Frontometaphyseal dysplasia: autosomal dominant or X-linked?

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SUMMARY The clinical and radiographic manifestations in a 45-year-old male with frontometaphyseal dysplasia (FMD) are documented and depicted. Deafness and degenerative osteoarthropathy in weight-bearing joints were the main clinical problems. Widespread patchy cranial sclerosis was reminiscent of Paget's disease, while digital deformity resembled rheumatoid arthritis.

On the basis of a review and tabulation of published reports, evidence emerges to support the concept of X-linked inheritance. The relationship between FMD and osteodysplasty remains a matter for speculation.

Frontometaphyseal dysplasia (FMD) is a rare condition in which a marked supraorbital prominence is associated with widespread modelling defects of the skeleton. The mandible is small with anterior constriction, and irregularity of the teeth may result in malocclusion. The limbs are long in proportion to the trunk and genu recurvatum is usually present. Progressive contractures develop in the digits and other inconsistent stigmata include muscle wasting, scoliosis, and genu valgus. Deafness often occurs but there is no involvement of the other cranial nerves. General health is good.

FMD was delineated by Gorlin and Cohen¹ and about 13 affected subjects have now been reported. The eldest of these was 23 years of age and the majority were children. In this paper we have documented the clinical and radiographic features in middle age. There has been considerable speculation concerning the genetic background of FMD and in an attempt to resolve this problem we have reviewed previous publications and tabulated relevant information.

Case report

DdW, an unmarried Afrikaner male born in 1929, presented at the age of 45 with progressive bilateral mixed deafness. His general health was good and apart from osteoarthropathy in the left knee and hip of several years' duration there had been no significant illness in the past.

He was 184 cm in height with mild disproportion-

tionate lengthening of the limbs and marked genu recurvatum. The inferior region of his forehead projected anteriorly and his lower jaw was small and narrow (fig 1). In the hands, the metacarpophalangeal joints were expanded with slight flexion and

FIG 1 DdW at the age of 45. The supraorbital region is very prominent and the mandible is constricted anteriorly. The limbs are disproportionately long in relation to the trunk.

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ulnar deviation of the digits. Similar abnormalities were present in the toes. These changes resembled rheumatoid arthritis but movements were full and painless and there was no evidence of inflammation. Apart from moderate deafness, the central nervous system was intact and no other abnormalities were found on clinical examination.

The patient's widowed mother, his younger brother, and his two younger sisters were all examined and found to be normal. The offspring of his sibs were said to be unaffected.

X-ray studies showed extensive Paget-like patchy sclerosis of the skull, with a visor-like anterior projection of the supraorbital region (fig 2). The vertebrae were dysplastic with mild flattening and irregularity of their endplates (fig 3). The pelvis was distorted with constriction of the cavity and flaring of the ilia (fig 4). The metaphyses of the long bones showed mild undermodelling (fig 5). The femoral necks were widened and the tibia and fibula had pronounced backward bowing. The phalanges lacked the normal midshaft constriction.

FIG 2 Lateral x-ray of the skull. The calvarium shows patchy sclerosis and a dense frontal prominence.

FIG 3 Lateral x-ray of the lumbar spine. The vertebral bodies are flattened and their endplates are irregular.

FIG 4 AP x-ray of the pelvis. The pelvic inlet is distorted and the iliac crests are flared.

FIG 5 AP x-ray of the proximal portion of the right humerus. The metaphyseal region is undermodelled.

TABLE Previous reports of frontometaphyseal dysplasia

Authors	Patients			
	Sex	Age when studied	Country of origin	Family history
Gorlin and Cohen ¹	M	19	USA	Parents, sister, and 2 brothers normal. No consanguinity
Danks <i>et al</i> ²	M	5-12	Australia (Italian stock)	Parents and younger brother normal. No consanguinity
Holt <i>et al</i> ³	M	11-18	USA	Mother and brother normal. No consanguinity
	F	6-13	USA	No affected kin. No consanguinity.
Arenberg <i>et al</i> ⁴	M	22	} Previously reported by Holt <i>et al</i> ³	
	F	17		
Danks and Mayne ⁵	M	15	} Previously reported by Danks <i>et al</i> ²	
Sauvegrain <i>et al</i> ⁶	M	11	France	Parents and sister normal
Jervis and Jenkins ⁷	M	18	USA (Negro)	Half brothers. Mother normal. Different fathers
	M	22	USA (Negro)	3 normal sisters
Kassner <i>et al</i> ⁸	M	8	USA (mixed ancestry)	Mother had minor x-ray changes. Half sister normal
	M	23	} Previously reported by Jervis and Jenkins ⁷	
	M	17		
Weiss <i>et al</i> ⁹	M	10	USA	Mother had minor stigmata. Father, half sib, and grandparents normal.
Von Kleinsorge and Böttger ¹⁰	F	16	Germany	Parents and sibs normal
Medlar and Crawford ¹¹	M	13	USA	Mother and 2 male sibs mildly affected

FIG 6 AP x-ray of the hand. The phalanges show marked undermodelling.

Routine biochemical investigations, including serum calcium, phosphorus, and alkaline phosphatase estimations, yielded normal results. Urine analysis and haematological parameters were also normal.

Studies of bone histology were undertaken on sections of petrous temporal bone which were obtained during an operation for decompression of the eighth cranial nerve. All fragments showed dense lamellar bone of a cortical type. The Haversian

systems were normal and had evidence of osteoclastic resorption. In a few peripheral areas, tongues of dense acellular fibrous tissue extended between plates of lamellar bone.

Discussion

Pertinent details of previously reported patients and their kindreds are shown in the table. There has been only one instance of affected full sibs, and no mention of any parental consanguinity. Some subjects have been described more than once in publications and it is hoped that this table will be of value in the clarification of this situation.

The genetic background of FMD has not been established with certainty but generation to generation transmission has been mentioned at least three times.^{8-9,11} These reports all concerned affected mothers and sons and in each instance the manifestations in the mothers were comparatively mild. Thus, although at first sight inheritance seems to be autosomal dominant with variable expression, these pedigrees could also be indicative of X-linked inheritance with partial expression in the carrier female. The overwhelming preponderance of sporadic males in other case reports is in accordance with this contention.

Metacarpal pattern profile analysis, which was developed by Poznanski *et al*¹² was undertaken in hand radiographs of four FMD patients by Holt *et al*³ and Weiss *et al*.⁹ Similar results were obtained in each instance but the findings were very different in the mildly affected mother of the boy reported by the latter authors. This observation might be taken as evidence for X-linked inheritance.

Support for the concept of X-linked inheritance

was also provided by Jervis and Jenkins,⁷ who described two Negro half-brothers with different fathers born to an ostensibly normal mother. Intelligence is usually unimpaired in FMD but, as these half-brothers were mentally retarded, it is possible that this phenotypic variation is indicative of heterogeneity and that there are distinct autosomal dominant and X-linked forms of FMD. So far, this situation remains unresolved. As yet, no studies of Xg blood groups have been reported in kindreds who ostensibly have X-linked FMD.

FMD has many features in common with another craniotubular dysplasia, osteodysplasty. It is possible that some reported FMD patients really had osteodysplasty and vice versa. Indeed, a boy previously studied by the author falls into this uncertain category.¹³ In view of this similarity, controversy has arisen as to whether or not FMD and osteodysplasty are separate disorders. In this context, it is of great interest that in the original description of osteodysplasty by Melnick and Needles,¹⁴ the manifestations in the 13 affected subjects (9 females and 4 males) in two kindreds were very variable. Several of the case descriptions were scanty, but apart from one doubtful instance, there was no male to male transmission of the disorder in these families. Subsequently, there have been eight case reports of osteodysplasty and all have concerned females, of whom six have been young girls.

It is certainly remarkable that virtually every report of FMD has pertained to a male, while the vast majority of osteodysplasty patients have been females. In view of the great similarity between these conditions, it is tempting to speculate that they might be the same entity and that the mildly affected females have been labelled 'osteodysplasty', whereas the more severely affected males have been designated 'frontometaphyseal dysplasia'.

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