Syndrome of the month

Edited by D Donnai and R Winter

Craniodiaphyseal dysplasia

L A Brueton, R M Winter

Craniodiaphyseal dysplasia is a very severe bone dysplasia characterised by massive generalised hyperostosis and sclerosis, especially involving the skull and facial bones. Progressive bony encroachment upon cranial foramina leads to severe neurological impairment in childhood.

In 1958, Joseph *et al*¹ described a child with severe sclerosis of the skull and facial deformity, noted the similarity of features to a case reported previously by Halliday,² and termed the condition progressive craniodiaphyseal dysplasia. At that time they considered it to be a variant of Camurati-Engelmann disease. Gorlin *et al*³ delineated the syndrome and cited published cases which had previously been described as cases of leontiasis ossea (craniofacial bony deformity leading to lion-like appearance).^{1 2 4 5} In 1974, MacPherson⁶ described three cases of craniodiaphyseal dysplasia, pointed out the variable manifestations of the condition, and emphasised the overlap in phenotype of CDD with some of the other craniotubular dysplasias and hyperostoses. He concluded that “perhaps the name craniodiaphyseal dysplasia should refer to a group of diseases”. CDD remains a rare disorder with fewer than 20 case reports published.

This review is based on previously published cases and one new unreported case (table).

Clinical features

CRANIOFACIAL ABNORMALITIES

Typically, patients with craniodiaphyseal dysplasia present in early infancy with facial abnormalities. Bony overgrowth results in paranasal bossing, apparent hypertelorism, and an increased head circumference. Recurrent dacryocystitis occurs in association with

progressive stenosis of the nasolacrimal ducts. The disorder is progressive. Fig 1 shows the evolution of the facial changes over a four year period.

Affected infants may come to medical attention because of respiratory difficulty owing to nasal obstruction before the characteristic facial appearance has developed.

NEUROLOGICAL ABNORMALITIES

Bony encroachment upon cranial foramina causing cranial nerve compression (especially of II and VIII) leads to progressive visual and auditory impairment, with ultimate blindness and deafness. Other reported ocular problems include strabismus, exophthalmos, and loss of binocular vision, in association with increasing hypertelorism. Seizures may occur^{2 5} and mental retardation has been reported.^{2 4 5} However, in the majority of cases developmental progress was normal until hindered by progressive deterioration in vision and hearing.

GENERAL MANIFESTATIONS

Growth may be markedly retarded^{4 5} and delayed sexual maturation has been reported.⁵

Radiographical manifestations (figs 2 to 4)

The whole skull, including the facial bones and mandible, shows severe sclerosis and hyperostosis with nasal obstruction and obliteration of the sinuses. Eventually, normal contours are lost in a thickened, homogenous opacity. The appearance of the long bones varies in severity and distribution from patient to patient, but the long bones are generally cylindrical in appearance because of diaphyseal, endosteal, cortical thickening, and exhibit a lack of modelling. The bones of the hands may be similarly affected. There is usually moderate thickening and sclerosis of the ribs, clavicles, and pelvis. Sclerosis of the spine has been found in some cases, the changes being more

The Kennedy Galton Centre, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ.
L A Brueton, R M Winter
Correspondence to Dr Brueton.

Summary of findings in patients with craniodiaphyseal dysplasia.

Features	Case					
	1 ⁴	2 ²	3 ⁵	4 ⁶	5 ⁹	6 ¹²⁻¹⁵
<i>Clinical</i>						
Developmental delay/ learning difficulties	Learning difficulties	Speech delay	Global delay	Global delay	—	Speech delay
Short stature	+	—	+	+	—	
Increased head circumference	+	+	+	+	+	+
Raised intracranial pressure	—	+	+	+	?	+
Cranial nerve palsies	—	VIII	—	—	—	I
Hearing impairment	+	+	+	+	+	
Visual impairment	Severe myopia, bilateral nystagmus	Optic atrophy, progressive loss of vision, nystagmus	Pale discs, vision moderate, proptosis	Optic atrophy, progressive visual loss	Optic atrophy, progressive visual loss	Strabismus, papilloedema, optic atrophy
Occlusion of lacrimal ducts		+	+	+	+	+
Hypertelorism	+	+	+	+	+	+
Facial distortion	+	+	+	+	+	+
Marked enlargement of maxilla and mandible	+	+	+	+	+	+
Nasal obstruction	+	+	+	+	+	+
Maleruption of teeth	—	+	+	+	—	—
Other	—	—	RV failure	—	—	Spastic paraparesis
<i>Radiographical</i>						
Cranial and facial sclerosis	+	+	+	+	+	+
No aeration sinuses and mastoid	+	+	+	+		
Diaphyseal expansion	+	+	+	+	+	+
Metaphyseal abnormalities	—	—	—	—	+	
Spinal involvement	+	+	—	+	+	
Delayed bone age			+			
<i>Biochemical</i>						
Calcium	Normal	Normal/low	Normal	Normal	Normal	Normal
Phosphorus	Normal	Normal	Normal	Raised	Raised	Raised
Alkaline phosphatase	—	—	Raised	calcitonin	Mg acid phosphatase	c'AMP
<i>Other</i>						
Progression	+	+	+	+	+	+
Survival	Alive at 11 y	Died at 10 y	Died at 13 y	Alive at 8 y	Died at 16 y	Alive at 7 y

The case reports by de Souza¹⁶ and Briani and Cavaliere¹⁷ have not been included in the table as the diagnosis of CDD is uncertain; Van

marked in the vertebral arches than in the vertebral bodies. Tucker *et al*⁷ described the evolution of the radiographical changes in CDD and showed variation in the distribution of increased bone density over a five year period, with the abnormalities in the long bones and spine becoming less pronounced, while the sclerosis of the skull increased.

Management and prognosis

Affected subjects develop severe problems with progressive bony encroachment upon cranial foramina and nasal passages leading to deafness, blindness, and respiratory difficulty.

In one case a possible disturbance of thyrocalcitonin metabolism was suspected and a total thyroidectomy performed in an attempt to halt the continuous deterioration.⁶ However, histologically the thyroid was found to be normal and the disease continued its relentless progress.

Surgical decompression of cranial foramina is

possible but the risk of brain stem compression caused by postoperative oedema is high, and such procedures are only of short term benefit as the bony overgrowth inevitably recurs.

Successful treatment of progressive loss of vision in craniometaphyseal dysplasia by optic nerve decompression in conjunction with administration of human calcitonin has been reported.¹⁸ Partial responsiveness of CDD to therapy with synthetic calcitonin has been suggested by a report of a fall in the velocity of increase in head circumference and changes in serum total and bone isoenzyme alkaline phosphatase in one case.⁸ However, side effects of calcitonin therapy include abdominal pain, nausea, and vomiting.

Clinical deterioration is frequently heralded by irritability and episodic early morning headaches. Symptoms of brain stem compression and raised intracranial pressure develop. Cardiac problems related to right ventricular failure may occur.^{5 8} Several severely affected children have died between the ages of 7 and 16 years.^{2 5 8 9}

Case						
7 ⁷	8 ¹	9 ¹¹	10 ¹¹	11 ¹⁰	12 ⁸	13 (our case)
+	—	—	—	Speech delay	Speech delay	—
—	+	—	—	—	—	—
+	+	+	—	+	+	+
+	+	—	—	+	+	—
+	?	VII	VI, VII, ?X	I, II, VII, VIII	+	VII, VIII
Papilloedema	Optic atrophy, progressive visual loss, strabismus	+	+	+	Papilloedema, optic atrophy, squint, proptosis, loss of binocular vision	+
+	+	—	—	+	+	+
+/-	+	+	Paranasal bossing only	+	+	+
+	+	+	+	+	+	+
+	+	—	—	—	—	—
—	—	—	—	Spastic tetraparesis	Cerebral atrophy RV dilatation	—
+	+	+	+	+	+	+
+	+	+	+	+	+	+
+	—	+	+	+	—	+
+/-	—	+	+/-	+/-	—	+/-
+	—	+	—	—	+	+
Normal	Normal	Normal	Normal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	Normal	Normal	Normal
Raised	Raised	Raised	Normal	Raised	Raised hydroxyproline	Raised parathormone
Alive at 6 y	+ Alive at 7 y	Slowly Alive at 27 y mother of case 10	Alive at 6 mth	+ Alive at 11 y	+ Died at 7 y	+ Alive at 5 y

Buchem's disease should be considered in the former and craniometaphyseal dysplasia in the latter.

Differential diagnosis

Craniodiaphyseal dysplasia must be distinguished from Camurati-Engelmann disease (diaphyseal dysplasia).¹⁹ In infancy differentiation may be difficult although in CDD the gross skull changes overshadow all others, whereas in Camurati-Engelmann disease the degree of craniofacial involvement is generally mild with the major changes occurring in the long bones. The course of Camurati-Engelmann disease is usually characterised by stasis or remission in adulthood, in contrast to the inevitable progression of CDD.

Autosomal dominant inheritance with occasional non-penetrance is well established in Camurati-Engelmann disease.²⁰

The combination of marked craniofacial and diaphyseal hyperostosis is also seen in Van Buchem's disease or 'generalised cortical hyperostosis'; however, the facial changes develop slowly becoming apparent in the second decade with mandibular enlargement being the predominant abnormality, while the head

circumference is only rarely enlarged.⁴¹ MacPherson⁶ discussed the overlap of CDD with some of the other craniotubular dysplasias including craniometaphyseal dysplasia and frontometaphyseal dysplasia. Prominence of the supraorbital ridge with irregular sclerosis throughout the rest of the skull are the typical features described in frontometaphyseal dysplasia that serve to differentiate this disorder from other conditions. There are both autosomal dominant and recessive forms of craniometaphyseal dysplasia. The clinical and radiographical features in the recessive form are much more severe than in the dominant type.³ Cases of recessive craniometaphyseal dysplasia resemble those of craniodiaphyseal dysplasia with similar facial distortion, enlargement of the skull, marked paranasal bossing, obliteration of the sinuses, and bony overgrowth causing cranial nerve compression. Radiological examination of the long bones distinguishes the two conditions. In craniometaphyseal dysplasia there is metaphyseal widening and cortical thinning giving rise to a club shaped con-

Figure 1 The evolution of the facial changes in a child with craniodiaphyseal dysplasia over a four year period. (a) The facial appearance at the age of 2 months. A minor degree of paranasal bossing is evident. (b) Aged 4 years showing the characteristic facies with an enlarged mandible, marked paranasal bossing, and hypertelorism. (c) Profile at the age of 4 years showing macrocephaly and obliteration of the nasal bridge.

figuration of the long bones, whereas in CDD diaphyseal changes give rise to a cylindrical appearance.^{6,7} In view of the considerable overlap between recessive craniometaphyseal dysplasia and craniodiaphyseal dysplasia there remains debate as to

whether the two conditions are separate entities or whether they are part of a disease spectrum.

Genetics and prenatal diagnosis

The clinical manifestations of CDD and disease progression (pattern and speed) are variable and it is quite possible that the condition is heterogeneous, although the question of heterogeneity is difficult to address given the small number of published cases. There appears to be a subgroup with a particularly severe type of CDD characterised by rapid progression in the first decade.^{1 2 5 6 8-10}

Autosomal recessive inheritance has been suggested on the basis of one affected sib pair¹⁶ and a report of parental consanguinity in one case.² However, upon review of the case reported by de Souza,¹⁶ we believe the features to be more compatible with the diagnosis of Van Buchem's disease than with CDD. Schaefer *et al*¹¹ reported an affected mother and child that they considered to have CDD, although the radiographical changes reported are not entirely typical of CDD and overlap with those described in craniometaphyseal dysplasia.¹¹

As the typical features of this disorder are generally not present at birth but gradually evolve during infancy, and the basic defect is unknown, reliable prenatal diagnosis is not possible at present.

In cases where the presenting feature has been respiratory distress, significant thickening and sclerosis of the clavicles have been noted on neonatal chest radiographs.⁸ In view of this observation it would be interesting to look for increased bone density (particularly of the ribs/clavicles) by detailed ultrasonography in at risk pregnancies to see if any early signs of the disorder can be detected.

Pathogenesis

The nature of the basic defect is not known. The earliest metabolic studies in CDD were described by Halliday,² the results of which suggested that increased calcium absorption had an important role to play. Reviewing the metabolic profiles of cases of CDD, the only consistent biochemical abnormality is that serum alkaline phosphatase is typically markedly raised (suggesting that a major abnormality is of grossly excessive osteoblastic activity); calcium and phosphate levels are, however, normal. The urinary excretion of c'AMP has been shown to be raised in one case.

Bonucci *et al*¹² reported the histological findings in bone biopsies from the skull (membranous bone) and pelvis (endochondral bone) of a case of CDD. In both sites many bony trabeculae were very thick and contained variable numbers of osteocytes within large and irregularly shaped lacunae. Almost invariably the trabeculae had very thick, uncalcified osteoid seams. Osteosclerosis was evident in both sites. These

Figure 2 Lateral skull x rays at 2 months (a) and 2 years (b). There is progressive generalised thickening of the calvarium with marked sclerosis of the facial bones and base.

Figure 3 Neonatal AP chest radiograph. The ribs and clavicles are thickened and sclerotic. There is also sclerosis of the spine.

Figure 4 Radiograph of the pelvis and femora at the age of 6 weeks. The femoral shafts are undermodelled and sclerotic.

morphological changes in the bone tissue show overproduction of bone with striking increase in volume on one hand, and poor calcification of the matrix and the presence of thick borders of uncalcified osteoid on the other.

To date, the primary abnormality has not been elucidated, the bone changes are not dependent on the developmental type of bone, and the reported ectopic calcification in voluntary muscle¹² may imply an abnormality in the calcium and phosphate metabolism or a more general connective tissue disorder not confined to the bony matrix.

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