Case Report

A case of infantile osteopetrosis: The radioclinical features with literature update

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A B S T R A C T

Background: Osteopetrosis is a rare hereditary metabolic bone disorder characterized by generalized skeletal sclerosis caused by a defect in bone resorption and remodelling. Infantile autosomal recessive osteopetrosis is one of three subtypes of osteopetrosis and the most severe form. The correct and early diagnosis of infantile osteopetrosis is important for management of complications and for future genetic counselling. Diagnosis is largely based on clinical and radiographic evaluation, confirmed by gene testing where applicable.

Methods: Therefore, in this case study the classical clinical and radiological signs of a boy with infantile osteopetrosis will be presented with a comprehensive literature update. The differentiating signs from other causes of hereditary osteosclerosing dysplasias are discussed.

Results: This case study and review of available literature show that there tends to be a highly unique clinical and skeletal radiographic pattern of affection in infantile osteopetrosis.

Conclusion: Although tremendous advances have been made in the elucidation of the genetic defect of osteopetrosis over the past years, the role of accurate clinical and radiological assessment remains an important contributor to the diagnosis of infantile osteopetrosis.

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1. Introduction

Osteopetrosis is a rare hereditary metabolic bone disorder characterized by generalized skeletal sclerosis caused by a defect in bone resorption and remodelling. The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also cause haematopoietic insufficiency. The actual incidence is unknown but it is estimated to be 1 case per 100,000–500,000 population (Stark and Savarirayan, 2009). Three distinct clinical forms of the disease—infantile, intermediate, and adult onset—are identified based on age and clinical features. Infantile autosomal recessive osteopetrosis is the more severe form that tends in the first few months of life. Hence, it is referred to as “infantile” and “malignant” compared to the autosomal dominant adult osteopetrosis (Stark and Savarirayan, 2009). The correct and early diagnosis of infantile osteopetrosis (IO) is important for management of complications and for future genetic counselling. Diagnosis is largely based on clinical and radiographic evaluation, confirmed by gene testing where applicable (Sit et al., 2015). It is therefore important to be familiar with the radiological features of IO. Therefore, in this case study the classical clinical and radiological signs of a boy with infantile osteopetrosis will be presented and a comprehensive literature update. The differentiating signs from other causes of hereditary osteosclerosing dysplasias are discussed.

2. Case report

A one and a half year old boy was brought to our outpatient clinic with complaints of delayed milestones. He was first in order to a first cousin parents. Birth and family history were unremarkable.

Clinical examination revealed macrocephaly with opened anterior fontanel, frontal bossing, nystagmus of left eye and retromicrognathia, near normal stature and proportions and abnormal dentition. He had small chest cavity with psoas liver and mildly enlarged spleen. The boy was only able to ambulate with parents’ assistance.
Radiographic examination of the axial and appendicular skeleton revealed generalized osteosclerosis within the medullary portion of the bone with relative sparing of the cortices. Detailed radiographic abnormalities are depicted in Figs. 1A, B and 2A, B, C, D. The pelvi-abdominal sonography revealed splenomegaly with no focal lesions. The blood picture revealed moderate anaemia. Our patient’s parents were informed that data concerning the case would be submitted for publication. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. No financing was received.
for this study. The study was authorized by the local ethical committee.

3. Discussion

The principles of clinical assessment of skeletal dysplasias include accurate history regarding time of onset of short stature prior to physical examination. Some dysplasias have prenatal onset, while others may only present either as newborns or beyond 2 to 3 years of age. Nonetheless some generalized bone mineralization abnormalities such as osteogenesis imperfects, some osteosclerotic disorders as osteopetrosis, and hypophosphatasia may present with near normal proportions (Krakow and Rimoin, 2010). Our patient presented with near normal stature and proportions, but other associated symptoms and radiologic findings presented in infancy. These findings go in line with those reported by the previous authors.

Osteopetrosis is considered to be the prototype of sclerosing dysplasia, it is characterized by wide clinical and genetic heterogeneity with a common end-pathway of failure of normal osteoclastic resorption of bone and increased density in medullary portions of bones with sparing of cortices. The diagnosis also relies greatly on radiographic appearance of the skeleton (Ihde et al., 2011; Vanhoenacker et al., 2000).

Panda and colleagues described in their recent review article, a radiographic approach and review of common non-lethal skeletal dysplasias (Panda et al., 2014). They reported the essential radiological features of OI. These include; diffuse sclerosis involving both the skull vault, multiple limb fractures despite increased density, metaphyseal flaring leading to (Erlenmeyer flask deformity), and “Bone-within-bone” appearance typically noted in spine, pelvis and short tubular bones. In spine, this is termed as a sandwich vertebrae appearance due to end-plate sclerosis and relative lucency of center of body. In the pelvis, they appear as multiple dense white lines parallel to the iliac crest.

Fig. 2. Radiographs showing antero-posterior (A) and lateral views (B) of the pelvis and both lower limbs. Antero-posterior view of the chest wall and both upper limbs (C) and left hand (D). Note the uniform sclerosis of the pelvis and long bones of the lower limbs (A, B) long bones of the upper limbs (C) and short tubular bones (D). The classic “bone-within-bone” appearance is recognizable in the pelvis and proximal femora (white arrows) (A) and upper limbs (white arrows) (C) and short tubular bones of the hand (hollow arrows) (D). Note the Erlenmeyer flask deformity type 2 which is characterized by absence of normal diaphyseal metaphyseal modelling of the distal femora with abnormal radiographic appearance of trabecular bone (hollow white arrows) and alternating radiolucent metaphyseal bands (hollow black arrows) (A).
### Table 1

| Dysplasia                          | Pathogenetics                                      | Onset/prognosis                           | Skeletal radiology                        | Clinical findings                                                                 |
|-----------------------------------|----------------------------------------------------|-------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------------------|
| Infantile ("classic") osteopetrosis (IO) | Target site: endochondral ossification (primary spongyosa). Inheritance: AR. Genetic defect: TCF7L1 with a localized defect located on chromosome 1q13. SXN10 mutation was recently shown in 45% of IO. There is defective osteoclast function and overgrowth of bone: which becomes thick dense and sclerotic, resulting in weak and brittle bones. Hypoplasia may occur. Inheritance: AR. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Perinatal/poor. Fatal in infancy, HSCT is a treatment option | Generalized osteosclerosis of the axial and appendicular skeleton within the medullary portion of the bone with relative sparing of the cortices. Bone within a bone appearance. Sandwich vertebrae, failure of modelling of distal femora (Erlenmeyer flask deformity), alternating radiolucent metaphyseal bands. Pathological fractures and osteomyelitis. | Pancytopenia, failure to thrive, cranial nerve deficits (II, VII, VIII), impaired vision, hepatosplenomegaly, obstructive hydrocephalus, poor dentition, and hypocalcemic seizures. Patients with SXN10 have less severe clinical picture. |
| Neurophathic IO                    |                                                    | Perinatal/poor. Fatal in infancy (extremely rare) | A homogenous and diffuse increase of density, consistent with osteopetrosis. Bone densitometry of lumbar spine showed a BMD at +10SD above the mean for age. | Seizures in the setting of normal calcium levels, developmental delay, hypotonia, retinal atrophy with absent evoked visual potentials and sensorineural deafness. |
| IO with renal tubular acidosis (RTA) | Inheritance: AR. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Infancy or early childhood, variable. May benefit from HSCT | Classical radiographic features of osteopetrosis are present. | Milder course where RTA and cerebral calcifications are typical. Other clinical manifestations comprise an increased frequency of fractures, short stature, dental abnormalities, cranial nerve compression, mental and developmental delay. |
| IO with immunodeficiency (OLEMID)   | Inheritance: AR. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Infancy/poor. Fatal in early childhood. | Classical radiographic features of osteopetrosis are present. | Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia and immunodeficiency (OLEMID). In AR subtype visual impairment, neurodevelopmental delay, hypocalcemic seizures, and recurrent infections may occur due to hypogammaglobulinemia. |
| IO with leukocyte adhesion deficiency syndrome (LAD-III) | Inheritance: AR. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Infancy or early childhood, variable. May benefit from HSCT | Classical radiographic features of osteopetrosis are present. | Recurrent infections accompanied by severe bleeding episodes and neurodevelopmental defects. |
| Intermediate osteopetrosis (IO)    | Inheritance: AR. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Infancy/poor. | Classical radiographic features of osteopetrosis are present. | Anaemia, extramedullary haematopoesis, occasional optic nerve compression, pathological fractures, osteomyelitis and dental abnormalities. |
| Autosomal dominant osteopetrosis (ADO) (Albers-Schonberg) | Inheritance: AD. Genetic defect: CLCN7, OSTM1. It is due to primary neurodegeneration not dissimilar to neuronal ceroid-lipofuscinosis, a lysosomal storage disorder. Electron microscopy of skin biopsies reveals swollen unmyelinated axons that contain spheroids, reduced numbers of myelinated axons and the presence of secondary lipofuscin-containing lysosomes in Schwann cells. Inheritance: AR. Carbonic anhydrase (CA) isoenzyme II deficiency. | Late childhood or adolescence/normal life expectancy | The classic bone-within-bone appearance was present in most but not all skeletal sites. Radiological penetration of the disease increased after 20 years of age. | Disproportionate dwarfism, pathologic long bone fractures. |
| Pyknody sostosis (osteopetrosis acro-osteolitica) | Target site: endochondral ossification (primary spongyosa). Inheritance: AR. Genetic defect: CTSL. Lysonosomal disorder due to genetic deficiency in Cathepsin K which has been mapped to chromosome 1q21. Cathepsin K is essential for normal osteoclast function. | Infancy or early childhood | Generalized osteosclerosis but with relative sparing of the medullary canal of long bones. Partial/total aplasia of terminal phalanges of the hand with sclerosis simulating acro-osteolysis which is considered an essentially pathognomonic feature. Marked delay in cranial suture closure and clavicle hypoplasia. In the spine characteristic sparing of the transverse processes Osteoclerotic foci that occur in the epiphyses and metaphyses of long bones, wrist, foot, ankle, pelvis, and scapula. Foci are either connected to adjacent trabeculae of spongy bone or attached to the subchondral cortex “enostosis” | Asymptomatic and incidentally found on radiographs. Bone strength is normal. It may manifest by multiple non tender subcutaneous nevi or nodules. Some individuals have both skin and bone manifestations, whereas others may lack skin or bone manifestations. Cooccurrence of osteopikilosis and melorheostosis has been observed. |
| Osteopikilosis (Buchke–Ollendorff syndrome) | Target site: endochondral ossification (primary spongyosa). Inheritance: AD. Genetic defect: LEMD3. Patches of dense cortical like bone complete with havessian canals located within the spongiosa, often just deep to the cortex mainly in the inner cortex. | Childhood or adulthood (rare) | |
recessive osteopetrosis involves mutations in SNX10 (Frattini et al., 2003). Nearly 4% of cases of autosomal recessive osteopetrosis involve mutation of TCIRG1 (Kornak et al., 2001). The clinical picture seems to be milder, loss of vision, anaemia and bone fragility is more common (Aker et al., 2012). OSTM1 gene causes a very severe form of the disease with frequent CNS manifestations, the mutation of which is responsible for 2% of cases of infantile autosomal recessive osteopetrosis (Pangrazio et al., 2006). A very mild phenotype that can regress with age is caused by mutation of PLEKHM1 gene (Van Wesenbeeck et al., 2007).

All these genes are involved in the acid secretion mechanism of osteoclasts, the mechanism by which osteoclasts cause bone resorption through its “extracellular lysosomes” (Teitelbaum and Ross, 2003). For example, the CLCN-7 gene encodes the chloride channel that resides in lysosomal vesicles and is thought to transport negative charge into the extracellular lysosomes, enabling the formation of the resorption lacunae. Osteoclasts secrete protons into the resorption lacunae, which are subsequently neutralized by the proton pump of osteoblasts.

4. Conclusion

Although tremendous advances have been made in the elucidation of the genetic defect of osteopetrosis over the past years, the role of accurate clinical and radiological assessment remains an important contributor to the diagnosis of infantile osteopetrosis.

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Table 1 (continued)

| Dysplasia | Pathogenetics | Onset/prognosis | Skeletal radiology | Clinical findings |
|-----------|---------------|-----------------|-------------------|-------------------|
| Osteopetrosis | Target site: endochondral ossification (secondary spongiosa). Inheritance pattern: X-linked dominant. Genetic defect: CLCN7. Unknown pathology. Variants: Osteopetrosis. | Childhood/incidental in adulthood. (rare) | Scherosis of the long bones and skull, and longitudinal striations visible on radiographs of the long bones, pelvis, and scapula | Presents in males with macrocephaly, cleft palate, mild learning disabilities. In females, the disorder is usually associated with foetal or neonatal lethality. Osteopetrosis without cranial sclerosis is typically asymptomatic, although there can be associated joint discomfort |
| Mixed sclerosing bone dysplasia | A very rare disorder characterized by a variable combination of melorheostosis, osteopoikilosis and osteopetrosis. | Childhood (rare) | Tends to be bilateral and symmetrical. Can affect any bone but there is a special predilection to the long bones. Osteosclerosis occurs along the periosteal and endosteal surfaces of long bones. The epiphyses are spared | Waddling gait, musculoskeletal aches, weakness. Patients can have hepatosplenomegaly and compressive optic neuropathy |
| Progressive diaphyseal dysplasia (Camurati–Engelmann) | Target site: intramembranous ossification. Inheritance pattern: AD. Genetic defect: TGFBI, R218C. It is due to osteoblastic overactivity. Alkaline phosphatase levels are commonly elevated | Childhood | Diffuse endosteal sclerosis osteosclerosis and hyperostosis of the skeleton, prominently observed in cranial and tubular bones | VBD: facial distortions, cranial nerve affection. Sclerosteosis: progressive skeletal overgrowth. Syndactyly is a variable manifestation. Worth disease: facial abnormalities, no facial nerve involvement, osseous prominence of the palate |
| SOST-related sclerosing bone dysplasias | Target site: intramembranous ossification. Van Buchem disease (VBD); inheritance: AR. Genetic defect: A deletion affecting the SOST gene alters expression of sclerostin in osteoblasts causing failure of osteoblastic bone formation. Sclerosteosis: inheritance: AD. Genetic defect: two independent mutations in SOST. Worth disease; inheritance pattern: AD | Childhood | (exceptionally rare) | |

Note: AR: Autosomal recessive, AD: Autosomal dominant, HSCT: Haematopoietic Stem Cell Transplantation.
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