A review of the osteopetroses

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Summary

The osteopetroses are a group of conditions which are characterized by varying combinations of bony sclerosis and modelling defects. Classical osteopetrosis may be inherited as an autosomal dominant or autosomal recessive: the former variety is benign, heterogeneous and comparatively common, while the latter is precocious, potentially lethal and rare.

Many other craniotubular dysplasias and hyperostoses are loosely grouped with the osteopetroses. The commonest of these is the autosomal dominant form of craniometaphyseal dysplasia, while the others which are well known include Pyle disease, and van Buchem disease. Sclerosteosis is a progressive condition in which massive cranial thickening is associated with syndactyly and gigantism.

Each of these disorders has specific clinical and radiographic features, which permit recognition. Diagnostic accuracy is crucial for treatment, prognostication and effective genetic management.

Introduction

In the wide sense, the term 'osteopetrosis' embraces a group of uncommon genetic disorders which are characterized by increased skeletal density and abnormalities of bony modelling. With the accumulation of clinical, radiographic and genetic data it has become obvious that this loose category contains a number of separate conditions. Some of these are comparatively benign, while others have a progressive course and fatal outcome. For this reason, diagnostic accuracy is crucial.

As many of these conditions are extremely rare, this review is confined to those which have been

encountered by the authors in clinical practice, and which were discussed at the Bristol symposium.

Nomenclature

Initially, conditions of this type were often lumped together under the designation 'Albers-Schönberg disease', 'marble bones' or 'osteopetrosis'. However, specific entities have now been delineated from within these groups. Although considerable nosological confusion remains, a critical analysis undertaken by Gorlin, Spranger and Koszalka (1969) did much to clarify the situation.

The classification which follows is based upon a synthesis of this analysis and the Paris' nomenclature for constitutional disorders of bone (McKusick and Scott, 1971). In keeping with modern usage, the possessive forms of eponymous designations have been discarded, and wherever possible a descriptive title has been employed.

(1) Osteoscleroses

Sclerosis predominates and changes in bony configuration are of minor degree. Osteopetrosis with precocious manifestations (autosomal recessive type); osteopetrosis with delayed manifestations (autosomal dominant type—heterogeneous); pycnodysostosis.

(2) Craniotubular dysplasias

Abnormality of modelling of long bones associated with sclerosis of the cranium. Metaphyseal dysplasia (Pyle); craniometaphyseal dysplasia—autosomal dominant and recessive forms; craniodiaphyseal dysplasia; frontometaphyseal dysplasia; dysosteosclerosis; oculo-dental-osseous dysplasia; tubular stenosis (Kenny-Caffey); osteodysplasty (Melnick-Needles).

(3) Craniotubular hyperostoses

Skeletal deformity results from bony overgrowth

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rather than defective modelling. Endosteal hyperostosis (van Buchem); sclerosteosis; osteoectasia with hyperphosphatasia; diaphyseal dysplasia (Camurati-Engelmann); infantile cortical hyperostosis (Caffey).

(4) Miscellaneous sclerosing and hyperostotic disorders

Other conditions which have a proved or possible genetic background and in which abnormalities of bony thickness or modelling are features. Osteopathia striata; osteopoikilosis; melorheostosis; pachydermoperiostosis; osteitis deformans (Paget).

(1) Osteoscleroses

Osteopetrosis with precocious manifestations (autosomal recessive type)

Clinical features. The manifestations of the autosomal recessive, precocious, malignant or congenita form of osteopetrosis are evident during infancy. Bony overgrowth is associated with marrow dysfunction and presenting symptoms include failure to thrive, spontaneous bruising, abnormal bleeding and anaemia. Hepatosplenomegaly develops and palsies of the optic, oculomotor and facial nerves may occur in the later stages.

Resistance to infection is diminished, the teeth become carious, and osteomyelitis of the jawbone is not uncommon. Bony fragility is often a feature, with painless pathological fractures.

Death from overwhelming infection or haemorrhage usually takes place in the first decade. However, there have been reports of atypical individuals who have survived to adulthood.

Radiological features. Generalized bony sclerosis is the predominant radiological feature. Penetrated films of long bones reveal transverse bands in the metaphyseal regions and longitudinal striations in the shafts.

As the condition progresses, the ends of the long bones, particularly the proximal humerus and distal femur, develop a flask-shaped configuration (Fig. 1).

Sclerotic foci termed 'endobones' or 'bones within a bone' form in the vertebrae, pelvis and distal long bones. These distinctive abnormalities are pathognomonic of osteopetrosis.

The skull becomes progressively thickened, the base being more severely affected than the calvarium. Encroachment upon the foramina of the cranial nerves may be demonstrable.

In the spine, thickening of the vertebral end plates gives rise to the characteristic 'rugger jersey' appearance (Fig. 2). (The jersey worn by rugby players traditionally carries transverse bands as this configuration produces an illusion of increased body bulk, thereby disconcerting the opposition.)

Genetics. There is little doubt that this form of osteopetrosis is inherited as an autosomal recessive.

FIG. 1. Anteroposterior radiograph of the lower limbs of an infant with the autosomal recessive 'precocious' form of osteopetrosis. The distal end of the femur has a flask-like configuration, with lucent transverse metaphyseal bands.

Affected siblings with normal parents have been observed in an inbred kindred (Enell and Pehrson, 1958), the condition has been noted in monozygotic twins (Hesseling, 1958) and parental consanguinity has been recorded (Tips and Lynch, 1962).

Osteopetrosis with delayed manifestations (autosomal dominant type)

Clinical features. The designation 'Albers-Schönberg disease' pertains to the autosomal dominant delayed, tarda or benign form of osteopetrosis. This condition is relatively common and it has a wide geographic and ethnic distribution.

Affected individuals may remain totally asymptomatic and the diagnosis is often reached by chance when radiographs are taken for some unrelated purpose. The facies, physique, mentality and life span are normal and general health is unimpaired. A mild anaemia is an infrequent complication.

In a proportion of patients, the presenting feature is facial palsy or deafness, consequent upon cranial nerve compression by bony overgrowth. Involvement of the optic and trigeminal nerves are rare late complications. Pathological fractures due to bony fragility have been reported in a few affected

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FIG. 2. Lateral radiograph of the lumbar spine in osteopetrosis. Bands of sclerosis produce the characteristic 'rugger-jersey' appearance.

individuals, but the majority have no problems of this type. Tooth extraction is sometimes difficult and osteomyelitis of the mandible occasionally develops.

Radiological features. The skeleton is usually radiologically normal at birth, bony sclerosis becoming increasingly apparent as childhood progresses. Striations and endobones also become evident during this period, although these changes usually disappear by the end of the second decade. Bony involvement is widespread but it may be patchy. Certain regions, particularly the extremities, are sometimes spared.

The changes in the skull are maximal in the base and the cranial nerve foramina may be distorted. The calvarium is dense and the sinuses may be obliterated (Fig. 3).

Some individuals have the classical 'rugger jersey' spine while in others the vertebral bodies are either uniformly dense or uninvolved.

Abnormal bony modelling is not usually a feature, but if it occurs at all, the lower ends of the femora are the site of predilection.

FIG. 3. Lateral radiographs of the skull from an adult with autosomal dominant osteopetrosis. The calvarium and base are sclerotic and the frontal sinus is obliterated.

Genetics. Autosomal dominant inheritance is well documented. Johnston *et al.* (1968) reviewed nineteen kindreds with eighty-five affected individuals, while other instances of generation to generation transmission have been reported by several authors, including McPeak (1936), Harnapp (1937) and Piatt, Erhard and Araj (1956).

There is considerable interfamilial variation in the manifestations and there is little doubt that the condition is heterogeneous. However, although the features are usually consistent within a particular family, there have been reports of anomalous situations such as mildly affected progeny of severely affected parents (Cocchi, 1950) or a severely affected son of a mildly affected mother (Thomson, 1949).

Pycnodysostosis

Maroteaux and Lamy (1962) defined the characteristics of pycnodysostosis and established it as an entity in its own right. Previously, the predominant clinical feature of shortness of stature led to confusion with other types of dwarfism, while the generalized skeletal sclerosis prompted some authors to consider the condition to be a form of osteopetrosis. Similarly, the clavicular hypoplasia which is present in a proportion of affected individuals had been held to be indicative of a possible link with cleidocranial dysostosis.

Clinical features. Disproportionate short stature becomes evident in early childhood and adult height does not exceed 150 cm.

Affected individuals resemble each other closely, having a small face, hooked nose, receding chin and carious misplaced teeth. The cranium bulges and the anterior fontanelle remains patent. The terminal phalanges are short, with dysplasia of the fingernails.

Bony fragility predisposes to spontaneous fracture. Other less consistent skeletal changes include narrowing of the thorax and spinal deformity.

The impressionist painter Toulouse-Lautrec is thought to have had pycnodysostosis (Maroteaux and Lamy, 1965). Indeed, his appearance and medical history serve as a useful 'aide-memoire' to the manifestations of the disorder. For instance, it is well known that he was of short stature, and the 'stove-pipe' hat which he habitually wore might have covered a patent fontanelle. Similarly, his beard may have been grown to conceal a receding chin. The stick which he carried is a reminder of the two femoral fractures which he suffered on minor trauma in childhood and which are indicative of the bony fragility. Finally, the fact that his aristocratic parents were first cousins is in keeping with the autosomal recessive inheritance of the condition.

Radiological features. Bony sclerosis appears during childhood and increases throughout the years of growth. In distinction to the osteopetroses skeletal modelling and bony contours are undisturbed and neither bony striations nor endobones are seen.

The calvarium is not particularly dense but patency of the fontanelles and the presence of multiple Wormian bones can usually be demonstrated. The facial bones and paranasal sinuses are hypoplastic and the angle of the mandible is obtuse (Fig. 4).

The terminal phalanges are foreshortened, with distal irregularity, similar to that encountered in acro-osteolysis. The clavicles may be gracile with underdevelopment of their lateral portions.

Genetics. Pycnodysostosis is inherited as an autosomal recessive. Sedano, Gorlin and Anderson (1968) have reviewed a number of kindreds in whom multiple affected siblings had normal parents. Parental consanguinity was present in several families, including those reported by Kajii, Homma and Ohsawa (1966), Almeida (1972) and Waziri, Zellweger and Seibert (1976). Reviewing the literature, Sedano *et al.* (1968) calculated that about 30% of patients were the offspring of consanguineous unions. More than fifty kindreds have now been reported (Diwan and Gogate, 1974).

An affected individual with a deletion of the short arm of a G group chromosome, probably chromosome 22, led Elmore *et al.* (1966) to speculate that the abnormal gene might be located at that particular chromosomal site.

The majority of case descriptions have emanated from Western Europe, the U.S.A. and Portugal.

FIG. 4. Lateral radiograph of the skull from an infant with pycnodysostosis. The fontanelle is patent, the facial bones are hypoplastic and the angle of the mandible is obtuse.

However, pycnodysostosis has been encountered in African Negroes (Wolpowitz and Matisonn, 1974), and a large series of affected individuals has recently been reported from Japan (Sugiura, Yamado and Koh, 1974).

(2) Craniotubular dysplasias

Metaphyseal dysplasia (Pyle disease)

Metaphyseal dysplasia or Pyle disease is an uncommon autosomal recessive disorder which is often the subject of semantic confusion with the craniometaphyseal dysplasias (see below). However, these latter conditions are separate entities, being distinguished by marked involvement of the skull.

Clinical features. Individuals with metaphyseal dysplasia are clinically normal, apart from valgus deformities of the knees. Muscular weakness, scoliosis, and bony fragility are occasional features.

Radiographical features. In contrast to the mild clinical stigmata, the radiographic changes are striking. The tubular bones of the legs have gross 'Erlenmeyer flask' flaring, particularly in the distal portions of the femora and proximal regions of the tibia and fibula. The long bones of the arms are also very undermodelled. The bony cortices are generally thin.

The skull is virtually spared, apart from a supra-orbital prominence. The angle of the jaw is obtuse and the bones of the pelvis and thoracic cage are expanded.

Genetics. Metaphyseal dysplasia is inherited as an autosomal recessive. Affected siblings featured in the original report of Pyle (1931).

Craniometaphyseal dysplasia (autosomal dominant form)

The autosomal dominant form of craniometaphyseal dysplasia is relatively common in comparison with the other conditions in this group.

Clinical features. Paranasal bossing develops during infancy and progressive expansion and thickening of the skull and mandible lead to distortion of the jaw and facies (Fig. 5). These changes, which are very variable in degree, become static in the third decade. Paradoxically, the paranasal bossing lessens with the passage of time. Bony encroachment leads to entrapment and dysfunction of the cranial nerves, particularly the seventh and eighth. The majority of affected individuals have some degree of facial palsy and deafness, which often appear in the first decade.

Malocclusion of the jaws may be troublesome, while partial obliteration of the sinuses predisposes to recurrent naso-respiratory infection.

The bones are not fragile and pathological fractures do not occur.

Radiographic features. The radiographic changes are age-related, usually becoming evident by the age of 5 years. There is considerable intrafamilial variation in the severity of the manifestations. The calvarium, facial bones and metaphyses of the

tubular bones are predominantly affected, while the flat bones are uninvolved. The main feature in the skull is sclerosis, which is maximal in the base, although the cranium is always involved to some degree. The long bones have widened metaphyses and normal diaphyses, presenting a club shaped configuration, particularly at the lower end of the femur (Fig. 6). These changes are much less severe than those encountered in Pyle disease. Minor degrees of expansion and cortical thinning are present in the ribs and clavicles, while the spine and pelvis are uninvolved.

Genetics. Although semantic confusion with Pyle disease bedevils any search through the literature, affected individuals in successive generations can be recognized in the reports of Spranger, Paulsen and Lehmann (1965); Lejeune *et al.* (1966); Gladney and Monteleone (1970); Stool and Caruso (1973) and Kubicz and Bienkowska (1974).

The authors have personal knowledge of a kindred, with branches in England and South Africa, in which there are more than eleven affected individuals in four generations. Male to male transmission has occurred in this family, and there is little doubt that the condition is inherited as an autosomal dominant (Spiro, Hamersma and Beighton, 1975).

There have been a few well documented reports of patients in which craniometaphyseal dysplasia

FIG. 5. Craniometaphyseal dysplasia in a young girl with the typical paranasal bossing.

FIG. 6. Craniometaphyseal dysplasia—anteroposterior radiograph of the knees of a child. The lower end of the femur is expanded into a club shape.

has been inherited as an autosomal recessive. In this rare disorder facial distortion is extreme, even in childhood.

(3) Craniotubular hyperostoses

Endosteal hyperostosis (van Buchem)

Using the designation 'hyperostosis corticalis generalisata familiaris', van Buchem, Hadders and Ubbens (1955) described two siblings with cranial sclerosis and widening of the diaphyses of the long bones. Further reports followed, all concerning individuals in Holland (van Buchem *et al.*, 1962; van Buchem, 1971). The eponymous designation is widely accepted for this condition.

Clinical features. Overgrowth and distortion of the mandible and brow become evident during the latter part of the first decade. Facial palsy and deafness have their onset in the same period, owing to entrapment of the cranial nerves.

Two siblings mentioned in the original case report were mentally defective, but other affected individuals have been of normal intelligence. The disorder is progressive, and optic nerve involvement may be a late complication. However, life span is not compromised, stature is normal and the bones are not fragile.

Radiographic features. Widening and sclerosis of the calvarium, cranial base and mandible are major features in affected adults. Bony density is increased in the spinous processes of the vertebrae.

In the tubular bones, endosteal thickening is present in the diaphyseal regions. However, bony outlines remain virtually normal.

Genetics. The form of the disorder reported by van Buchem *et al.* (1955, 1962) is undoubtedly autosomal recessive. None of these Dutch patients had affected parents or offspring. Furthermore, parental consanguinity was present in one kindred, and amongst the affected individuals in other families were a brother and sister and a set of twins of different sex.

There have been reports of kindreds with an autosomal dominant variety of endosteal hyperostosis (Worth and Wollin, 1966; Maroteaux *et al.*, 1971). Recently, Owen (1976) studied the condition in six members of three generations of a British kindred. Although the radiological features are very similar to those of the autosomal recessive type, the clinical course is milder, and cranial nerve involvement is not a problem. Another case report emanating from Britain, which may concern this latter condition, is that of Scott and Gautby (1974).

Sclerosteosis

Truswell (1958) recognized the existence of this disorder as a separate entity when he described six affected individuals, under the title 'osteopetrosis with syndactyly; a morphological variant of Albers-

Schönberg disease'. The designation 'sklerosteose', which was subsequently coined by Hansen (1967), is now generally accepted in its anglicized form.

About thirty cases have been reported, the majority among the Afrikaner community of South Africa (Beighton, Durr and Hamersma, 1976c). The only other known patients are a sibship in New York (Higinbotham and Alexander, 1941) and a young woman in Japan (Sugiura and Yasuhara, 1975).

Clinical features. Progressive overgrowth and sclerosis of the skeleton, particularly the skull, develop in early childhood. Height and weight are often excessive. Deafness and facial palsy due to cranial nerve entrapment may be a presenting feature, preceding distortion of the facies. Disfigurement is apparent by the age of 10 years and eventually becomes gross (Fig. 7). In adulthood, elevation of intracranial pressure may cause severe headache. Several affected adults have died suddenly from impaction of the brain stem in the foramen magnum.

Syndactyly of the second and third fingers, either cutaneous or bony, serves to distinguish sclerosteosis from the other disorders in this group. The terminal phalanges are deviated radially, with dystrophy of the finger nails. The bones are resistant to trauma, and pathological fractures do not occur.

Radiographic features. Gross widening and sclerosis of the skull is the major radiographic feature (Fig. 8). Hypertrophy of the mandible and

FIG. 7. Sclerosteosis—the typical facies, with overgrowth and distortion of the forehead and mandible, facial palsy and deafness.

FIG. 8. Sclerosteosis—lateral skull radiograph, showing massive hyperostosis. Craniotomy has been undertaken to relieve raised intracranial pressure.

FIG. 9. Osteopathia striata—anteroposterior radiograph of the lower end of the femur showing typical longitudinal striations.

frontal regions leads to relative mid-facial hypoplasia.

The vertebral bodies are generally spared although their pedicles are sclerotic. The pelvic bones are also sclerotic, but their contours are normal.

Sclerosis and hyperostosis of the cortices of the long bones is prominent. However, in distinction to endosteal hyperostosis, the tubular bones in sclerosteosis are markedly undermodelled, with lack of the usual diaphyseal constriction (Beighton, Cremin and Hamersma, 1976a).

Genetics. Sclerosteosis is inherited as an autosomal recessive. Consanguinity was present in five of fifteen Afrikaner kindreds, into which a total of twenty-five affected individuals had been born. None of the parents had the disorder and the five offspring of three patients were all normal. In the Afrikaner community, the minimum prevalence of sclerosteosis is 1 : 75000, with a gene frequency of 0.0035 (Beighton *et al.*, 1976b).

Calvarial thickening was evident in lateral skull radiographs from a number of obligatory heterozygotes, and if this observation proves to be consistent, it could provide a basis for recognition of the carrier of the gene.

(4) Miscellaneous sclerosing and hyperostotic disorders *Osteopathia striata*

Osteopathia striata is usually considered to be an inconsequential condition in which multiple lines of increased density are detected radiologically in the long bones and the pelvis. This designation was

used by Fairbank (1935), following the initial description by Voorhoeve (1924). Striations of this type are also a component of other disorders, including the osteopetroses, osteopoikilosis and focal dermal hypoplasia.

Clinical features. Affected individuals are asymptomatic and the skeletal changes are usually detected by chance. The benign nature of the condition is exemplified by the fact that the radiographic abnormalities in Voorhoeve's two original patients were unchanged when Fermin (1962) re-examined them three decades later.

Radiographic features. Multiple parallel regular lines of sclerosis run along the shafts of the tubular bones (Fig. 9). In the ilia, the striations have a

fan-shaped configuration. The contours of the bone are undisturbed.

Genetics. Osteopathia striata was observed by Voorhoeve (1924) in a father and his daughter. In the kindred reported by Rucker and Alfidi (1964), under the designation 'Fairbank disease', members of three generations were affected. It is likely that inheritance is autosomal dominant, with varying expression of the gene. Some individuals with osteopathia striata have cranial sclerosis, facial distortion and cranial nerve palsies (Jones and Mulcahy, 1968; Walker, 1969). In this context, the authors have personally studied a kindred in which five individuals in three generations had osteopathia striata, mild prognathism and palsies of the seventh and eighth cranial nerves. The severity of the changes varied considerably between affected members of the family. As father to son transmission of the gene had occurred, there is little doubt that this condition is inherited as an autosomal dominant.

Comment

In view of the complexity of the terminology, it is not surprising that there has been considerable confusion in the literature concerning this group of conditions. Indeed, the designation 'osteopetrosis' is still frequently used indiscriminately for all forms of craniotubular dysplasias and hyperostosis. However, it is anticipated that growing appreciation of the importance of diagnostic accuracy will promote increasing semantic precision.

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Figure 5 appeared in the *South African Medical Journal*, 49, 839, 1975 and it is reproduced with the permission of the editor.

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