

Case Report


Autosomal dominant osteopetrosis type II

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Abstract

Osteopetrosis ("marble bone disease") is a descriptive term that refers to a group of rare, heritable disorders of the skeleton characterized by increased bone density on radiographs. The overall incidence of these conditions is difficult to estimate but autosomal recessive osteopetrosis (ARO) has an incidence of 1 in 250,000 births, and autosomal dominant osteopetrosis (ADO) has an incidence of 1 in 20,000 births. Osteopetrotic conditions vary greatly in their presentation and severity, ranging from neonatal onset with life-threatening complications such as bone marrow failure (e.g. classic or "malignant" ARO), to the incidental finding of osteopetrosis on radiographs (e.g. osteopoikilosis). Classic ARO is characterised by fractures, short stature, compressive neuropathies, hypocalcaemia with attendant tetanic seizures, and life-threatening pancytopenia. The presence of primary neurodegeneration, mental retardation, skin and immune system involvement, or renal tubular acidosis may point to rarer osteopetrosis variants, whereas onset of primarily skeletal manifestations such as fractures and osteomyelitis in late childhood or adolescence is typical of ADO. Osteopetrosis is caused by failure of osteoclast development or function and mutations in at least 10 genes have been identified as causative in humans, accounting for 70% of all cases. These conditions can be inherited as autosomal recessive, dominant or X linked traits with the most severe forms being autosomal recessive. Diagnosis is largely based on clinical and radiographic evaluation, confirmed by gene testing where applicable, and paves the way to understanding natural history, specific treatment where available, counselling regarding recurrence risks, and prenatal diagnosis in severe forms. Treatment of osteopetrotic conditions is largely symptomatic, although haematopoietic stem cell transplantation is employed for the most severe forms associated with bone marrow failure and currently offers the best chance of longer term survival in this group. The severe infantile forms of osteopetrosis are associated with diminished life expectancy, with most untreated children dying in the first decade as a complication of bone marrow suppression. Life expectancy in the adult onset forms is normal.

Key words

Osteopetrosis, Hematopoietic stem cell transplantation (HSCT), Bone-within-bone appearance, Erlenmeyer-flask deformity.

Introduction

Osteopetrosis is a family of bone diseases characterized by osteoclast failure and impaired bone resorption [1]. It was first identified by Albers-Schönberg and described as “marble bone disease” due to intense sclerosis of the skeleton [2]. It is found in humans, but also in rodents with similar hallmarks among species [3]. Osteopetrosis presents with various symptoms and heterogeneous severity, from asymptomatic to fatal in infancy. Presently, there is no effective treatment, while hematopoietic stem cell transplantation (HSCT) is performed only for the most severe forms. However, N50% of failure and high risk (25%) of disease progression has been reported, with the worst survival (24%) for recipients of HLA-haplotype-mismatch HSCT [4]. Nevertheless, significant advance has been made in recent years and the disease is now better understood both genetically and clinically. This review will summarize recent knowledge on the pathogenesis of osteopetrosis and will discuss future challenge and developments for therapy.

Osteopetrosis is a rare inherited genetic disease characterized by sclerosis of the skeleton caused by the absence or malfunction of osteoclasts. The aim of this case report was to present the clinical and radiographic features of a 35-year-old female patient with autosomal dominant osteopetrosis type II who exhibited features of chronic generalized periodontitis, and the radiographs revealed generalized osteosclerosis and hallmark radiographic features of ado type ii, that is, “bone-within-bone appearance” and “erlenmeyer-flask deformity.”

Case report

A 35-year-old patient reported with the chief complaint of deposits on teeth from the past 6-7 months. While recording the case history, the patient complained of intermittent mild pain in the lower back region from the past three months

which aggravated on daily activity and was relieved by rest, and pain was radiating to both the lower limbs. Blood investigation and X-ray water's view and x-ray cervical spine were done (**Photo – 1A, 1B**).

Photo – 1A, 1B: Water's view and lateral cervical spine x-ray.



Paranasal sinuses and the cervical spine (PNS, lateral skull, and cervical spine) which revealed increased bone density of all the bones of the skull, face, and the cervical spine. These views revealed thickening of the cortical boundaries of all the bones with obliteration of the marrow spaces. Lateral skull view revealed thickening of the inner and outer cortical tables and widening of the diploic space. The base of the skull appeared highly radiodense with loss of trabecular pattern, and there was hypoplasia of foramen magnum, and other foramina were obliterated. The nasal cavity and the sinuses were also hypoplastic showing high areas of radiodensity. Anteroposterior view of cervical spine showed increased radiodensity in all the cervical vertebrae.

Discussion

Osteopetroses are a heterogeneous group of bone diseases in which inherited transmission allowed the first bone researchers to distinguish between a dominant (ADO) and a recessive (ARO) form: this distinction was already settled at the beginning of the last century and was extremely interesting from a clinical point of view. Indeed, the phenotype was very severe in the recessive form, but usually mild or even asymptomatic in the dominant one, which was sometimes dubbed as “benign.” Retrospectively, the idea that all forms of human osteopetrosis were osteoclast rich was not well founded. Osteoclasts can be demonstrated at autopsy, but there were very few reports of osteopetrosis autopsy [5-8]. The other way to assess the presence of osteoclasts is to perform bone biopsy studies in living patients. However, this is an invasive procedure, albeit modest, and it is rarely performed in infants who are severely ill, as many clinicians believe that is not worth carrying out, since so far it has not contributed anything to patient management. Moreover, due to the abnormal bone remodeling, bone specimens do not always reflect the presence of osteoclasts, since these cells could be present outside of the small area investigated by the biopsy. However, when the RANKL/RANK/TRAF6 axis was identified and

mice deficient for these molecules were shown to have an osteopetrotic phenotype, several researchers, including ourselves, tried to investigate these genes in humans, initially without finding any mutations, thus suggesting the idea that such defects did not contribute to human osteopetroses.

Conclusion

ado type II is the most common form of osteopetrosis with an estimated prevalence of 1 in 20,000 births. Age of onset of ado type II is late childhood or adolescence. The diagnosis of osteopetrosis is based on radiological and clinical features and these findings are sufficiently characteristic to make a definite diagnosis, and there is no need to perform a genetic study to confirm the disease.

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