening (previously not reported) and sucking difficulties. Facial, cochlear, and glossopharyngeal nerves were involved resulting in bilateral sensory deafness and a significant swallowing disorder requiring a gastrostomy. In one patient the trigeminal sensory nerve was also involved causing severe bilateral corneal clouding with impaired vision. Both patients showed only minimal developmental progress since birth and had no speech production. Furthermore, they had vertebral and rib anomalies. The patients died at the age of 15 and 32 months, respectively, due to intercurrent infections. The majority of patients reported previously were affected less severely. The presented patients may represent the severe end of the spectrum.

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Correspondence
E. Boltshauser
Department of Pediatric Neurology
University Children's Hospital of Zurich
Steinwiesstrasse 75
8032 Zurich
Switzerland
Tel.: +41/44/266 73 30
Fax: +41/44/266 71 63
Eugen.Boltshauser@kispi.uzh.ch

Introduction

Barth et al. described recently four unrelated children with a new complex hindbrain malformation named "pontine tegmental cap dysplasia" (PTCD) [1]. All these patients showed hearing impairment. Other neurological findings were horizontal gaze palsy, impaired swallowing, facial palsy, bilateral sensory trigeminal nerve involvement, and ataxia. Extracranial malformations included bony vertebral anomalies. Six additional patients were recently added by Jissendi-Tchofo et al [3].

We report two additional cases extending the spectrum of this malformation, presenting clinical findings not yet described; and we point out the potential severe consequences.

Case Report

Patient 1

The girl was born at 38+5 weeks gestation by spontaneous vaginal delivery as the third child of healthy, unrelated Austrian parents. The family history was unremarkable, pregnancy and delivery were uneventful. Significant feeding problems due to impaired mouth opening and sucking difficulties were recognized after birth and nasogastric tube feeding was started. Electromyography of M. masseter was not performed. The limitation of mouth opening was not considered to result from trismus. Neurological examination showed bilateral facial nerve palsy, but complete eye closure could be achieved. Corneal reflexes were absent, ocular movements unrestricted, and pupillary reflexes symmetrical. Oral inspection including tongue movements was normal, sucking reflex weak, and truncal musculature hypotonic. At the age of 3 months she suffered from bilateral purulent conjunctivitis with subsequent marked corneal clouding (**Fig. 1**). To this age she showed poor developmental progress. The oculodigital sign was observed frequently. Because of hearing impairment (otoacoustic emissions and brainstem auditory responses could not be evoked on repeated examinations), bilateral hearing aids were supplied. At the age of 12 months, she opened her eyes spontaneously, followed a light source, and showed normal vertical and horizontal gaze, but still demonstrated the oculodigital sign frequently. Additionally, positional plagiocephaly, thoracic levoscoliosis and lumbar dextroscoliosis, poor head control,

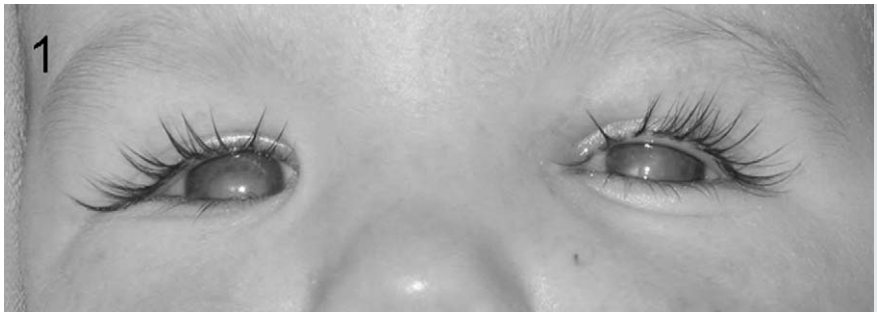

Fig. 1 Frontal view of patient 1 at the age of 12 months showing significant bilateral corneal clouding.

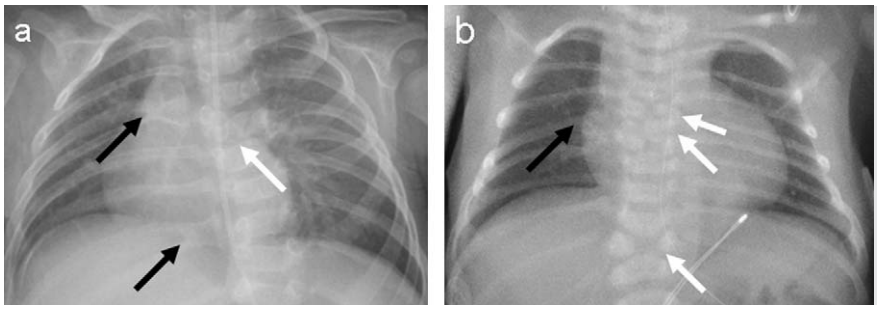

Fig. 2 a Chest radiograph of patient 1 showing on the right side only 11 ribs and partial fusion of the dorsal part of both pairs of ribs 5/6 and 9/10 (black arrows), butterfly shape of the vertebral body T5, wedge-shaped of vertebral body T6 (white arrow), and nasogastric tube. **b** Chest radiograph of patient 2 showing on the right side fusion of ribs 4/5 (black arrows), butterfly shape of the vertebral body T4, T5, and T9 (white arrows), and nasogastric tube.

marked muscular hypotonia, and poor spontaneous movements were noted. She could not turn, crawl, sit unaided, nor speak, and non-verbal contact was poor. Due to significant swallowing difficulties a gastrostomy was necessary. She was a happy child and had normal sleep-wake behaviour. Cochlear implants were not felt to be indicated because of the impaired function of both cochlear nerves. As there was a high recurrence risk of corneal clouding due to the persistence of absent corneal reflexes, corneal transplantation was not pursued. She suffered from recurrent respiratory infections and died at the age of 15 months as a result of one. Several laboratory studies including TORCH screen were all within normal limits. Chromosomal analysis revealed a normal female karyotype (46,XX). Chest radiograph showed only 11 ribs and a partial fusion of ribs 5/6 and 9/10 on the right; the vertebral body T5 was butterfly-shaped and the vertebral body T6 was wedge-shaped **(** **Fig. 2a)**. CT of the inner ear was normal as were the dimensions of the inner acoustic meatus, CT of the viscerocranium showed mandibular hypoplasia with normal mandibular joints. Echocardiography at the age of 3 months showed a hemodynamically relevant atrial septal defect without necessity of treatment. Cranial MRI at the age of six months demonstrated typical findings of PTCD (**Fig. 3**).

Patient 2

The girl was born at 40 weeks gestation by spontaneous vaginal delivery after an uneventful pregnancy as the child of healthy, unrelated German parents. It was the mother's third pregnancy; one spontaneous abortion, one unsuccessful twin pregnancy with one fetus being acardic leading to a TRAP (twin reversed arterial perfusion) sequence in the other twin. Generalized muscular hypertonia, marked feeding problems due to impaired mouth opening and absent sucking were recognized after birth. A duodenal feeding tube was started because of a hiatal hernia with considerable gastroesophageal reflux disease. During the following months she presented with muscular trunk hypotonia but limb hypertonia, bilateral facial nerve palsy with incomplete eye closure, horizontal gaze palsy, and sensorineural hearing loss (otoacoustic emissions and brainstem auditory responses could not be evoked). Major swallowing difficulties persisted. Pupillary reflexes were symmetrical and tongue movements normal. She developed marked spinal scoliosis. Mild dysmorphic signs such as low frontal hairline, long eyelashes, microretrognathia, and soft ear cartilage were present. Due to the swallowing difficulties, a gastrostomy was performed. At the age of two years and eight months she was unable to crawl, sit unaided, or speak. She developed recurrent aspiration pneumonias as well as other febrile infections. Several laboratory studies were all within normal limits. Chromosomal analysis revealed a normal female karyotype (46,XX). On radiological exams, ribs 4/5 were fused on the right-hand side and vertebral bodies T4, T5, and T9 were butterfly-shaped **(** **Fig. 2b**); moreover, hip dysplasia and subluxation were seen. Cranial MRI performed at the age of one month as well as at two years and six months showed characteristic findings of PTCD (**Fig. 4**). Uroflowmetry revealed vesicoureteral reflux.

Discussion

Pontine tegmental cap dysplasia (PTCD) represents a newly reported hindbrain malformation with a distinct pattern including a flat profile of the ventral pons, vaulted pontine tegmentum, hypoplasia and dysplasia of the vermis cerebelli, shortening of the mesencephalic isthmus, lateralized course of the superior cerebellar peduncles, absence of the inferior olivary nucleus, and subtotal absence of the middle cerebellar peduncles [1]. Similar characteristic MR imaging findings have been recently confirmed in six sporadic patients [3]. Shape and orientation of the superior cerebellar peduncles produce the impression of a molar tooth sign (MTS). However, this appearance is different from a classic MTS in Joubert syndrome where the superior cerebellar peduncles are thickened and elongated and their orientation is more horizontal [2,5,7]. Additionally, the brainstem configuration in Joubert syndrome is different. The presence of a molar tooth-like malformation as well as the absence of the decussation of the superior cerebellar peduncles suggest an impairment of axonal navigation and/or migration as possible cause of PTCD [3]. The same hypothesis has been postulated by Barth et al.

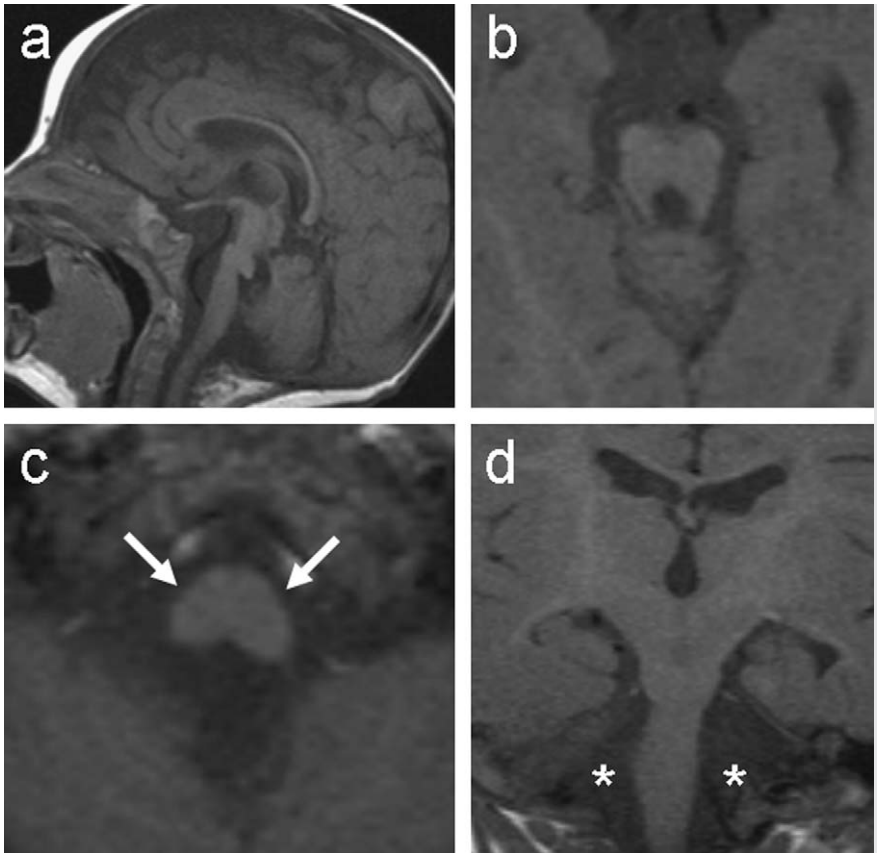

Fig. 3 MRI of patient 1 at 6 months. **a** Midsagittal T_1-weighted MRI showing the flat profile of the ventral side of the pons, the vaulted structure protruding into the fourth ventricle, shortening of the mesencephalic isthmus, and dysplastic superior vermis. **b** Axial T_1-weighted MRI revealing abnormal shape of the superior cerebellar peduncles producing a "molar tooth" appearance. **c** Axial T_1-weighted MRI at the level of the medulla oblongata demonstrating the absence of the contours of the inferior olivary nuclei (arrows). **d** Coronal T_1-weighted MRI showing the absence of both middle cerebellar peduncles (asterisks), slightly enlarged lateral ventricles, and dysplastic hippocampi with reduced inrolling.

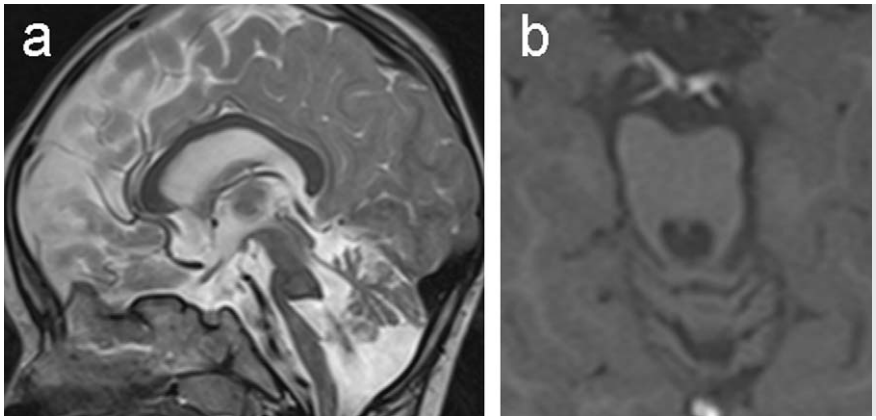

Fig. 4 MRI of patient 2 at 2 years and 6 months. **a** Midsagittal T_2-weighted MRI showing the flat profile of the ventral side of the pons, the vaulted structure protruding into the fourth ventricle, shortening of the mesencephalic isthmus, and dysplastic superior vermis. **b** Axial T_1-weighted MRI revealing abnormal shape of the superior cerebellar peduncles producing a "molar tooth" appearance.

because of an ectopic transverse fiber bundle at the site of the pontine tegmentum and the complete absence of transverse fibers in the ventral pons [1]. Therefore, axonal guidance molecules such as netrin, ephrins, semaphorins, and their receptors may be candidate genes [3]. Barth et al. analyzed the *NTN1* gene encoding netrin1 and *DCC* encoding its receptor, the most plausible candidate genes according to mouse models. However, no obviously pathogenetic mutations in both genes could be identified [1]. The genetic basis of PTCD remains unknown ◉ **Table 1**.

The clinical findings were dominated by the involvement of several cranial nerves. In all 12 patients including both presented here, cochlear nerves were involved, causing bilateral sensory deafness in eight patients [1,3]. The facial nerve was involved in nine, and the trigeminal sensory nerve in six patients. Involvement of the trigeminal sensory nerve caused corneal anesthesia and absent corneal reflex resulting in corneal ulcers in three children. The glossopharyngeal nerve was involved in four cases causing swallowing disorders necessitating gastrostomy. Eight patients showed ocular movement abnormalities: oculomotor apraxia (2), impaired smooth pursuit (2), impaired horizontal gaze (2), nystagmus (1), and near absent voluntary eye movements (1). Speech was impaired in the children described by Barth et al: two were mute, the other two presented severe speech disorder and indistinct language. Three children learned sign language. Also our patients showed no language development. Cerebellar signs were present in all patients that could be tested: ataxia in five, uncoordinated movements in three, and head titubation in two patients. Two children reported by Barth et al. could walk at four and six years, respectively, but both were clearly atactic. Developmental delay was present in eight of nine tested patients, and was severe in six. One child had an overall IQ of 94. Six patients had rib and/or vertebral malformations, three a congenital heart defect, one a submucous cleft palate and bilateral inguinal hernias, another horseshoe configuration of the

Table 1 Clinical data of two patients with pontine tegmental cap dysplasia.

Patient no	1	2
male/female	female	female
ethnic origin	Austrian	German
parental consanguinity	no	no
first sign	impaired mouth opening as neonate	impaired mouth opening as neonate
brainstem sensory nerves involved	V (corneal anesthesia), VIII (bilateral sensory deafness)	VIII (bilateral sensory deafness)
brainstem motor nerves involved	VII, IX	VII, IX
supranuclear eye movements	not affected	full vertical but no horizontal gaze
swallowing	impaired; Gastrostomy	impaired; Gastrostomy
external dysmorphia	no	low frontal hairline; Long eyelashes; Microretrognathia; Soft ear cartilage
extracranial malformations	only 11 ribs on the right side; Dorsal part of ribs 5/6 and 9/10 partially fused; Vertebral body T5 butterfly shaped; Vertebral body T6 wedge shaped; Atrial septal defect	ribs 4/5 on the right side fused; Vertebral body T4, T5, T9 butterfly shaped; vesico- ureteral reflux
global development	lack of development progress since birth	lack of development progress since birth
age at death (months)	15	32
karyotype	46,XX	46,XX
BAER	absent	absent

BAER, brainstem auditory evoked response

kidneys. Mild external dysmorphic features were described in only two patients. Neither cochlear implants nor corneal transplantations were performed in the affected patients. Four children died, one at the age of 6 months because of a parainfluenza pneumonia, one at two 2 years from unknown cause, and patients 1 and 2 in the present report at the age of 15 and 32 months, respectively.

A hindbrain malformation identical to PTCD has been described previously in two single case reports. Maeoka et al. reported a 2-year-old girl with sensory deafness, absent blink reflex, mild truncal ataxia, and mild developmental delay [4]. At the age of two years, this girl could walk alone and spoke a few words. Other anomalies were not described. MR imaging showed pontine hypoplasia and a vaulted structure protruding into the fourth ventricle. The cerebellum appeared normal. Ouanounou et al. reported a 3-month-old boy with bilateral 6th and 7th cranial nerve deficits, classified as Moebius syndrome [6]. Auditory tests, swallowing, and corneal reflexes were normal. MR imaging demonstrated hypoplasia of the pons, a vaulted structure protruding into the fourth ventricle, complete absence of the middle cerebellar peduncles, and prominent superior cerebellar peduncles. The cerebellum was normal. Although the MR images of these two patients are consistent with PTCD, these children seem to be less severely affected [1, 3].

The patients presented here showed impaired mouth opening (previously not described) and severe developmental delay with lack of developmental progress since birth, poor spontaneous movements, and no speech. The facial, cochlear, and glossopharyngeal nerves were involved in both patients. Additionally, one girl suffered from bilateral trigeminal sensory palsy. Both children had a scoliosis and vertebral and rib anomalies. A hemodynamically relevant atrial septal defect was present in one girl. These two children were more severely affected than most the other reported patients, suggesting that the same neuroradiological pattern characteristic of PTCD is associated with clinical symptoms of varying severity. Our patients may represent the severe end of this spectrum.

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Affiliations

[1] Department of Pediatrics, Paracelsus Medical University of Salzburg, Salzburg, Austria
[2] Department of Pediatric Neurology, University Children's Hospital of Zurich, Zurich, Switzerland
[3] Institute of Clinical Genetics, Medical Faculty Carl Gustav Carus, University of Technology, Dresden, Germany
[4] Department of Radiology, Paracelsus Medical University of Salzburg, Salzburg, Austria
[5] Department of Pediatric Radiology, Children's Hospital, Medical Faculty Carl Gustav Carus, University of Technology, Dresden, Germany

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