CASE REPORTS

Orofaciodigital syndrome type I in a girl with unilateral tibial pseudarthrosis

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Abstract

The orofaciodigital syndromes are a group of possibly seven different malformation syndromes including oral, facial, and digital malformations. Type I has X linked dominant inheritance whereas the other types show autosomal recessive inheritance. An exact diagnosis is therefore important for genetic counselling. We here report a girl with orofaciodigital syndrome type I. She had cystic kidney disease at the age of 8 months which has not previously been reported in an infant with orofaciodigital syndrome. In addition she had unilateral tibial pseudarthrosis which has only rarely been reported in the orofaciodigital syndromes and in type II only. (J Med Genet 1992;29:827-30)

Orofaciodigital syndromes (OFD) are a heterogeneous group of disorders. In a recent review, Toriello described seven different variants. OFD type I has X linked dominant inheritance and is by far the most frequent variant. In addition to oral, facial, and digital anomalies, patients with OFD I may have structural brain anomalies and sometimes adult onset polycystic kidney disease. We report here a girl with probable OFD I who had cystic kidney disease detected by ultrasonography at 8 months and in addition had a left sided tibial pseudarthrosis.

Case report

The patient was a girl born at 37 weeks' gestation after a normal pregnancy. Birth was induced because of threatened asphyxia. Birth weight was 3040 g and length 49 cm. Multiple malformations were noted immediately.

FACE
She had a flat face, hypoplastic nasal alae, a flat, broad nasal bridge, median pseudocleft of the lower lip, low set ears, and micrognathia (fig 1).

HAIR AND SKIN
Her hair was normal but her skin was very dry. She had no milia.

EXTREMITIES
The right hand had syndactyly of fingers 2 and 3, and of fingers 4 and 5, and clinodactyly of finger 5. The left hand was seemingly normal. Radiographs showed irregular shortening and dysmorphism of several phalanges on both hands and irregular bone mineralisation. Bone...
age was delayed, corresponding to 2½ years at chronological age 3½ years (fig 2). The right foot was normal. The left foot had a duplication and shortening of the first toe (fig 3). She had a left sided tibial pseudarthrosis and a cystic lesion situated in an identical position in the right tibia (fig 4). There was also cortical thickening of the left femur. No other skeletal malformations were found.

KIDNEYS
Ultrasoundography of the kidneys at 8 months showed bilateral enlarged diameters (+3.5 SD) and diffusely increased echogenicity thought to represent microcysts as well as macrocysts. Repeated examination at 21 months and 3½ years showed kidney size to be within normal limits and there was no increase in size of cysts (fig 5). Ultrasoundography of the liver did not show any cysts.

BRAIN
Cerebral CT scan without contrast at the age of 2 years showed multiple structural brain anomalies including agenesis of the corpus callosum and of the lower part of the cerebellar vermis, atrophy of the pons, and a small Dandy-Walker cyst (fig 6).

PSYCHOMOTOR DEVELOPMENT
Mental development was within the normal range. At the age of 3 years she seemed to have normal language development but she had dysarthria probably because of her oral malformations. She did not walk, but moved about
by crawling and bottom shuffling. She had some atrophy of the shoulder and leg muscles and a considerable static and kinetic ataxia affecting truncal functions and extremities. Hearing was normal. She had a normal female karyotype. A selective deficiency of IgA immunoglobulin (less than 0·1 g/l) was found on routine examination.

FAMILY HISTORY
The patient is the first child of healthy and unrelated parents. A younger sister is normal. Both parents had a normal face without any dysmorphic features or oral or digital malformations. Ultrasonography showed no kidney cysts in the mother. There were no malformations in the close family. However, by history the father’s paternal grandmother had a sister with syndactyly of the feet which seemed to be inherited as a dominant disorder in her part of the family.

Discussion
OFD type I shows X linked dominant inheritance whereas the other types show autosomal recessive inheritance. Fenton and Watt-Smith have pointed out the wide variation in clinical expression of the OFD syndromes and the need to distinguish only between type I and the remaining types. Our patient had the following characteristic features of OFD I: cystic kidney disease, agenesis of the corpus callosum, and preaxial unilateral polydactyly of the foot. She also had irregular mineralisation of the hands and feet, which has been suggested to be pathognomonic of OFD I. However, in addition, she had a tibial pseudarthrosis which has been reported in OFD II only.

Polycystic kidney disease has been described in OFD I only, but not previously in an infant. Most cases have been found by clinical manifestation of renal failure. In a review of six patients with OFD type I, Salinas et al found polycystic kidney disease in three of the six patients, including a mother and daughter. The mother also had liver cysts. The renal cysts were found in the daughter at 10 years of age, which is the earliest diagnosis of polycystic kidney disease in OFD previously reported. In another patient with OFD I described by Stapleton, cysts were found at 11 years. In our patient pathological changes in the kidneys could already be detected at 8 months. Childhood manifestations of autosomal dominant adult polycystic kidney disease (APKD) is also seen, but Bear et al have shown that the probability of ultrasonographic diagnosis of the disease is only 0·11 at ages 0 to 9 years in contrast to 0·39 at ages 40 to 49 years. Linkage studies have shown no evidence of heterogeneity. It is therefore probable that the manifestations of cystic disease at a very early age, as was the case in this patient,
indicates variance in phenotype and not heterogeneity.

In addition to agenesis of the corpus callosum, the patient had atrophy of the cerebellar vermis. Cerebellar anomalies are characteristic features of OFD type VI, whereas other cerebro malformations including agenesis of the corpus callosum are characteristic of type I. However, patients with type VI also have a characteristic forking of the hand metacarpals which this patient lacked.15

In X linked dominant inheritance, the patient will be a mosaic for cells with the normal and cells with the mutated X chromosome as the active X chromosome, and random X inactivation may lead to a random distribution of the malformations. The asymmetrical distribution of the malformations of the extremities is also in favour of X linked inheritance, although this distribution could, in theory, also be found in somatic mosaics for one of the other types of OFD. It is therefore highly likely that this patient has OFD I.

OFD with tibial involvement has been reported by several authors.14-19 Burn et al.20 described two sisters with OFD, bilateral tibial dysplasia, and generalised mesomelia. The defects of the long bones were found to justify a new variant of the OFD syndromes, OFD type IV. However, pseudarthrosis in OFD patients seems to be very rare. Fenton and Watt-Smith described two patients with OFD II and unilateral pseudarthrosis. Another condition associated with pseudarthrosis is neurofibromatosis. Both neurofibromatosis and OFD are associated with hamartomas. It is therefore possible that the pseudarthrosis is the result of hamartomas of the tibia. The presence in this patient of a pseudarthrosis which previously has only been described in OFD II illustrates the difficulty in genetic counselling in the OFD syndromes.
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