Craniofrontonasal dysplasia

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The term 'craniofrontonasal dysplasia' (CFND) was introduced by Cohen¹ in 1979 when describing a 14 year old girl with coronal craniosynostosis, hypertelorism, limitation of shoulder movement, and digital abnormalities. The child's mother was also affected. In the same volume of *Birth Defects*, Slover and Sujansky² reported similar findings in three female sibs, both of whose parents had hypertelorism, as did the paternal grandmother.

These papers established CFND as a distinct entity. Subsequent reports have expanded the phenotype to include numerous trunk and limb abnormalities.^{3–6} This condition is probably not

exceedingly rare. Approximately 25 cases from 10 families have been well documented, as reviewed recently by Sax and Flannery⁴ and Kumar *et al.*,⁵ and the abstract by Reich *et al.*⁶ provides brief details of a further 21 cases. The author is aware of three cases in Leicestershire which has a population of 850 000.

Clinical features

There is evidence that CFND may show considerable variation in severity even within a family. The following observations are based on a review of published and personally encountered patients showing marked dysmorphism and in whom the diagnosis is undoubted.

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FIG 1 AP and lateral views of a patient aged three months. Note the facial asymmetry and absent nasal tip. (Reproduced with permission from *Clinical Genetics* 1984;25:473.)

CRANIOFACIAL

The skull usually shows brachycephaly (82% of cases), presumably as the result of premature coronal synostosis. Plagiocephaly, acrocephaly, and dolichocephaly have also been noted. Frontal bossing is characteristic and may be asymmetrical (fig 1). A low hairline posteriorly and a widow's peak anteriorly are found in over 50% of patients.

Orbital hypertelorism occurs in all patients recognised as having CFND and has been noted in otherwise normal relatives, a point discussed in the section on inheritance. The palpebral fissures may slope downwards (figs 1 and 2) or upwards (fig 3). Two of the three patients known to the author have strabismus. The nose has a broad root and bifid tip. Overt facial clefting is unusual, but the palate is often high arched (81%) and the teeth may be widely spaced and malerupted.

THORACIC

Some patients show no thoracic involvement. Others have striking abnormalities (figs 2 to 4) with neck webbing (40%), rounded shoulders (95%), abnormal and occasionally asymmetrical clavicles (52%), and raised scapulae (52%). These percentage figures are derived from the abstract by Reich *et al.*⁶ One of the unpublished cases known to the author has a scoliosis, pectus excavatum, and asymmetrical breast development (fig 2).

FIG 3 Face and trunk of a seven year old patient. Note the upward slanting palpebral fissures, wide mouth, and narrow thoracic inlet.

FIG 2 Face and trunk of a 17 year old patient. Note the striking asymmetry of clavicles and thorax.

FIG 4 Posterior view of the child shown in fig 3. Note the low hairline, rounded shoulders, and high scapulae.

FIG 5 Longitudinal splitting of the nails. This is the same child as shown in figs 3 and 4.

LIMBS

The most commonly reported abnormality is longitudinal splitting of the nails (fig 5). Other abnormalities noted include syndactyly, preaxial polydactyly, clinodactyly, deviated distal phalanges of the fingers and toes (fig 6), digital hypoplasia (fig 6), and a wide space between the first and second toes. The patient shown in fig 2 had both pre- and postaxial polydactyly involving the left and right feet respectively.

FIG 6 The feet of the patient shown in fig 2. Note the hypoplastic hallux and distal deviation of the other toes.

Differential diagnosis

This will embrace all conditions in which craniosynostosis occurs. A useful review is provided by Cohen.⁷ Hypertelorism may occur in the Apert and Crouzon syndromes, which should be readily distinguishable from CFND by careful examination of the limbs and thorax.

Hypertelorism, frontal bossing, and polydactyly also occur in the acrocallosal syndrome, described by Schinzel and Schmid,⁸ in association with agenesis of the corpus callosum and severe mental retardation. This disorder shows clinical overlap with the Greig cephalopolysyndactyly syndrome.⁹ Frontofacionasal dysostosis¹⁰ also features in the differential diagnosis and is characterised by a severe midline defect of the face, major eyelid malformations, and autosomal recessive inheritance.

Natural history

Most published cases and the three children known personally to the author have been of normal intelligence. Mild developmental delay was noted in the three sibs reported by Slover and Sujansky,² and the affected mother of the proband described by Kumar *et al*⁵ was educationally subnormal. It is not clear whether mild intellectual impairment represents a primary manifestation of CFND or is secondary to the effects of premature fusion of the skull sutures.

Inheritance

CFND has been noted to show vertical transmission in several families, but insufficient data are available

to establish with certainty the exact mode of inheritance. Several theories have been proposed to explain the marked excess of affected females over affected males. These include metabolic interference,¹¹ sex linked dominance with male lethality,¹² and segregation distortion analogous to the T locus in mice.⁴

Examples of male to male transmission have been reported⁶ making both sex linked and cytoplasmic inheritance untenable unless CFND is aetiologically heterogeneous. It has been suggested that affected males may show only very mild features of the condition, for example, borderline hypertelorism, and that appropriate males in these families should be carefully assessed both clinically and radiologically³ (R J Gorlin, 1986, personal communication).

For practical purposes any patient with CFND should be alerted to a risk of at least 50% for offspring, particularly if the fetus is female. In view of the severe cosmetic problems associated with this disorder some families might feel that prenatal diagnosis would be justified using ultrasonography or fetoscopy or both, with the option of termination if severely affected.

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