SYNDROME OF THE MONTH

Otopalatodigital syndrome type II

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Otopalatodigital syndrome type II (OPD type II) is a rare, severe, X linked, semidominant skeletal dysplasia with characteristic facies, limb defects, and radiological abnormalities. Carrier females may have mild features of the condition. Otopalatodigital syndrome type I (OPD type I) has similar, but milder, dysmorphic features, as well as less severe radiological changes. OPD type II has many similarities to the severe form of Melnick-Needles syndrome seen in males, and it is possible that these two conditions are allelic.

Historical introduction

The combination of abnormal ears, cleft palate, microstomia, flexed overlapping fingers, and syndactyly in two male sibs was first reported by Fitch *et al*¹ in 1976. One of these sibs also had polydactyly. With the subsequent reporting of similar cases,² the term otopalatodigital syndrome type II was adopted in 1983 by Fitch *et al*.³ Since then, only a further seven convincing cases have been reported.⁴⁻⁶ We have recently seen another case

(figs 1 to 7) and have reviewed the clinical and radiological features found in this condition.

Major clinical features**CRANIOFACIAL**

At birth, the infants have characteristic facies (fig 1) with downward slanting palpebral fissures and hypertelorism, severe micrognathia, microstomia and cleft palate, posteriorly rotated ears, and a flat nasal bridge. Widely separated sutures and a large anterior fontanelle are also commonly found.

Affected boys frequently do not survive the

Figure 1 Facial appearance in neonate with OPD type II showing hypertelorism, broad nasal bridge, microstomia, and micrognathia.

Figure 2 The same child as in fig 1 at 15 months of age showing severe micrognathia and posteriorly rotated ears.

Figure 3 Flexed fingers and postaxial polydactyly.

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Figure 4 Bowing of the forearm with skin dimple over ulna.

neonatal period, the main cause of death being respiratory difficulties owing to recurrent aspiration and infection.² Fig 2 shows our case at 15 months of age with persisting severe micrognathia and low set, posteriorly rotated ears.

LIMB ABNORMALITIES

Flexed, overlapping fingers with postaxial polydactyly and variable degrees of syndactyly are characteristic (fig 3). The long bones are bowed (fig 4) and the hips may be dislocated. The thumbs and halluces are broad and short (fig 5) and the tips of the fingers broad. Occasionally, the halluces may be absent.⁶

Figure 5 Broad hallux.

Figure 6 Chest x ray showing sinuous ribs.

OTHER FEATURES

Various other features have been described in individual case reports, and these include dental abnormalities,³ pectus excavatum,^{3,4} cryptorchidism,² hydronephrosis,¹ and a mixed type of hearing loss.^{2,3}

Radiological features

Radiographs of the skull show poorly ossified membranous bones with dense supraorbital margins and petrous bone.¹ Wormian bones may be present.^{3,7} The mandible is usually hypoplastic with an obtuse angle.

The long bones are dense and abnormally curved, with cortical thickening at the site of curvature. Dislocation or subluxation of the hips, knees, elbows, and wrists is common. The thorax is narrow and the ribs 'sinuous', that is, wide posteriorly, narrowed in their middle portion, and then widened again anteriorly (fig 6).

The hands and feet show a wide range of abnormalities. These include hypoplastic metacarpals and metatarsals, short, thick phalanges, and various abnormalities of the distal

Figure 7 Radiograph showing bifid distal phalanx of thumb.

phalanx of the thumb (fig 7). The presence of a transverse capitate bone (an extra bone in the capitate-hamate complex) and clinodactyly of the second finger have also been described. Dysharmonic bone maturation, with retarded carpal age and advanced phalangeal age, is also seen.

The spine may show non-specific abnormalities, such as kyphosis/scoliosis and flat vertebral bodies, as well as failure of fusion of some neural arches and spondylolysis. The evolution of these radiological features is poorly documented, but generally the prognosis for the bony abnormalities is good.³ The curvature of the long bones lessens with age, and the osteosclerosis, with the exception of the skull, also improves.

Prognosis

Postnatal growth failure is a common feature in survivors. The case reported by Fitch *et al*⁸ had normal psychomotor development and intelligence at 6 years of age. The development of our case (now aged 18 months) also seems to be within the normal range.

The limb abnormalities are usually amenable to surgery and the curvature of the long bones lessens as the child grows.^{3,7}

The two half brothers reported by Kozlowski *et al*⁷ had mild mental retardation. There seems to be considerable variation in the severity of the condition; our case appears to be mildly affected, whereas the cases of Andre *et al*² all died within a few weeks of birth.

Inheritance

Inheritance is X linked semidominant. Carrier females may exhibit mild dysmorphic features such as broad face, antimongoloid slant of the palpebral fissures, and a cleft palate or bifid uvula.² Radiological features, such as hyperostosis of the skull bones, may also be present.²

Differential diagnosis

Otopalatodigital syndrome type II shows a considerable degree of overlap with several other skeletal dysplasias. These include Melnick-Needles syndrome, OPD type I, Yunis-Varon syndrome, and atelosteogenesis type III.

OPD type II shows many similarities to the severe form of Melnick-Needles syndrome seen in males. Melnick-Needles syndrome is usually seen in females, and appears to be inherited as an X linked dominant condition, the disorder being invariably lethal in hemizygous males born to affected females.^{8,9} Affected males who survive would appear to be new mutations.⁹ Similarities to OPD type II include a small mandible, hypertelorism, and full cheeks, and similar radiographical changes such as poor calvarial ossification, thin irregular ribs, and curved long bones. Severely affected males with Melnick-Needles syndrome may also have exomphalos, exophthalmos, mandibular hypoplasia, hypoplastic or absent halluces, and more severe radiological

changes.^{9,10} The limb abnormalities in particular are very similar to the changes seen in the case of OPD type II described by Ogata *et al*.⁶

OPD type I is generally a milder, X linked, semidominant condition, with a better prognosis for long term survival.¹¹ The clinical features include mild mental retardation, short stature, cleft palate, and 'pugilist' facial appearance with a broad nose, depressed nasal bridge, and hypertelorism. Affected subjects also have a prominent forehead, a small jaw, and 'tree frog' appearance of the hands and feet, with short thumbs and halluces, clinodactyly of the digits, and broad terminal phalanges. Polydactyly is not a feature of the condition. Hearing problems are usually of a conductive nature owing to abnormalities of the middle ear ossicles and the cleft palate. There is a generalised bone dysplasia which is less severe than that seen in OPD type II.¹²

The autosomal recessive syndrome described by Yunis and Varon^{13,14} has a number of features in common with both OPD type II and the severe form of Melnick-Needles syndrome, but facially it is quite distinct. There is poor ossification of the calvaria and micrognathia, variable soft tissue syndactyly, absence of the thumbs and halluces, and various radiological abnormalities (such as thin ribs and thin diaphyses of the long bones). However, cleft palate, microstomia, and marked curvature of the long bones are not found, and distal aphalangia and hypoplasia or aplasia of the clavicles are characteristic. All the patients described with the Yunis-Varon syndrome to date have died in the neonatal period.

Atelosteogenesis type III (AO type III), a short limbed dwarfism recently delineated by Stern *et al*,¹⁵ has a number of clinical and radiological features in common with OPD type II, but affects both males and females, and to date only sporadic cases have been reported. Clinical features such as hypertelorism, midface hypoplasia, a flat nasal bridge, microstomia, micrognathia, and cleft palate are seen in both conditions. However, the radiological features are quite distinct and permit differentiation. In AO type III during infancy, the proximal phalanges are large and wide, with a characteristic 'tombstone' appearance. The distal phalanges are short and block-like. Abnormalities of skull ossification are not seen in AO type III, and the spinal changes, typically mild in OPD type II, are more varied and severe in AO type III. Finally, in AO type III the pelvic abnormalities consisting of hypoplastic and rounded iliac wings with an inferior projection are in marked contrast to the tall narrow iliac wings seen in OPD type II.

Conclusion

The phenotypic expression of OPD types I and II seems to be consistent within male sibships,^{1,2,4,7,11,12} suggesting that they are, indeed, separate conditions. As yet, there are no definite reports of affected sibs with the severe form of Melnick-Needles syndrome, although a recent abstract¹⁶ in which a provisional diagnosis of OPD type II was made in two grossly

abnormal male offspring of a dysmorphic mother may well turn out to be Melnick-Needles syndrome on review.

The clinical and radiological similarities between OPD types I and II and Melnick-Needles syndrome suggest possible allelism at a common locus, but further linkage and molecular studies are needed to investigate this possibility.

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