Congenital anterolateral bowing of the tibia with ipsilateral polydactyly of the great toe associated with cerebral cyst: a new entity?

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We present two patients with congenital anterolateral bowing of the tibia with polydactyly who had, in addition, cerebral malformations including agenesis of the corpus callosum and a large cerebral cyst. We discuss phenotypic overlap with the acrocallosal syndrome. *Clin Dysmorphol* 18:195–200 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Congenital anterolateral bowing of the tibia with polydactyly (CABTP) is a recognized entity in the literature. We report two unrelated individuals with the same manifestations, who present the additional features of major cerebral malformations including agenesis of the corpus callosum and a large intracranial cyst. The phenotypic overlap of this condition with acrocallosal syndrome indicates a common pathogenesis of these conditions and raises the possibility that these are the expression of a single disorder and thus part of a single spectrum.

Clinical report

Patient 1

Patient 1 is the first child of healthy, unrelated parents. He was already briefly described by Fryns *et al.* (1991) (case 1). Family history is negative with regard to malformations or mental handicap. During pregnancy, an episode of bleeding was observed at 2 months. A few days before delivery, at a routine ultrasound scan, a cystic cerebral structure was noted. The boy was born at a gestational age of 37 weeks with birth weight 3.570 g (90th percentile), length 50 cm (75th percentile) and head circumference 38 cm (>97th percentile; 97th percentile = 35.5 cm). At birth, he presented with a unilateral incurvation of the right leg and ipsilateral preaxial polydactyly of the foot, with a supernumerary hallux, lacking a nail (Figs 1 and 2). The foot was in an equinovarus position. In addition, there was mild cutaneous syndactyly of fingers III–IV. The forehead was broad and bulging, and the anterior fontanel was large. Clinical examination was otherwise unremarkable.

The radiographs of the right leg showed anterolateral bowing in the middle-third of the tibia and a normal fibula. No osseous components were detected in the medial part of the duplicated hallux. Complementary investigations including karyotype, eye examination, and skeletal survey were normal. Computed tomography and MRI of the brain revealed agenesis of the corpus callosum and the presence of a large, interhemispheric cyst, expanding asymmetrically to the left side (Fig. 3).

At the age of 4 months, drainage of the arachnoid cyst was performed, because of rapidly increasing head circumference (47.5 cm, 2.5 cm >97th percentile). Pylorotomy was performed at age 6 months. At age 34 months, development, evaluated by means of the Stutsman, revealed a mental age of 32 months, [corresponding to an IQ (intelligence quotient) of 94]. Fine and gross motor development were more delayed. At age 10 years, a full scale Wechsler Intelligence Scale for Children–revised edition IQ of 79 was obtained with verbal IQ 78 and performal IQ 80. He followed special schooling for persons with mild learning disabilities. The 6 cm leg-length discrepancy between both tibias was corrected surgically (Ilizarov) at age 16 years. Currently, at age 19, he has no medical problems. Height is 169.5 cm (25th percentile), weight 86.2 kg (>97th percentile) and head circumference 61.8 cm (>97th percentile). Mutation analysis of *GLI3* was normal and no chromosomal imbalances were detected by means of a bacterial artificial chromosome/P1-derived artificial chromosome array with 1 Mb resolution performed as described (Menten *et al.*, 2006).

Fig. 1

Preaxial polydactyly of the right foot in patient 1 (a). Radiographs show no osseous components in the medial part of the duplicated hallux (b).

Fig. 2

Anterotlateral bowing of the right tibia in patient 1 (a) and patient 2 at age of 6 weeks (b).

Fig. 3

Transverse computed tomography (a) and coronal MRI images (b) of the brain showing a large, interhemispheric cyst, expanding asymmetrically to the left side in patient 1 at the age of 4 months.

Patient 2

Patient 2 is the third child of healthy, unrelated parents. Family history is negative with regard to mental handicap or congenital malformations. Bowing of the right lower limb was detected antenatally. During the 34th week of gestation, ultrasound revealed the presence of a large cerebral cyst. He was born at 36 weeks of gestation with weight 2.915 g (75th percentile), length 47.5 cm (50th percentile), head circumference 38.3 cm (> 97th percentile). MRI of the brain showed a large, multicystic mass most likely originating from the third ventricle. There was agenesis of the corpus callosum, aqueduct stenosis, and a hypoplastic right cerebellar hemisphere. Polymicrogyria was noted on the left side, with an aberrant left Rollandic sulcus (Fig. 4).

There were associated limb anomalies. The right tibia was bowed. On radiograph, there was anterolateral bowing at the middle of the tibia, which appeared denser. The fibula was normal (Fig. 2). There was a right preaxial polydactyly with incomplete duplication of the nail of the first ray. Radiographs showed the presence of two phalanges. The second toe was deviated. The left foot appeared normal. The right hand showed clinodactyly of the fifth finger, with an irregular second phalanx. The left hand showed cutaneous webbing between the first and second ray, surgically corrected at the age of 3 months (Fig. 5), and hypoplasia of the distal phalanx of the second finger. Further clinical examination was unremarkable.

At the age of 2.5 months, he presented signs of increased intracranial pressure, with feeding difficulties, and accelerated head growth. Occipitofrontal circumference was 43.3 cm (> 97th percentile), weight 4.080 g (25th percentile), and length 53.8 cm (25th percentile). Computed tomography scan of the brain showed an

Fig. 4

Transverse and coronal MRI images of the brain in patient 2 at birth, showing a large, multicystic mass originating from the third ventricle, and agenesis of the corpus callosum. There is polymicrogyria on the left side, with an aberrant left Rollandic sulcus.

Fig. 5

Patient 2. Preaxial polydactyly of the right foot (a) and cutaneous webbing between the first and second ray of the left hand (b).

increased volume of the cerebral cyst, and a cystoperitoneal drainage was performed. After this, he was more alert and feeding difficulties resolved. At age 8 months, he developed absence and myoclonic epilepsy which was multidrug resistant. A nervus vagus stimulator was implanted at the age of 2 years. Bayley Scales of Infant Development—second edition was performed at the age of 11 months. His motor abilities were scored around 6 months, his mental abilities were scored around 7–8 months. At age 1 year, he underwent surgical excision of the supernumerary toe. No causal imbalances were detected by SNP array (Affymetrix 6.0, Santa Clara, California, USA).

Discussion

The association between unilateral congenital bowing of the tibia and ipsilateral preaxial duplication of the first toe has been reported before in the literature, and is referred to as minor tibia duplication in the London Dysmorphology Database. This is based on the apparent duplication of the tibia on radiographs in the patient reported by Adamsbaum *et al.* (1991). However, most authors refer to the condition as congenital anterolateral

bowing of the tibia with ipsilateral polydactyly of the great toe (CABTP). Up to now, and including the present two patients, 21 cases have been described (Newell and Durbin, 1976; Adamsbaum *et al.*, 1991; Watanabe *et al.*, 1992; Weaver *et al.*, 1996; Kitoh *et al.*, 1997; Bressers and Castelein, 2001; Manner *et al.*, 2005; Lemire, 2007; Evans *et al.*, 2008). In none of them, additional major malformations were observed and all reported cases to date have been sporadic (Table 1). In several instances, minor anomalies of the hands were associated, such as cutaneous syndactyly and clinodactyly of fifth fingers. Broad thumbs were also noted. The anomaly of the big toe is strikingly similar in all cases; there is a partial duplication and marked varus position of the first toe. Moreover, the condition is unilateral in all instances. However, unlike these previously reported cases, the present two patients have, in addition, a large intracranial

cyst, with associated agenesis of the corpus callosum, and one of them also had cortical malformations (polymicrogyria) and refractory epilepsy.

The association of polydactyly and agenesis of the corpus callosum is described in the acrocallosal syndrome. In this condition, polydactyly is seen both in hands and feet, and can be bilateral. The condition is associated with severe mental retardation. Interestingly, in approximately 25% (10 of 38) of published cases of acrocallosal syndrome, intracranial cysts were observed, including arachnoid (two), porencephalic (three), interhemispheric (two), supratentorial (one), and Dandy–Walker cysts (two). Of interest, these cases often have a less severe mental handicap (Koenig *et al.*, 2002). There is also a preponderance of males, with an observed sex ratio of males 21/females 13 (Koenig *et al.*, 2002). In the literature, some

Table 1 Reported cases of congenital anterolateral bowing of the tibia with polydactyly

Reference	Case no.	Sex	Age	Lower limb involved	Hand anomaly	Other limb defects	CT of bowed tibia
Adamsbaum <i>et al.</i> (1991)	1	Female	17 months	Left	Syndactyly, bifid thumb	Mild equinovarus (right)	Focal tibial duplication
	2	Male	12 years	Right	Bilateral clinodactyly V		Small postero-medial cortical split
	3	Male	10 years	Left	Unilateral clinodactyly V		
	4	Male	7 months	Right	Clinodactyly II and III, broad first ray (right)		
	5	Male	6 years	Right	Normal		
Watanabe <i>et al.</i> (1992)	1	ND	ND	ND	Bilateral broad thumb, syndactyly, clinodactyly, central-ray polydactyly		
	2	ND	ND	ND	Normal		
	3	ND	ND	ND	Normal		
Weaver <i>et al.</i> (1996)	1	Male	9 months	Left	Bilateral camptodactyly V	Prominent fibular head	
	2	Male	6 years	Left	Bilateral radial deviation second ray	Prominent fibular head	
Kitoh <i>et al.</i> (1997)	1	Male	13 years	Right	ND		Posteromedial cortical cleft
	2	Male	18 months	Right	ND		Partial cleft
Bressers and Castelein (2001)	1	Male	17 months	Left	Normal		Bony intrusion of posteromedial cortex into medullary canal (MRI)
Newell and Durbin (1976)	3	Male	3 years	Left	ND		
Manner <i>et al.</i> (2005)	1	Female	5–6 years	ND	ND	Prominent fibula head	Focal tibial duplication (MRI)
	2	Male	5–6 years	ND	ND	Prominent fibula head	Focal tibial duplication (MRI)
	3	Female	5–6 years	Right	ND	Duplicated navicular, cuneiform and metatarsal bones, prominent fibula head	Focal tibial duplication (MRI)
Lemire (2007)	1	Male	2.5 years	Right	Radial deviation of second ray left		Tapering and cortical thinning (MRI)
Evans <i>et al.</i> (2008)	1	Male	ND	Right	ND		
This report	1	Male	19 years	Right	Cutaneous syndactyly III–IV		
	2	Male	2 years	Right	Clinodactyly V (right), cutaneous webbing I–II (left), hypoplasia distal phalanx II (left)		

CT, computed tomography; ND, not defined.

cases that have been described as acrocallosal syndrome resemble the present two cases. For instance, Thyen *et al.* (1992) reported on a boy with bilateral preaxial polydactyly of the feet, with a right club foot and 'tibial recurvation'. There was preaxial polydactyly of the left hand and clinodactyly (left II and V, right III). Agenesis of the corpus callosum with an interhemispheric cyst was also observed. A similar case with unilateral incurvation of the right leg and ipsilateral preaxial polydactyly of the foot was reported by Fernandez *et al.* (2008) (case 1). This male fetus presented with corpus callosum agenesis with multiple interhemispheric cysts and agenesis of the posterior cerebellar vermis. Both hands showed cutaneous syndactyly IV–V and camptodactyly. In addition, there was an interfrontal extra bone within the anterior fontanel, a typical feature of the murine Xt *GLI3* mutant, a homologous mouse model of Greig encephalopolysyndactyly (Hui and Joyner, 1993). Of interest, Elson *et al.* (2002) reported a case diagnosed with acrocallosal syndrome who carried a *GLI3* mutation, suggesting that some cases of acrocallosal syndrome represent the severe end of the spectrum of *GLI3* mutations.

The foot anomalies strikingly resemble those seen in oro-facial-digital syndrome type 1 (OFD1), where typically unilateral partial duplication of the big toe is seen, with varus position. Hallucal anomalies are rarely bilateral (Stapleton *et al.*, 1982). Often, brachydactyly and syndactyly of the other toes is observed. Malformations of the hands include clinodactyly, syndactyly, and brachydactyly. Orstavik *et al.* (1992) reported a case with unilateral duplication of the big toe associated with ipsilateral bowing of the tibia, thought to represent a pseudarthrosis. Central nervous system malformations are frequent, including agenesis of the corpus callosum, cerebellar anomalies as well as abnormal gyration and arachnoidal cysts (Odent *et al.*, 1998).

However, this condition is X-linked dominant, and thus only seen in girls, whereas the present condition shows a striking preponderance in males (13 boys/three girls). Moreover, facial and oral manifestations are typical of OFD1, and are lacking in the patients reported here.

OFD2, an autosomal recessive condition, is characterized by bilateral preaxial polydactyly of the feet. However, central nervous system malformations are rare. In one case, an arachnoidal cyst with vermis hypoplasia was reported (Reardon *et al.*, 1989), and another case had, what was described as unilateral pseudarthrosis of the tibia, associated with bilateral partial duplication of the halluces (case 5 in Fenton and Watt-Smith, 1985). In OFD type IV, tibial dysplasia is a characteristic feature, but it is unlikely that this is a distinct entity (Toriello *et al.*, 1997). Fontaine *et al.* (1979) reported on a child which represents features of both conditions: unilateral

bowing of the tibia with ipsilateral preaxial polydactyly and varus position of the first toe. There was cutaneous syndactyly of fingers IV–V of the right hand and camptodactyly and clinodactyly of the other fingers. There was a postminimus on the right side. The first toe on the left was broadened. In addition, she presented mild oral manifestations of OFD syndrome, that is, multiple upper and lower intraoral frenulae and irregular alveolar ridges. There was no midline cleft lip.

Of interest is the phenotypic overlap with mesomelic dysplasia type Werner (OMIM 18770), featuring symmetrical tibial aplasia, preaxial polydactyly of hands and feet, and a five-fingered hand with absence of the thumb. However, these limb anomalies are usually bilateral and asymmetric. Moreover, several familial cases have been reported suggesting autosomal dominant inheritance with variable expressivity and incomplete penetrance (Richieri-Costa *et al.*, 1990, Goldenberg *et al.*, 2003).

Proximally placed preaxial polydactyly, particularly when associated with segmentation anomalies of the spine and tibial hemimelia, is suggestive of diabetic embryopathy (Adam *et al.*, 2009). However, maternal diabetes was reported only in one case of CABTP (Bressers and Castelein, 2001).

Recently, mutations in the *PITX1* gene were shown to cause asymmetric lower-limb malformations in a family with idiopathic clubfoot segregating as an autosomal dominant condition with incomplete penetrance. The proband presented with bilateral preaxial polydactyly of the feet and right-sided tibial hemimelia (Gurnett *et al.*, 2008). No *PITX1* mutations were identified in both of our cases.

In conclusion, there exists phenotypic overlap of CABTP and acrocallosal syndrome as well as with certain cases of OFD1/2. This indicates a related pathogenesis. The sporadic occurrence of CABTP and most cases of acrocallosal syndrome contrasts with the hereditary cause of OFD1/2, indicating etiological heterogeneity. However, given the skewed sex ratio in both acrocallosal and CABTP syndromes and remarkable clinical overlap, it is not excluded that both conditions are the expression of a single disorder with variable expression.

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