

Dysosteosclerosis: a report of three new cases and evolution of the radiological findings

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We present three patients with dysosteosclerosis with clinical and radiographic changes ranging from birth to 14 years. Dysosteosclerosis (MIM 224300) is a rare bone dysplasia associated with neurodevelopmental deterioration. There is sclerosis and platyspondyly with progressive metaphyseal expansion and alteration of bone density. The early craniotubular bone modelling and clinical presentation resemble osteopetrosis. It was first delineated by Spranger *et al*¹ in 1968. Prognosis is poor. In addition to neurological and psychological deterioration, the children have delayed milestones and are probably retarded from the beginning. They have dysmorphic features with a round face, sagging cheeks, and a prominent forehead. Dentition is abnormal. Optic atrophy from cranial nerve compression develops early and some have fits, even status epilepticus. Skin changes occur in some and consist of red-violet spots over the entire body, with a patchy distribution.² There is sclerosis of the skull base, the ribs (which are wide), clavicles, scapulae, and mid-diaphyses. The metaphyses show progressive expansion and, as in the spine, develop sclerotic islands in areas of relative radiolucency. There is mild platyspondyly with wide intervertebral spaces. The vertebral bodies are small with irregular end plates and pronounced anterior notches. The tubular bones are short with progressive bowing and fractures are a complication.^{3–5} Inheritance is usually autosomal recessive but a large X linked pedigree has been described.⁶

CASE REPORTS

Case 1

Case 1 is a 14 year old Asian girl with short stature and limb deformities. She is blind and mentally retarded without any useful speech. Her weight was 28.2 kg (<3rd centile) and her height was 118.5 cm (<3rd centile). Her parents were healthy and not consanguineous. They have two other children who are alive and well but had a further affected boy (case 2).

She was a term (42 weeks) normal delivery, weighed 3400 g, and was noted at birth to have a bifid right thumb and systolic murmur. Her chest radiograph at that time showed thick bones. Her condition was not discovered until she had follow up radiographs which showed marked osteosclerosis. She was noticed to have limited vision, roving eye movements, and nystagmus soon after birth. When she was 7 months old her length and head circumference were on the 50th centile and weight on the 10th centile. She was mildly developmentally delayed being unable to sit, but had head control and was babbling. She was completely blind. CT brain scan at this time showed thick and dense bones, markedly narrowed optic foramina, normal ventricles, but prominent basal cisterns and frontal subarachnoid spaces. EEG and BERA were within normal limits but ERG and VEP showed gross loss of function of visual pathways. A diagnosis of osteopetrosis was made. Bone marrow transplantation was not performed as there was already significant clinical impairment and no HLA compatible donor was identified.

At the age of 10 months, she was significantly delayed especially in the locomotor area, but was responding to voices

and imitating sounds. She had been making some progress with speech and could say 50 words in both English and Punjabi and form sentences. She regressed and had lost all speech by the age of 7 years with no expressive language. She responded only to keywords.

She had repeated fractures during childhood, often following trivial injury, although in her teens the fracture incidence has reduced. She has had malunion of various fractures with resulting deformity and is confined to a wheelchair. Her carbonic anhydrase estimation (total carbonic anhydrase 17.2 U/mg Hb and carbonic anhydrase II 6.4 U/mg Hb) were within normal limits.

She has developed neither deafness nor bone marrow failure although she suffers from other problems. She appears to be severely developmentally delayed and currently attends a school for children with disabilities. She has also received behavioural therapy. The most striking aspect of her development has been the total speech regression for which there is no explanation.

At the age of 12 years her hearing (only distraction testing) and brain stem evoked potential studies were normal. She had a very high arched palate and tooth eruption was delayed. The only teeth present at this time were the worn deciduous upper and lower central incisors. She has also had persistent and recurrent problems with her teeth with abscess formation, controlled by prophylactic antibiotics. Her immunological profile was normal.

She has had a long standing history of obstructive sleep apnoea. Her poor sleeping pattern has resulted in poor concentration and drowsiness during the day. When she was 14 years old, surgery for her nasal septal deviation and adenotonsillectomy has improved the obstructive sleep apnoea.

The radiographs were all performed at the age of 14 years. The AP and lateral views of the skull showed sclerosis of the base, periorbital sclerosis, but a normal density and thickness of the vault. The dentition was abnormal and the condyles of the mandible hypoplastic and featureless (fig 1A). The thorax was narrow and there was generalised osteosclerosis. The ribs were slightly short, mildly expanded, and featureless. At their posterior ends there was a tongue of very dense bone extending from the costovertebral end towards the shaft. Several fractures were in the process of healing. The lateral view of the spine showed mild platyspondyly, most pronounced in the thoracic region with widening of the intervertebral spaces and an increase of the AP diameters of the vertebral bodies. There was mild vertebral end plate irregularity with concave anterior and posterior surfaces of the vertebral bodies (fig 1B). The pelvis showed generalised sclerosis. The iliac wings were narrow and the femoral necks wide. The long bones of the upper and lower limbs had striking expansion of their metadiaphyses and irregular sclerosis. The mid-diaphyses were uniformly sclerotic and had normal modelling. The metaphyseal ends were irregular and the adjacent epiphyses uniformly sclerotic. There were bowing deformities of the long bones (fig 1C-E). In the hands, the short tubular bones had relative lucency of



Figure 1 (A-F) Skeletal survey of case 1 aged 14 years. (A) Skull, lateral. (B) Spine, lateral. (C) Femur. (D) Tibia and fibula. (E) Upper limb. (F) Hand.

their diaphyses and irregular metaphyses. The epiphyses and carpal bones were densely sclerotic (fig 1F).

Case 2

Case 2 was the affected younger brother of case 1. At the age of 5 weeks he presented with incipient blindness because of optic nerve compression and underwent frontal craniotomy with decompression. He sustained a middle cerebral infarct and had a left hemiplegia. Bone marrow transplantation using a matched unrelated donor was performed at the age of 9 weeks. This failed and a further transplant was undertaken six weeks later. This also failed; he had recurrent septicaemia, CMV chest infections, and went into renal failure. He sustained a further major cerebrovascular accident. Both sides of the brain were affected by this stage resulting in spastic quadriplegia. He died when he was 10 months old.

The radiological evaluation of the chest as a neonate showed diffuse generalised sclerosis with irregularity of the proximal humeral metaphyses. By 3 months of age, the humeral metaphyses showed some expansion with mottled and patchy sclerosis and there was expansion and cupping of the anterior ends of the ribs (fig 2A). At 7 months, the chest showed, in addition to generalised sclerosis, further bulbous expansion of the upper humeral metaphyses and of the anterior ends of the ribs with mottled sclerosis (fig 2B). At the age

of 9 months, the lateral view of the chest showed mild platyspondyly with wide intervertebral spaces. There was prominent vascular notching of the anterior borders of the vertebral bodies. The anterior ends of the ribs were expanded (fig 2C). The radiograph of the pelvis showed a relatively lucent rim of bone around the ilia. The upper limb had bulbous expansion of the relatively lucent proximal metaphysis of the humerus with patchy islands of sclerosis extending into the metadiaphysis. There was diaphyseal sclerosis (fig 2D).

Case 3

Case 3 was an 18 month old child with blindness, developmental delay, failure to thrive, dysplastic pulmonary valves, and pulmonary hypertension. She also had a history of increasing head circumference and progressive lethargy. CT and MRI scans of the brain confirmed ventriculomegaly with no foramen magnum abnormality and a ventriculoperitoneal shunt was inserted. She also had been admitted to intensive care for episodes of respiratory distress. After the use of low flow oxygen at home her quality of life had improved significantly; however, she died of an overwhelming respiratory infection when she was 2 years old.

Radiological evaluation at 6 months of age showed sclerosis with slender ribs and some cupping of their anterior ends. The spine at the same age showed mild platyspondyly with wide

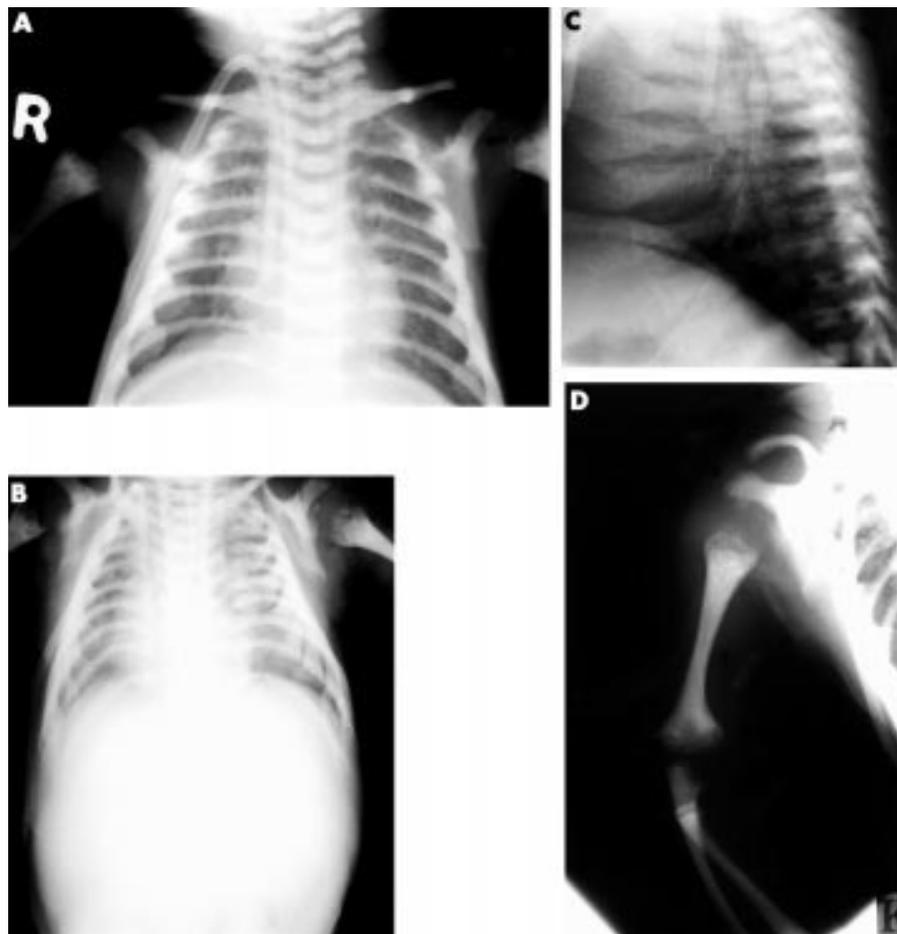


Figure 2 (A-D) Skeletal images of case 2. (A) Chest, 3 months. (B) Chest, 7 months. (C) Lateral chest, 9 months. (D) Upper limb, 7 months.

intervertebral spaces. There was a generalised increase in bone density but the contours of the vertebral bodies were indistinct and there were pronounced anterior notches of the upper lumbar vertebral bodies (fig 3A). In the pelvis, bone density was increased except at the proximal femora and around the margins of the iliac wings and ischia where it appeared reduced. In addition, the upper femoral metaphyses were flared and frayed with indistinct ends. The femoral shafts were mildly bowed. The lucent lines across the superior pubic rami represent the junctions of separate ossification centres, a common normal variant finding (fig 3B). The lower limbs had diaphyseal sclerosis and central sclerosis of the distal femoral epiphyses. The metaphyses were markedly flared and frayed with reduced bone density (fig 3C).

At the age of 1 year, there was normal thickness and density of the skull vault, but the base was sclerotic. The teeth appeared abnormal and the mandibular condyle was hypoplastic (fig 3D). In the chest, there was still generalised sclerosis but there was evidence of fluctuating bone density at the growing ends of the bones with a stippled, flocculated appearance. There was quite striking abnormality of bone modelling with bulbous expansion of the anterior ends of the ribs and proximal humeral metaphyses. The posterior parts of the ribs were slightly expanded with sclerotic, irregular ends and a relatively lucent area adjacent to this (fig 3E). In the spine there was mottled or patchy sclerosis of the vertebral bodies. There was mild platyspondyly with relatively wide intervertebral spaces (fig 3F). There was generalised sclerosis except at the expanded proximal femora and around the iliac wings. The metaphyseal margins and the iliac crests had irregular contours. There were mild bowing deformities of the femora

(fig 3G). In the upper limb, there was diaphyseal sclerosis, bulbous metaphyseal expansion with stippled, relatively radiolucent ossification, and sclerotic irregular metaphyseal ends of the long bones. In the hands, there was relative lucency of the metaphyses (fig 3H).

DISCUSSION

In later childhood, the appearances of dysosteosclerosis are more variable, showing metadiaphyseal expansion, either with osteopenia and cortical thinning or with relative sclerosis and bowing.⁷ At the age of 14 years in case 1, the main diagnostic differentiation is from the intermediate form of osteopetrosis in which there would be a striking bone-in-a-bone appearance.^{8,9} The sclerotic blueprint of the outline of the neonatal bone would be seen in the diaphyseal region of the tubular bones and the epiphyses and carpal bones would have alternating circumferential layers of sclerotic and normal density bone compared with the uniformly dense sclerosis in this case. Bowing of the long bones is not a feature of osteopetrosis, which in case 1 is especially striking in the humeri. The tibiae have an S shaped bowing deformity, a feature of other craniotubular disorders such as metaphyseal and craniometaphyseal dysplasia and osteodysplasty. The clinical presentation with blindness and the subsequent speech and psychological deterioration are all features of dysosteosclerosis. She has not developed deafness or bone marrow failure or hepatosplenomegaly, as would be expected in osteopetrosis. Sleep apnoea and airway obstruction may be seen in patients with sclerosis and overgrowth of the skull base, but in our patient it was related to adenoidal hypertrophy and a deviated nasal septum. No cases of dysosteosclerosis have been

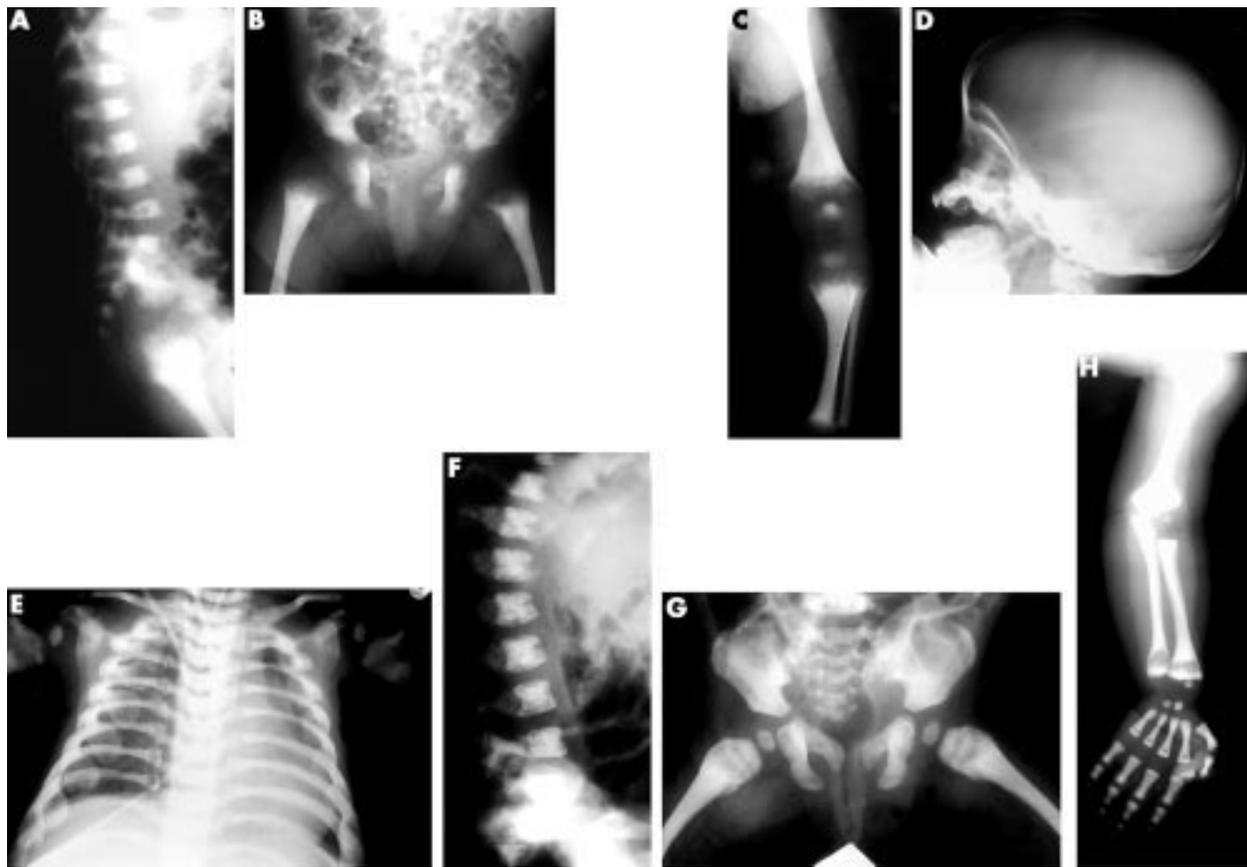


Figure 3 (A-H) Skeletal images of case 3. (A) Lateral spine, 6 months. (B) Pelvis, 6 months. (C) Lower limb, 6 months. (D) Lateral skull, 1 year. (E) Chest, 1 year. (F) Lateral spine, 1 year. (G) Pelvis, 1 year. (H) Upper limb, 1 year.

reported in adults. It is likely that dysosteosclerosis is relatively underdiagnosed with cases incorrectly identified as osteopetrosis,¹ but other cases published as dysosteosclerosis represent different forms of craniotubular disorders.¹⁰

In early childhood, the radiological features differentiating dysosteosclerosis from the infantile forms of osteopetrosis become apparent. In dysosteosclerosis, the metadiaphyses become bulbous and expanded with relative radiolucency but remain sclerotic adjacent to the growth plate, and while abnormal modelling also occurs in osteopetrosis the expanded areas are sclerotic rather than osteopenic and a characteristic bone-in-a-bone appearance develops. In the skull, sclerosis predominantly affects the base in dysosteosclerosis but there is also significant vault sclerosis in osteopetrosis. The prognosis in the severe infantile type of osteopetrosis is poor with a high mortality rate under the age of 2 years. The cause of death is bone marrow failure and overwhelming infection. Bone marrow transplantation is the only treatment shown significantly to improve the course of the disease.¹¹ The success of engraftment and the outcome is dependent on the availability of a suitable HLA match.¹² Successful transplantation results in a gradual reduction of osteosclerosis with return to normal bone modelling.¹³ No new metaphyseal transverse sclerotic striations develop and the bone modelling is normal with no metaphyseal expansion.

In case 2, the progressive mottled metaphyseal sclerosis and expansion are the changes expected in dysosteosclerosis and would not be expected to occur following BMT in patients with osteopetrosis. The evidence of platyspondyly in the thoracic spine is also in favour of dysosteosclerosis. He had at least two major cerebrovascular accidents resulting in cerebral infarction and although this complication has also been described in patients with osteopetrosis,¹⁴ his medical

condition may have contributed. Both bone marrow transplants failed and it is not possible from this isolated case to evaluate the future role of this type of therapy.

In infancy, the majority of cases of dysosteosclerosis are diagnosed as the severe infantile autosomal recessive form of osteopetrosis. However, these patients are not usually anaemic.¹⁵ Clinically, the facial features in osteopetrosis consist of macrocephaly and a square shaped head, frontal bossing, ptosis, and strabismus. Progressive pressure on cranial nerves leads to optic atrophy, deafness, and facial palsy. The teeth are abnormal and decay easily and osteomyelitis of the mandible is a complication. Hypochromic anaemia and pancytopenia develop and hepatosplenomegaly results. Radiologically there is early, generalised osteosclerosis with subsequent development of alternating bands of sclerotic and normal bone density and pronounced anterior vascular notches of the vertebral bodies.¹⁶ In the latest International Classification and Nomenclature of Constitutional Disorders of Bone,¹⁷ two additional forms presenting in infancy are recognised, one with infantile neuroaxonal dysplasia¹⁸ and one with renal tubular acidosis resulting from carbonic anhydrase II deficiency.^{19, 20} The latter condition results in the radiological changes of rickets superimposed on the generalised osteosclerosis of osteopetrosis and is associated with cerebral calcification. The rickets manifest as flared, frayed, relatively osteopenic metaphyses; however, the commoner severe infantile form of osteopetrosis may show pseudorachitic changes at the metaphyses.

The radiological appearances of case 3, at the age of 6 months, have many features consistent with the diagnosis of neonatal autosomal recessive osteopetrosis. However, the marked flaring and fraying of the metaphyses has the appearance of rickets and would raise the diagnostic possibility of the

carbonic anhydrase II deficiency type of osteopetrosis. The bone density at the metaphyses in this case appears to be less than normal and the degree of flaring and fraying present here would be unusual in the common neonatal form of osteopetrosis but would be consistent with the carbonic anhydrase II deficiency form. Platypondyly, however mild, associated with increased width of the intervertebral spaces is not a feature of the different forms of neonatal osteopetrosis.

The features at the age of 1 year which differentiate case 3 from osteopetrosis are the normal skull vault with no sclerosis, the bulbous expansion of the rib ends and metaphyses, and the patchy, sclerotic nature of the ossification in these areas and in the spine with mild platyspondyly. Early bowing deformities of the femora are present. In addition, the characteristic bone-in-a-bone appearance usually seen in the metacarpals, other tubular bones, and vertebral bodies in osteopetrosis is not present. The bulbous metaphyseal expansion is quite unlike the fluctuating modelling abnormalities of osteopetrosis, in which mild localised widening occurs in association with periods of bone sclerosis, resulting in alternating sclerotic transverse metaphyseal bands. Widening does not occur in areas of normal or relatively reduced bone density.

The role of bone marrow transplantation in this condition remains unclear. It is possible that the skeletal component may be improved; however, it is unlikely that the progressive unexplained neurological deterioration will respond to bone marrow transplantation. Its role in future management of dysosteosclerosis requires further evaluation.

Infantile osteopetrosis is a genetically heterogeneous disease. Currently, two different genes have been identified, one encoding a specific subunit of a vacuolar proton pump, *TCIRG1*, located in 16p13^{21,22} and the other, *CLCN7*, located in 11q13.4-q13.5.²³ The milder, adult, autosomal dominant form of osteopetrosis has been considered to be genetically homogeneous, also located in 16p13.²⁴ Dysosteosclerosis has some clinical and radiological features which overlap with the different forms of osteopetrosis. It will be interesting to see whether patients with dysosteosclerosis will link with either of these genes.

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