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REVIEW ARTICLE

Sclerosing bone dysplasias: genetic, clinical and radiology update of hereditary and non-hereditary disorders

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ABSTRACT

There is a wide variety of hereditary and non-hereditary bone dysplasias, many with unique radiographic findings. Hereditary bony dysplasias include osteopoikilosis, osteopathia striata, osteopetrosis, progressive diaphyseal dysplasia, hereditary multiple diaphyseal sclerosis and pyknodysostosis. Non-hereditary dysplasias include melorheostosis, intramedullary osteosclerosis and overlap syndromes. Although many of these dysplasias are uncommon, radiologists should be familiar with their genetic, clinical and imaging findings to allow for differentiation from acquired causes of bony sclerosis. We present an overview of hereditary and non-hereditary bony dysplasias with focus on the pathogenesis, clinical and radiographic findings of each disorder.

INTRODUCTION

Hereditary bone dysplasias are caused by a variety of genetic factors, each leading to specific disruptions in the bone ossification pathway.

Hereditary bone dysplasias include osteopetrosis, pyknodysostosis osteopoikilosis, osteopathia striata (Voorhoeve disease), progressive diaphyseal dysplasia (Camurati–Engelmann disease), hereditary multiple diaphyseal sclerosis (Ribbing disease), hyperostosis corticalis generalisata and endosteal hyperostosis (Van Buchem's disease and Worth disease).[1,2]

Dysplasias can be categorized according to the site of abnormal bone formation. Disorders of endochondral bone formation lead to changes in the axial skeleton, long bones and flat bones, whereas disorders of intramembranous bone formation lead to changes in the skull, face and nose and diaphysis of the long bones and flat bones.[1,2]

During the seventh week of embryogenesis, endochondral ossification forms the primary spongiosa. Failure of resorption of this primary spongiosa leads to accumulation of the calcified cartilage matrix within the medullar cavity. Osteopetrosis and pyknodysostosis are examples of this failure. During the ninth week of embryogenesis, after transformation of the primary into the secondary spongiosa, osteoclasts remodel the spongiosa into the trabeculae and medullary cavity. Failure results in focal densities (osteopoikilosis) or striations inside the medullary cavity (osteopathia striata).

Intramembranous ossification occurs without a cartilage matrix and continues after closure of the growth plates. Disorders of intramembranous ossification include progressive diaphyseal dysplasia, hereditary multiple diaphyseal sclerosis and hyperostosis corticalis generalisata.

Hereditary bone dysplasias may be symptomatic and present in childhood or be asymptomatic and be incidentally discovered in adults.

Non-hereditary dysplasias include intramedullary osteosclerosis, melorheostosis (Leri disease) and overlap syndromes.[1,2]

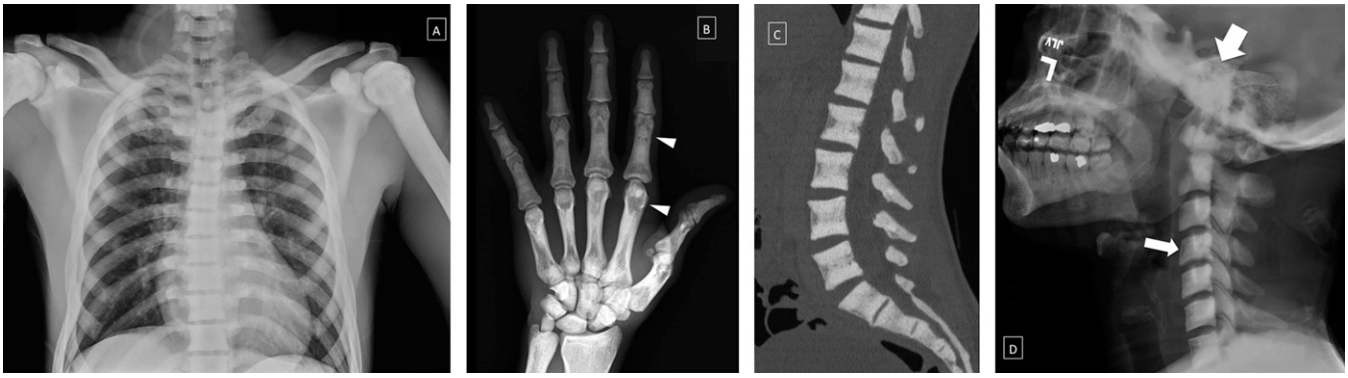
DISCUSSION

Hereditary dysplasias

Failure in resorption of primary spongiosa

Osteopetrosis Osteopetrosis is a dysplasia of primary spongiosa, and may be caused by several gene mutations,

Figure 1. Osteopetrosis. (a) A 26-year-old male. Chest radiograph. Note the uniform sclerosis of the spine, ribs and long bones with undertubulation. (b) Radiograph of the left hand showing "bone-within-bone" appearance at the ends of the diaphysis of the digits (best seen within the second-finger proximal phalanx and metacarpal) (arrowheads). (c) Sagittal CT image of the lumbar spine showing "sandwich vertebrae" with increased sclerosis of the vertebral endplates. (d) Radiograph of the cervical spine with increased sclerosis of the cranial vault and cervical vertebra (arrows).



with at least 10 genes identified to date accounting for 70% of all cases. These gene mutations include TCIRG1, OSTM1 and CLCN7 in the severe neonatal or infantile form of the condition.[3–5] On radiographs, increased sclerosis within the medullary space is typical. The disorder is characterized by decreased osteoclastic activity with an impaired repair mechanism, leading to an increased bone mass. The resultant bone is less capable of undergoing bone remodelling and is prone to fractures.[6–8]

Two subtypes of the disorder exist.[3–8] The infantile (malignant) form has an autosomal recessive inheritance pattern and typically leads to stillbirth or early demise. It is characterized by cranial nerve dysfunction, caused by sclerosis of the skull bones. Generalized bone sclerosis is apparent with loss of differentiation between the cortex and medullar cavity. Replacement of the marrow elements with bone leads to anaemia and thrombocytopenia.[9]

The adult (benign) form has an autosomal dominant inheritance pattern and is also known as Albers-Schönberg disease.[1] Similar to the infantile form, diffuse osteosclerosis (Figure 1a) is seen although to a somewhat lesser degree. Loss of tubulation of the long bones may be evident, as well as a "bone-within-bone" appearance at the ends of the diaphysis (Figure 1b). "Sandwich vertebrae" may be seen as a result of increased sclerosis of the vertebral endplates (Figure 1c). The autosomal dominant form is further divided into two types. In Type I, pronounced sclerosis of the cranial vault is apparent. Other findings include uniform sclerosis of the long bones and axial skeleton (Figure 1d). In Type II, sclerosis of the skull base is present and sclerosis of the vertebral endplates may be seen. The iliac wings may show sclerotic arcs ("bone-within-bone appearance").[5–8]

Pyknodysostosis Pyknodysostosis has an autosomal recessive inheritance pattern and is caused by mutations in the cathepsin-K gene, which is a lysosomal cysteine protease

Figure 2. Pyknodysostosis. (a) Unknown gender and age (from teaching file). Radiograph of the hand showing pointed finger tufts (arrowheads). (b) Lateral radiograph of the skull showing prominent sclerosis of the skull base (circle).

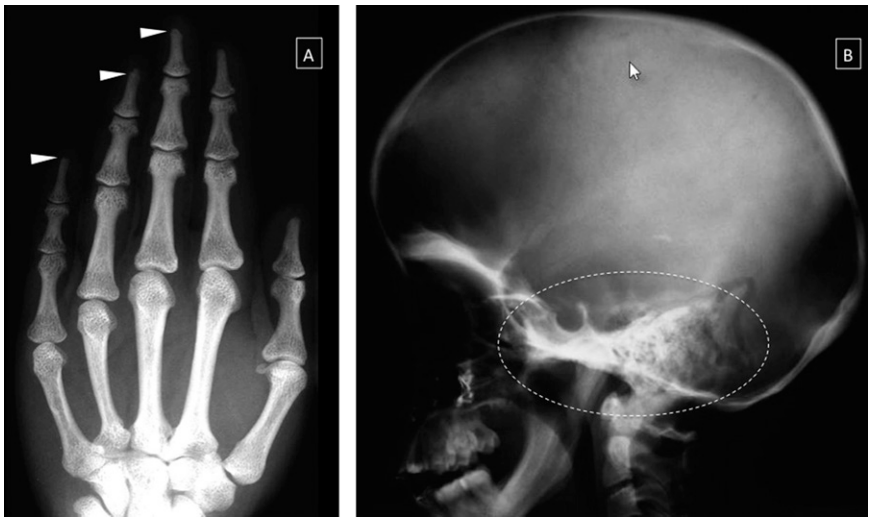
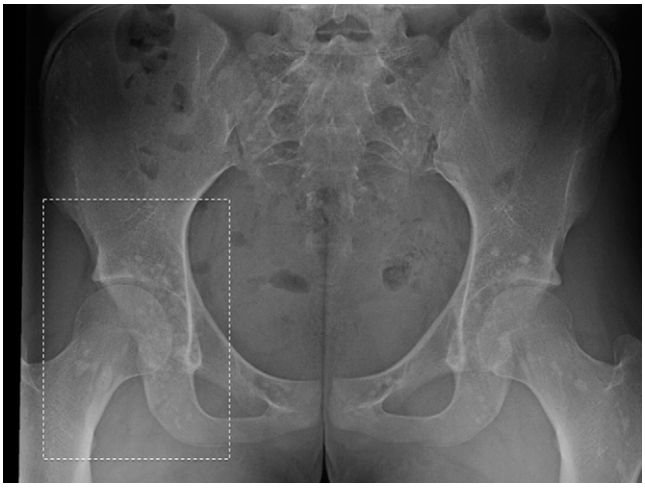


Figure 3. Osteopoikilosis. A 14-year-old female. Pelvis radiograph showing multiple bilateral rounded lesions within the sacrum, iliac wings, pubic branches, acetabuli and femur (square).



expressed in osteoclasts. This enzyme is essential for the degradation of collagen.[10,11] Clinically, the disorder is characterized by dwarfism and pectus excavatum. Radiographically, osteosclerosis is seen. The appearance may mimic osteopetrosis, although the medullary space of the long bones is usually preserved. Because the marrow elements are typically maintained, anaemia is less common than in osteopetrosis. Other findings include acro-osteolysis of the distal phalanges (Figure 2a), which is an essential pathognomonic feature.[1,11] Clavicular dysplasia, hypoplasia of the facial bones and sclerosis of the skull base also may occur (Figure 2b), as well as decreased pneumatization of the paranasal sinuses and delayed suture closure.[10] Kyphoscoliosis and lumbar hyperlordosis may be present, and the vertebral bodies appear dense with sparing of the transverse processes. Overall, the bones are quite brittle, making them prone to fractures.

Failure in resorption of the secondary spongiosa

Osteopoikilosis Osteopoikilosis has an autosomal dominant inheritance pattern and is caused by an inactivating mutation in the LEMD3 gene (also known as MAN1 gene). This causes a failure in resorption of the secondary spongiosa and results in focal deposits of the dense lamellar bone in the spongiosa.[12] Multiple small areas of sclerosis resembling enostoses are apparent. These are typically seen at the ends of small tubular bones, meta-epiphyseal region of long bones, in the tarsus and carpus and in the pelvic bones (Figure 3). These findings are typically an incidental finding. Occasionally, patients may present with joint pain. An association with the connective tissue disorder dermatofibrosis lenticularis disseminata has been reported.[1] Osteopoikilosis is frequently associated with other bone dysplasias and in that case, the disorder is designated "overlap syndrome". Rare cases of misdiagnosis of this benign condition mimicking sclerotic bone metastasis have also been described.[13]

Osteopathia striata Osteopathia striata, also designated Voorhoeve disease, is a disorder of the secondary spongiosa and has an X-linked dominant inheritance pattern. Deletions in the WTX locus may be found.[14–16] It occurs mainly in females. Rare cases of osteopathia striata with cranial sclerosis and colorectal and ovarian cancer or Wilms' tumour have been reported. WTX is also known as a tumour suppressor gene, and somatic mutations in that gene have been identified in Wilms' tumour.[14]

Dense linear striations along the long axis of the diaphysis and metaphysis of the tubular bones are typically seen (Figure 4b). In the pelvis, these striations appear fan-like. An association exists with cranial sclerosis (osteopathia striata and cranial sclerosis complex) (Figure 4a), and there is also a triad of osteopathia

Figure 4. Osteopathia striata with cranial stenosis. A 10-year-old female. (a) Frontal radiograph of the lower legs showing longitudinal sclerotic striations in the metaphysis of both the femora and tibia. Note the aplasia of the proximal right fibula (arrow). (b) Axial CT image (in the bone window) of the skull. Note the thickened bone with ground-glass appearance of the spongiosa in the skull base. Note the sclerosis of the inner auditory canal (arrowhead), narrowing of the cranial neuroforaminae (arrow) and lack of pneumatization of the mastoids (curved arrow). (c) Three-dimensional CT reconstruction of the skull showing a well-demarcated cleft palate (arrow).

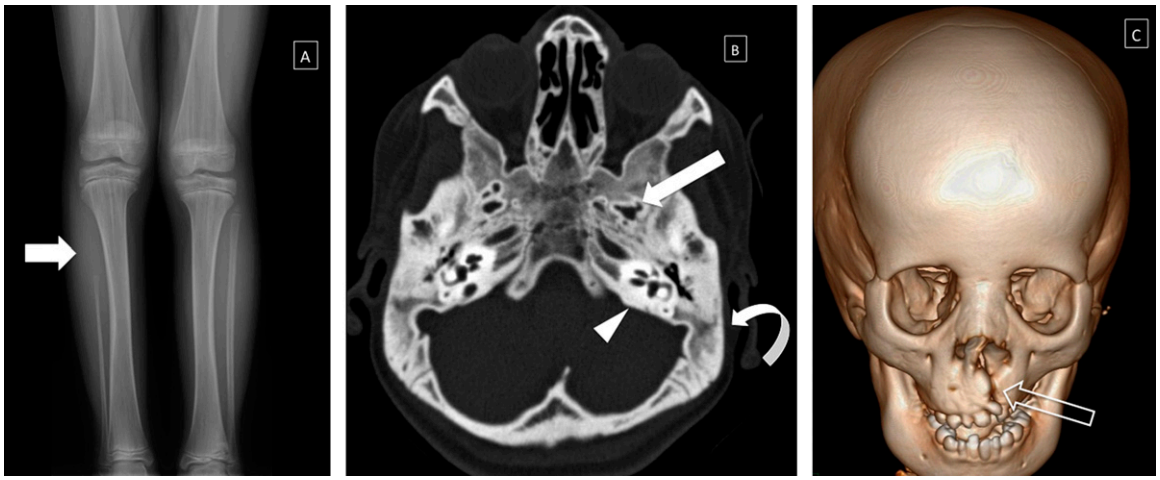
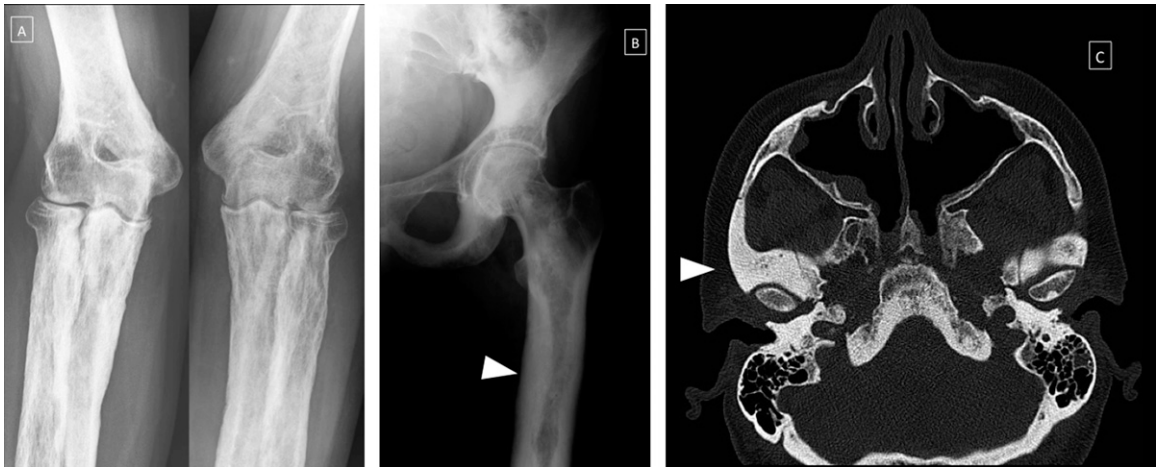


Figure 5. Progressive diaphyseal dysplasia. A 50-year-old female. (a) Frontal radiograph of both elbows showing bilateral symmetric hyperostosis along the periostal and endosteal surfaces of the diaphysis of the long bones. (b) Frontal radiograph of the left hip showing sclerosis of the left iliac wing, ischium and diaphysis of the femur, with narrowing of the medullary canal and increase in the diaphyseal diameter (arrowhead). (c) CT scan of the skull base. Note the sclerosis of the skull base and around the temporomandibular joints (arrowhead). Note that maxillary sinus surgery has been performed.



striata, macrocephaly and high-arched or cleft palate (Figure 4c).[14] Hearing loss and other cranial nerve palsies may occur. Osteosclerosis is also seen in the vertebrae and ribs and occasionally, malformations of hands and feet such as polydactyly may be evident.

Disorders of intramembranous ossification

Progressive diaphyseal dysplasia Progressive diaphyseal dysplasia or Camurati–Engelmann disease is a disorder of intramembranous ossification and has an autosomal dominant inheritance pattern with variable penetration.[17] Mutations in the TGF-β1 gene occur.[18] Bilateral symmetric hyperostosis along the periosteal and endosteal surfaces of the diaphysis of the long bones is evident and the medullary space appears narrowed (Figure 5a). The metaphyses and epiphyses are typically spared because they are formed by endochondral bone formation (Figure 5b). The diameter of the diaphysis may increase as much as twofold.[17,18] Sclerosis of the skull, mandible and vertebral endplates is often present (Figure 5c). Clinical symptoms start in early childhood, with dull bone and muscle pain, weakness and a waddling gait. It can be incorrectly diagnosed as a chronic sclerosing osteomyelitis in the initial presentation owing to its rare nature or other similar sclerosing bone dysplasias. The disease may regress by adulthood, and patients tend to be taller than their peers.[1,17–19]

Multiple diaphyseal sclerosis Multiple diaphyseal sclerosis or Ribbing disease is also a disorder of intramembranous ossification. Its precise cause is not known, although an autosomal recessive inheritance pattern has been suggested.[20,21] It resembles progressive diaphyseal dysplasia (Camurati–Engelmann disease) and is considered a variant of this disease by some authors.[20] The disorder presents after puberty. Periosteal and endomedullary bone overgrowth confined to the diaphysis of the long bones (Figure 6) is seen, usually limited to the lower extremities.[21,22] The affliction occurs in a unilateral or bilateral asymmetric manner, typically in the tibia or femur.[21] Clinically, the disease presents with progressive pain in the affected bones and is often misdiagnosed initially as chronic sclerosing

Figure 6. Multiple diaphyseal sclerosis (Ribbing disease). A 35-year-old female. Frontal radiograph of the lower legs showing bilateral asymmetrical endostal and periosteal sclerosis confined to the diaphysis of both tibia (arrowheads).

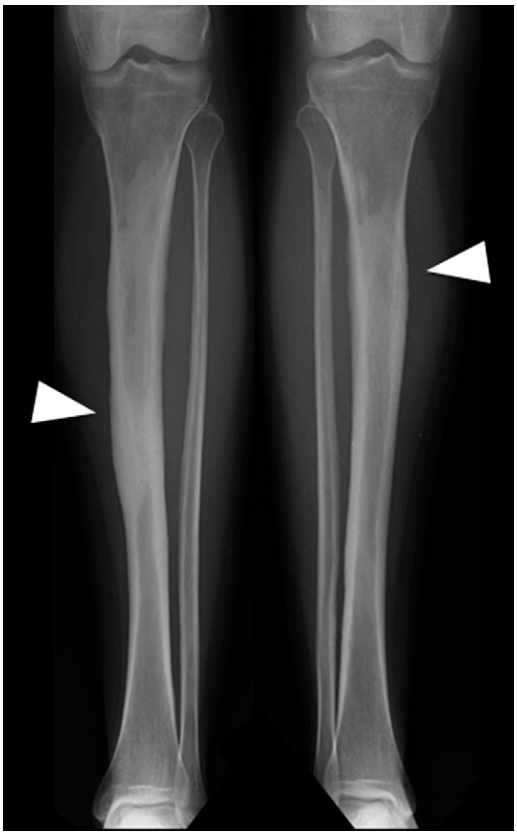
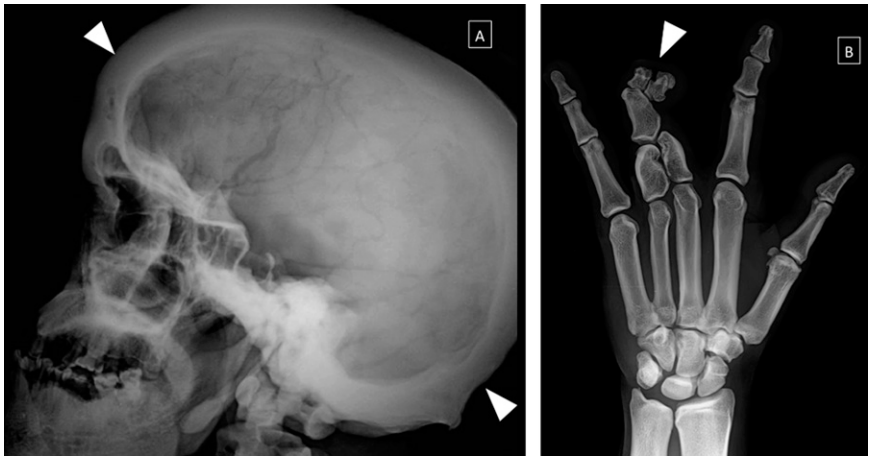


Figure 7. Truswell–Hansen disease. (a) Lateral skull radiograph showing extensive cortical thickening (arrowheads). (b) Frontal radiograph of the hand showing marked syndactyly of the third and fourth fingers (arrowhead). (Courtesy of S Deepak Amalnath, MD, India).

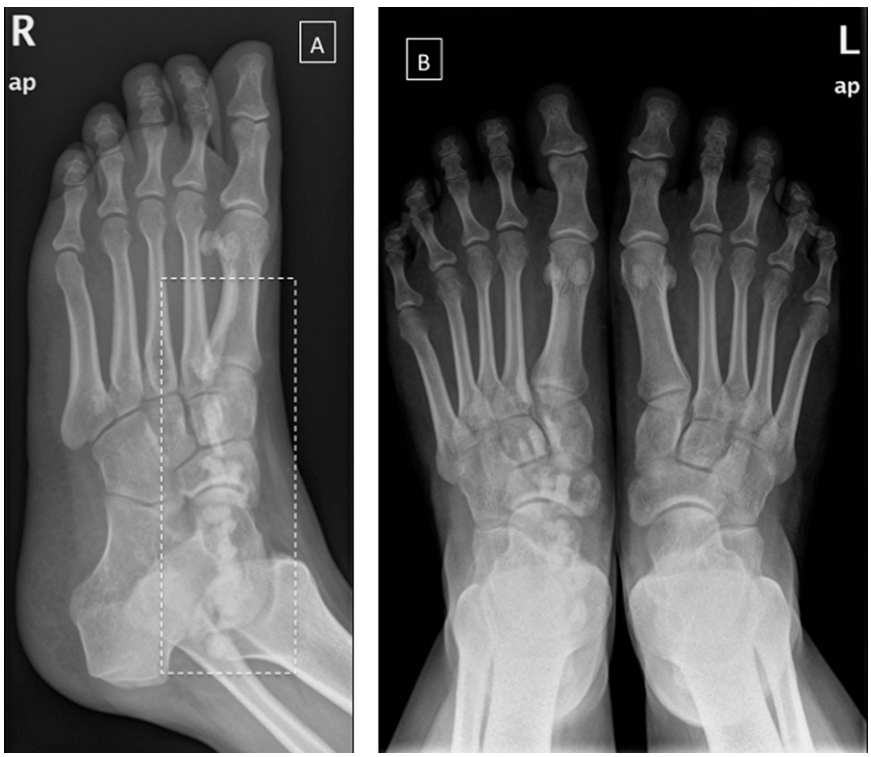


osteomyelitis or Camurati–Engelmann disease. The age of onset as well as the symmetry of the disease, however, are key differentiating factors.[1,20,21]

Hyperostosis corticalis generalisata Hyperostosis corticalis generalisata refers to a heterogeneous group of diseases caused by mutations in the Wnt pathway. This mutation results in the accumulation of β-catenin in the cytoplasm of osteoblasts. Osteoblasts proliferate, and bone formation increases. Radiographically, dense homogeneous cortical thickening of the skull, facial bones and mandible are evident. The long bones, axial skeleton, pelvis and ribs may also be affected. The medullary space is typically narrowed.

Three subtypes are recognized. Van Buchem's disease has an autosomal recessive inheritance pattern and is caused by the lack of a regulatory element of the SOST gene, which encodes for sclerostin, an osteocyte-derived negative regulator of bone formation.[22] Its characteristics are severe asymmetrical enlargement of the jaw during puberty. Recurrent facial nerve palsy, deafness

Figure 8. Melorheostosis. A 28-year-old female. (a) Radiograph of the right foot showing cortical and endomedullary hyperostosis of the diaphysis of the first metatarsal, first and second cuneiformes and navicular and talar bones (square). (b) Radiograph of the feet. This bilateral view shows unilateral (hemimelic) involvement.



and optic nerve atrophy from narrowing of the cranial nerve foramina are frequently encountered. Endosteal cortical thickening and narrowing of the medullary canal is characteristic. The thickened calvarium, skull base and mandible will be correlated with increased bone mineral density and biochemical measurements.[23,24] Remodelling of the surface of the long bones is absent.[23,24]

Sclerosterosis or Truswell–Hansen disease (Figure 7) is similar to Van Buchem's disease, but occurs in early childhood, especially in Afrikaners or others of Dutch ancestry. Syndactyly of the second and third digit, nail dysplasia and a tall stature are typical.[1,2,24]

Worth disease has an autosomal dominant inheritance pattern and is similar to the two former diseases but is less severe. It usually presents during adolescence. Increased thickness of the cortices of the long bones and increased density of the axial skeleton are seen. Abnormalities of the facial skeleton consist of flattening of the forehead and elongation of the mandible. The presence of a torus palatinus is common.[24]

Non-hereditary disorders

Intramedullary osteosclerosis

Intramedullary osteosclerosis is a disorder typically affecting the mid-diaphyseal region of one or both tibia, but the fibula and femur can also be involved. It is seen in adult females.[25] There is no genetic cause, nor is it associated with an infection, trauma or systemic illness. It is usually discovered incidentally on radiographs performed in patients with chronic leg pain with physical exertion.[5] Increased sclerosis of the medullary canal is seen, but in contrast to progressive diaphyseal dysplasia (Camurati–Engelmann disease) or hereditary multiple diaphyseal sclerosis (Ribbing disease), cortical thickening and periosteal reaction are absent. The imaging features do resemble many other more common sclerosing bone dysplasias, and a tendency to present in the mid-tibia with activity-related lower leg pain places stress fractures, infection and endocrine disorders within the differential. It is therefore essential that the imaging features be correlated with the clinical information and laboratory analysis to arrive at the correct diagnosis.[25,26]

Melorheostosis

Melorheostosis, or Leri disease, is a mixed sclerosing bone dysplasia. Abnormalities in both endochondral and intramembranous ossification are present.[5] It is equally prevalent in males and females. It usually presents in the second decade of life, but it may occur in any age group. It affects the skeleton and adjacent soft tissues, and associated abnormalities of the ipsilateral blood and lymph vessels may occur. Cortical and endomedullary hyperostosis of a single bone (monostotic form) or multiple adjacent bones (polyostotic form) is typical (Figure 8a,b). A candle-wax appearance is characteristic, hence its Greek name (melos: limb; rhein: to flow; ostos: bone). The disorder tends to be segmental and unilateral (hemimelic) and follows the distribution of sclerotomes (areas of the bone innervated by an individual spinal sensory nerve). This particularity suggests a defect in the early embryologic stage, where cartilage-forming cells migrate from the sclerotomes to the limb buds. An association with osteopoikilosis has been described.

Overlap syndromes

Overlap syndromes are mixed sclerosing bone dysplasias, with features of more than one bone dysplasia. Hereditary and non-hereditary dysplasias may occur in combination. The most common overlap syndrome is the association of osteopoikilosis, melorheostosis and osteopathia striata.[1,2] Other well-known associations are osteopathia striata and cranial sclerosis.[14,15] The association with unilateral vascular anomalies such as lymphangiectasia, capillary haemangiomas and arteriovenous malformations has been described.[14]

CONCLUSION

Sclerosing bone dysplasias form a heterogeneous group of disorders with a wide variety in age of onset and disease severity. The radiographic appearance, distribution, clinical manifestations and associated findings help differentiate these disorders. Osteopetrosis and pyknodisostosis, with decreased osteoclast activity, are frequently associated with fractures. Fractures are typically less common in disorders of intramembranous ossification.

Although most of the non-acquired bone dysplasias are uncommonly observed in clinical practice, an awareness of their existence is important. Differentiation from acquired bony sclerosis such as osteoblastic metastasis, Paget disease, Erdheim–Chester disease, myelofibrosis and sickle-cell disease is important.

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