Case Report

Osteopetrosis: A rare case

Niladri Das, Pranab Kumar Sahana[1], Silima Subhasnigdha Tarenia[2], Prashant Manohar Gaikwad, Arjun Baidya, Nilanjan Sengupta, Soumik Goswami

Department of Endocrinology and Metabolism, Nilratan Sircar Medical College and Hospital, [1]Department of Endocrinology and Metabolism, Institute of Postgraduate Medical Education and Research, [2]Department of Endocrinology and Metabolism, Medical College, Kolkata, West Bengal, India

Abstract

Osteopetrosis is a rare inherited metabolic bone disease characterized by failure of osteoclasts to resorb bone leading to impairment of bone modeling and remodeling. The defect in bone turnover results in skeletal fragility despite increased bone mass, hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth failure. It has two major clinical forms: an autosomal dominant benign type or an autosomal recessive malignant type. The recessive form is usually fatal whereas the dominant type is more compatible with life. A rare autosomal recessive (intermediate form) is more prevalent and has less severe presentation. A 12-year-old boy presented with short stature, bilateral progressive vision loss, and backache. X-ray of nondominant hand for bone age estimation showed bone in bone formation. Followed which skeletal survey was done which showed characteristic radiological findings suggestive of osteopetrosis. Osteopetrosis is a rare disease transmitted by autosomal dominant or recessive inheritance having variable penetrance. We report here intermediate form of osteopetrosis. Although the genetic test is used to differentiate between the subtypes, diagnosis is mainly radiological.

Keywords: Metabolic bone disorder, osteopetrosis, short stature

Address for correspondence: Dr. Niladri Das, No. 166/A Nakari Mondal Road, North 24 Parganas, Kanchrapara - 743 145, West Bengal, India.
E-mail: niladri.medmamc@gmail.com
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INTRODUCTION

Osteopetrosis also known as marble bone disease or Albers-Schonberg disease named after the German radiologist reported first description of the condition in 1904.[1] It is characterized by the failure of osteoclasts to resorb bone leading to impairment of bone modeling and remodeling. The defect in bone turnover results in skeletal fragility despite increased bone mass, hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth failure. The estimated prevalence is 1 in 100,000–500,000 birth.[2] It is present as either an autosomal dominant benign type or an autosomal recessive malignant type. In the recessive form, caused by biallelic mutation of any one genes involved in osteoclast function or differentiation namely TCIRG1, CLCN7, OSTM1, SNX10, PLEKHM1, TNFSF11, TNFRSF11A; the child is severely symptomatic early in life and usually fatal. The dominant type, caused by a heterozygous missense mutation of CLCN7 gene on the other hand is more compatible with life. However, an intermediate type[3] due to carbonic anhydrase II deficiency is more prevalent in practice and has less severe presentation.

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CASE REPORT

A 12-year-old boy presented with poor gain of height noticed since 6 years of age along with bilateral progressive vision loss and backache. He was born out of nonconsanguineous marriage, with a birth weight of 1.6 kg by normal vaginal delivery at term, cephalic presentation with uneventful perinatal and antenatal history. There was no history of headache, nausea, vomiting, polyuria, and any chronic systemic illness. There was no history of head injury, radiation present. On anthropometry, height is 118.5 cm (< 3rd percentile) with standard deviation score (SDS) -4.33 and height age of 6.5 years. weight is 21 kg (< 3rd percentile), SDS -1.86 and weight age 6.5 years. Midparental height 162.75 cm and target height 164.8cm with SDS -1.13. Upper segment 62.5cm , lower segment 56cm. The child was prepubertal and bilateral testicular volume is 2 ml. Systemic examination is within normal limit, except presence of caries teeth, and visual acuity of finger counting in bilateral eyes. X-ray hand was done for bone age estimation, which shows bone in bone formation [Figure 1]. In view of these typical imaging findings, the skeletal survey was done, which shows the base of skull sclerosis [Figure 2] hypoplastic sinuses, reduced medullary cavity of long bones, erlenmeyer flask deformity of long bones [Figure 3] sandwich vertebra [Figure 4]. In view of characteristic imaging findings suggestive of osteopetrosis, further investigations were done for complications screening. Magnetic resonance imaging (MRI) LS SPINE done showed compression of nerve roots with disc bulge at L4-5 and L5-S1, straightening of the lumbar spine, and diffuse decreased bone marrow signal-intensity suggestive of myelofibrosis. Computed tomography brain done which shows communicating hydrocephalus. Pure tone audiometry showed a mild conductive loss in the right ear. Complete blood count showed only anemia with other cell lines remaining unaffected. Other baseline investigations are given in Table 1. Visual evoked potential showed bilateral optic atrophy. In view of the clinical diagnosis of osteopetrosis, the skeletal survey of the sibling was done, which also shows characteristic radiological findings, though he was asymptomatic with normal height for age.

DISCUSSION

Clinical manifestation of osteopetrosis ranges from asymptomatic to fatal course depending on the mode of inheritance. Our index case had clinical features consistent with an intermediate form of disease whereas his elder sibling is asymptomatic which denotes that the disease was likely inherited as autosomal recessive form with varying severity in the family members. The main features are short stature, visual and hearing loss, nerve entrapment syndromes, anemia, and hepatosplenomegaly. The characteristic clinical features of different types of osteopetrosis are given in Table 2.

Short stature is due to impaired longitudinal growth and dysmorphic craniofacial appearance is caused by macrocephaly and bossing of the forehead.[4] Due to continued bone formation, hematopoiesis is affected resulting in bone marrow failure, pancytopenia, and compensatory extramedullary hematopoiesis leading to hepatosplenomegaly, increased susceptibility to infection. The abnormally thickened bone also causes narrowing of cranial foramina resulting in nerve entrapment and hence facial palsy, deafness, and blindness.[5] The decrease in height age and bone age along with weightage could be explained by associated decrease in appetite and hence malnutrition secondary to systemic involvement of the disease and associated suspected renal tubular acidosis.

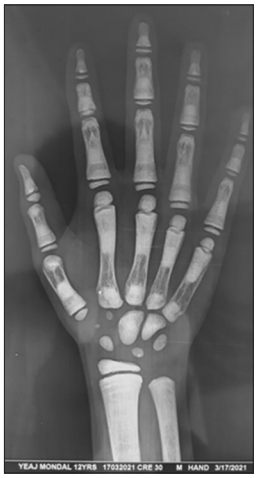

Figure 1: X-ray hand showing bone in bone formation

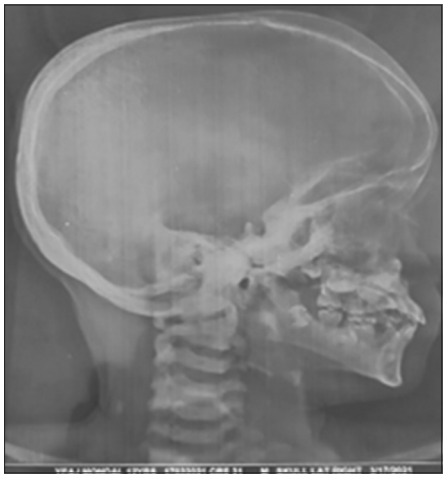

Figure 2: X-ray skull showing sclerosis of base of skull

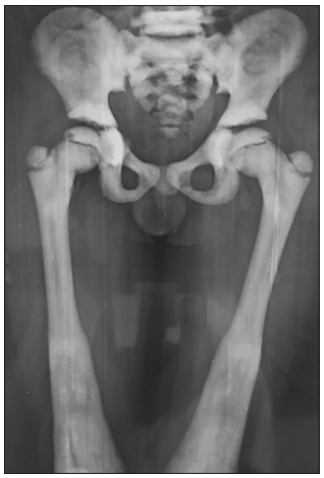

Figure 3: X-ray leg showing Erlenmeyer flask deformity of long bones, narrowing of medullary cavity

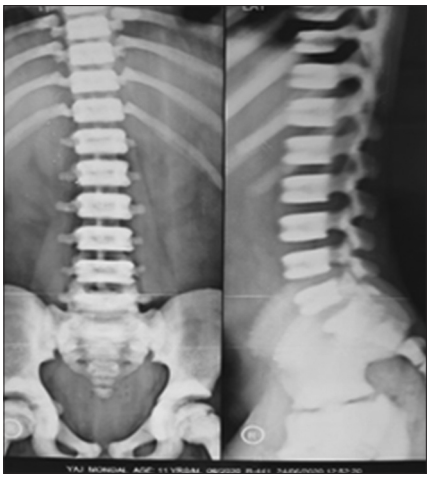

Figure 4: X-ray spine showing sandwich vertebra

Diagnosing osteopetrosis is mostly relied on skeletal radiology. On plain radiographs, osteopetrosis can present as osteosclerosis or dense bones. Four classic features appear in radiographs of patients: (1) diffuse sclerosis, affecting the skull, spine, pelvis, and appendicular bones; (2) metaphysis long bone defects known as "Erlenmeyer flask deformity," and characteristic lucent bands; (3) "bone-in-bone" appearance of the vertebrae and phalanges; and (4) sclerosis of skull base, pelvis, and vertebral end plates, giving rise to "sandwich" vertebrae, and "rugger-jersey" spine.[6] Genetic testing can be used to confirm the diagnosis and distinguish between various osteopetrosis subtypes, but not done in our case due to economic constraints.

The differential diagnoses include other disorders which can cause osteosclerosis, such as pyknodysostosis, hypervitaminosis D, Paget's disease, bone metastasis of breast or prostate cancer, fluoride, lead or beryllium toxicity.

Hematopoietic stem cell transplantation (HSCT) is the only treatment for osteopetrosis. HSCT using HLA identical donors results in 73% 5 years disease free survival.[7] Interferon-gamma 1b (IFNγ1b) treatment has been tried in patients with osteopetrosis variants unresponsive to HSCT or as a bridging therapy to transplantation. IFNγ1b leads to improvement in immune function, increased bone resorption, and increase in bone marrow space.[8] Other medications which can be administered in osteopetrosis include (1) Vitamin-D supplements which stimulate the dormant osteoclasts, resulting in bone resorption and (2) corticosteroids-stimulate bone resorption. While some may be asymptomatic, many of these patients require orthopedic surgery at some point in their lives for fractures.

Table 1: Baseline relevant investigations

Biochemical Test	Values (Reference range)
Urine pH	6 (4.6-8)
Blood pH	7.41 (7.35-7.45)
pCO_2	22.6 mmHg (35-45)
Serum HCO_3	17 mEq/L (22-30)
Serum chloride	106 mEq/L (96-106)
Anion gap	14 mmol/L (8-16)
TSH	2.3 miu/ml (0.4-4.5)
Free T4	1.2 ng/dl (0.8-1.8)
Calcium	9.72 mg/dl (8.5-10.5)
Phosphorus	4.0 ng/dl (3.5-4.5)
Serum potassium	4.7 mEq/L (3.5-5.5)
25 (OH) Vitamin D	16 ng/ml (<20 ng/ml)
8 AM cortisol	15 ug/dl (5-25)
LH	<0.01 miu/ml (0.8-7.6)
FSH	1.3 miu/ml (0.7–11)
IGF1	348 ng/ml (173-420)
LDH	>2078 IU/L (105-333)

IGF1: insulin like growth factor 1, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, LDH: Lactate dehydrogenase, TSH: Thyroid stimulating hormone

Table 2: Clinical classification of osteopetrosis

Characteristics	Adult onset	Infantile	Intermediate
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Bone marrow failure	None	Severe	None
Prognosis	Good	Poor	Poor

CONCLUSION

Although osteopetrosis is a rare disease, the diagnosis should be considered in children presenting with short stature, nerve entrapment syndromes, anemia, and radiological survey is required to confirm the diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to

be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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