Infantile Osteopetrosis in Two Siblings: Case Report

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Introduction

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 [1]. 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 [2,3]. 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 pancytopaenia [4]. 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 [5,6]. 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 [1]. 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 [7]. 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[8]. 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. It is anticipated that further understanding of the molecular pathogenesis of these conditions will reveal new targets for pharmacotherapy [9].

Case report

A 30 months old female child, of consanguineous parents was admitted in TTH with progressive pallor ,growth retardation and impairment of vision. She was born normally and had uneventful pregnancy and postnatal history. She had delay in

developmental milestones at presentation. On examination, her weight was 9.5 kg, length was 82 cm and head circumference was 42.5 cm. There was prominent frontal bossing. Patient was pale. Heart rate was 94/ min, respiratory rate was 28/min. Liver was enlarge, firm, non-tender, smooth surface and spleen was also enlarged. Visual impairment was found and hearing was normal. Skin and mucous membrane were also normal. Examination of other systems reveals no abnormality.

Investigation revealed: Hb: 7.4 gm/dl, WBC count : 10,400 * 10^9/L, Neurtophil-75%, Lymphocyte-15%, Monocyte-8%, Eosinophil-2%,Basophil-0%. Blood film shows anisopoikilocytosis of red blood cells, mostly normocytic. A fair number of tear drop cells and a small number of fragmented cells were present. Reti

culocyte count was 2.5 %.Platelets count was 80 * 10^9/L.

S. calcium: 2 mmol/L, Serum phosphate: 2 mmol/L. blood urea 2.6 mmol/L and serum creatinine: 50 mmol/L, serum alkaline phosphatase: 229 U/L, Serum ALT , AST 59,44 U/L respectively. Blood group 'B' positive.

An unenhanced CT scan of the head performed showed marked sclerosis and cortical thickening predominantly within the skull base with mild focal and mild frontal region cortical atrophic changes and prominent ventricular system .

A radiographic skeletal survey revealed diffuse bony sclerosis and a bone within bone appearance involving the long bones, thoracolumbar spine, and bony pelvis with increased thickness of vault in lateral skull radiograph and generalised increased bone density in anteroposterior radiograph of hand and wrist figures 1,2. These findings with the history and clinical presentation were consistent with the diagnosis of osteopetrosis.

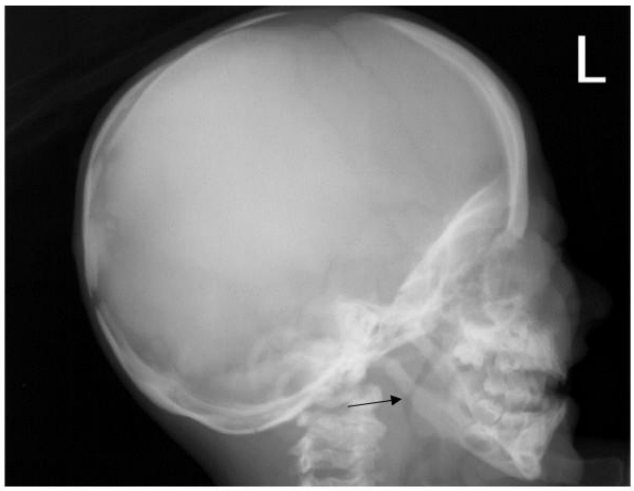

Figure (1): Lateral skull radiograph note increased thickness of vault.

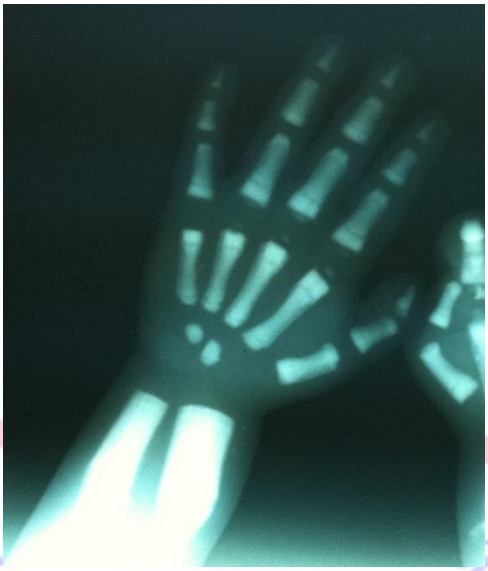

Figure (2): Hand and wrist radiograph, notice generalised increased bone density.

Bone marrow study showed a cellular marrow trails and fragments. Megakaryocytes seen in a good number with normal form. Erythropoiesis: active with normoblastic maturation. Myelopoesis: active with all series of maturation. Blast 2% of ANC. C:B ratio 12:1.lymphocyte 30% of ANC.

Hemoglobin electrophoresis show HbA 95.49% and HbA2 4.51 % with raised HbA2 density .Direct Coombs test was negative.

Here younger brother is 3 months old boy, born normally with uneventful pregnancy and delivery. He started to have progressive pallor 1 month after delivery with recurrent chest infection. On examination, his weight was 4 kg and length was 55 cm. Patient was pale. Heart rate was 120/ min, respiratory rate was 38/min. Liver and spleen were enlarged.

Investigation revealed: Hb: 8.6 gm/dl, WBC count : 35.000 * 10^9/L, Neurtophil -23%, Lymphocyte -45%, Monocyte-4%, Eosinophil-3%,Basophil-2. Blood film shows normchromic normocytic with polychromasia and many nucleated red blood cellsReticulocyte count was 15 %.Platelets count was 53 * 10^9/L.WBC show leukocytosis with immature cells of granulocytic series with blast cell expression.

S. calcium: 2.6 mmol/L, Serum phosphate: 1.4 mmol/L. blood urea 4.7 mmol/L and serum creatinine: 50 mmol/L, serum alkaline phosphatase: 410 U/L, Serum ALT , AST 32,46 U/L respectively. Blood group 'B' positive.

Hemoglobin electrophoresis show HbA 97.46 % and HbA2 2.54 % with normal hemoglobin A pattern and bone marrow aspiration shows normal trails.

A radiographic skeletal survey revealed diffuse bony sclerosis figure 4. CT sacan of the brain was normal.

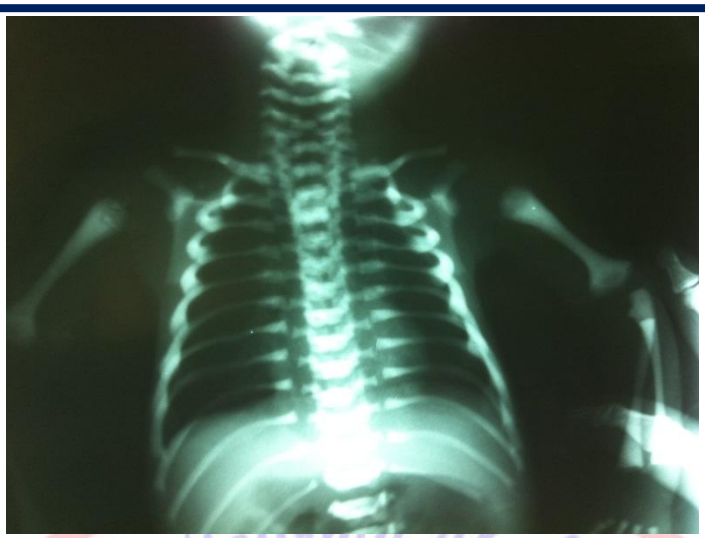

Figure (3): Radiograph shows diffuse bony sclerosis.

Both patients were diagnosed as a case of Malignant Infantile Osteopetrosis and was treated with blood transfusion.

Discussion

Malignant infantile osteopetrosis (MIOP) is a rare genetically heterogeneous autosomal recessive disorder of bone metabolism, which if untreated has a fatal outcome. The disease is caused by defect or mutation in gene ATP6i (vacuolar proton pump) or gene CIC-7 (chloride channel) [10,11]. Localization of gene causing autosomal dominant osteopetrosis type I was found in chromosome 11q12-139. The pathogenic defects may be intrinsic to either the osteoclast monocyte lineage or the mesenchymal cells that constitute the microenvironment which supports osteoclast ontogeny and activation [12]. Because of heterogeneity of genetic defect, the disease presents with spectrum of clinical variants. MIOP is presented in early life. Our patients were symptomatic since first month of age with severe progressive anemia and recurrent infections and growth failure which was evidenced by severe stunting and underweight, moderate wasting. Defective resorption of osseous tissue tends to replace bone marrow which causes marrow failure. Patient may have recurrent infection, anaemia and hepatosplenomegaly which were present in our cases. Recurrent infection is common due to defect in the immune systems and extramedullary erythropoiesis may result in hepatosplenomegaly [13].

The major clinical features derived from bony overgrowth of the marrow space and compression of optic and auditory nerve, which pass through the major foramina of the skull [14]. Although MIOP is a disease of bone, but most serious consequence is seen in nervous system [10,11]. Cranial nerve neuropathies occur due to failure of foramina in the skull to widen completely. Deafness, blindness, optic atrophy, proptosis, carpal tunnel syndrome may be the presenting features. Stroke is also reported in MIOP [11]. Patient may also present with nasal stuffiness due to mastoid and paranasal sinus malformation. But these manifestations were absent in our cases. Gingival hyperplasia and nystagmus were reported in a 2 months old female child [15]. Dentition may be delayed1 but in our first case Ghalia teeth were present. In osteopetrosis bones are fragile and can cause fracture easily. Osteomyelitis of

mandible is also common because of abnormality in blood supply [13]. Rickets which is termed osteopetrorickets is found as a complication of osteopetrosis with variable features [14,16]. This is due to failure of osteoclasts to maintain normal calcium and phosphorus level in extracellular fluid [16]. Presence of rickets may worsen the symptoms of osteopetrosis which is associated with increased lethargy, irritability, poor feeding, growth retardation and pathological fracture. No features suggestive of rickets were found in our case. Parathyroid hormone is also found elevated in MIOP [13,12]. Parathyroid hormone was not assessed in our case. The diagnosis of osteoptrosis depends on the presence of positive radiographic features in bone [15,17]. Increased density is found in all types of bones which were found in our case. Bone density test and bone biopsy can confirm the diagnosis [15]. In our case bone marrow examination has confirmed the diagnosis.

Whatever therapies are given, the only potential curative therapy for MIOP at this time is a successful hemapoietic stem cell bone marrow transplant using either bone marrow or peripheral blood stem cells from a suitable matched sibling [15,14,18,19-16,20,21[1]. An alternative option is hemapoietic stem cell bone marrow transplant from a partially matched family donor such as a parent or children [22]. Other management of patients with osteopetrosis requires a comprehensive approach to characteristic clinical problems including hematologic and metabolic abnormalities, fractures, deformity, bone pain, ostcomyelitis and neorologic sequelae[12] . Supportive treatment includes blood transfusion for anaemia, antibiotic for infection and orthopaedic treatment for fracture [23]. Optic nerve decompression, splenectomy has been performed in cases where indicated. Corticosteroid has been used in some cases with benefit for controlling anemia and thrombocytopenia and stimulating bone resorption but has been of no benefit in other cases [13,12,24]. Calcitriol has been used by some author leading to clinical improvement [12,25]. It is a bone resorbing agent which stimulates dormant osteoclasts and thus stimulates bone resorption. Erythropoetin can be used to correct anemia in osteopetrosis [14]. Treatment with gamma interferon improves white cell function that tremendously decreases the incidence of new infection [13,12]. Nutritional support and calcium supplementation are necessary to treat malnutrition and rickets. If untreated infantile osteopetrosis usually results in death by the first decade of life [23].

We have to remember osteopetrosis when the diagnosis of anemia couldn't be reached.

References:

[1] Superti-Furga A US, and the Nosology Group of the International Skeletal Dysplasia Society: Nosology and Classification of Genetic Skeletal Disorders: 2006 Revision. American Journal of Medical Genetics Part A 2007, 143A:1-18.

[2] Loria-Cortes R, Quesada-Calvo E, Cordero-Chaverri C: Osteopetrosis in children: a report of 26 cases. J Pediatr 1977, 91:43-47.

[3] Bollerslev J, Andersen PE Jr: Radiological, biochemical and hereditary evidence of two types of autosomal dominant osteopetrosis. Bone 1988, 9:7-13.

[4] Al-Tamimi YZ, Tyagi AK, Chumas PD, Crimmins DW: Patients with autosomal-recessive osteopetrosis presenting with hydrocephalus and hindbrain posterior fossa crowding. J Neurosurg Pediatrics 2008, 1:103-106.

[5] Jacquemin C, Mullaney P, Svedberg E: Marble brain syndrome: osteopetrosis, renal acidosis and calcification of the brain. Neuroradiology 1998, 40:662-663.

[6] Whyte MP: Carbonic anhydrase II deficiency. Clin Orthop Relat Res 1993, 52-63.

[7] Waguespack SG, Hui SL, White KE, Buckwalter KA, Econs MJ: Measurement of tartrate-resistant acid phosphatase and the brain isoenzyme of creatine kinase accurately diagnoses type II autosomal dominant osteopetrosis but does not identify gene carriers. J Clin Endocrinol Metab 2002, 87:2212-2217.

[8] Key L, Carnes D, Cole S, Holtrop M, Bar-Shavit Z, Shapiro F, Arceci R, Steinberg J, Gundberg C, Kahn A, et al.: Treatment of congenital osteopetrosis with high-dose calcitriol. N Engl J Med 1984, 310:409-415.

[9] Del Fattore A, Peruzzi B, Rucci N, Recchia I, Cappariello A, Longo M, Fortunati D, Ballanti P, Iacobini M, Luciani M, et al.: Clinical, genetic, and cellular analysis of 49 osteopetrotic patients: implications for diagnosis and treatment. J Med Genet 2006, 43:315-325.

[10] Frattini A, Pangrazio A, Susani L, Sobacchi C, Mirolo M, Abinun M et al. J Bone Miner Res 2003; 18: 1740-47.

[11] Steward CG. Neurological aspect of osteopetrosis. Neuropathol Appl Neurobio 2003; 29: 87-97.

[12] Kocher MS, Kasser JR. Osteoptrosis. Am J Ortho 2003; 32: 222-28.

[13] http://www.emedicine.com/med/topic 1962.htm- BhargavaA, Blank R. Osteopetrosis. 2002.

[14] Kulkarni ML. Osteopetrosis - Case reports. Indian Pediatr 2003; 40: 561-62.

[15] Mohn A, Capanna R, Delli Pizzi C, Morgese G, Chiarelli F. Autosomal malignant ostcopertrosis: From diagnosis to therapy. Mincrva Paediatr 2004; 56: 115-18.

[16] Kirubakaran C, Ranjini K, Scott JX, Basker M, Sridhar G. Osteopetrorickets. J Tro Paed 2004; 50: 185-65.

[17] Stoker DJ. Osteopetrosis. Semin Musculoskeletal Radiol 2002; 6: 299-05.

[18] Berkow R. The Mark Manual of Diagnosis and therapy. Osteopetrosis. 14th edition, MSD, 1982 S, 1234-38.

[19] Van Hut E, Gram J, Bollerslew J, Van WL, Mathysen D, Andersen PE. Localization of the gene causing autosomal dominant osteopetrosis type I to Chromosome 11 q 12-13. J Bone Miner Res 2002; 17: 1111-17.

[20] Chen CJ, Chao TY, Chu DM, Janckila AJ, Cheng SN. Osteoblast and osteoclast activity in a malignant infantile Osteopetrosis patient following bone marrow transplantation. J Pediatr Haematol Oncol 2004; 26: 5-8.

[21] Drissen GJ, Gerritsen EJ, Fischer A, Fasth A, Hop WC, Veys P, et al. Long term outcome of haematopoetic stem cell transplantation in autosomal recessive Osteopetrosis: an EMBT report. Bone marrow transplant 2003; 32: 657-63.

[22] hltp: // www.stjude.omf/disease-Rare disease: Osteopetrosis (malignant infantile form) summarise, Jan 2005.

[23] Tabib SMSB, Halim MA, Islam MN. Osteopetrosis – A case report, Bang J Med Sci 1996; 391: 27-31.

[24] Barr DGD, Geol KM. Disorder of bones and Collageu. In: Campbell AGM, McIntosh N, editors. Forfar and Arneil's Text book of Pediatrics. 4th ed. ELBS Churchill Livingstone UK; 199. P. 1656.

[25] Key L, Carnes D, Cole S. Treatment of congenital osteopetrosis with high dose calcitriol. N Engl J Med 1984; 310: 409-15.