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A Case Report: Malignant Infantile Osteopetrosis (MIOP)

Medical Science

KEYWORDS : Osteopetrosis; Infant; Hepatomegaly; Splenomegaly

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ABSTRACT

Background: Malignant infantile osteopetrosis (MIOP) presents early in life with extreme sclerosis of the skeleton and reduction of bone marrow spaces. Since there is a defect in the bone marrow, the disease can cause anaemia, extra medullary haematopoiesis secondary to anaemia leading to hepatosplenomegaly, cranial nerves compression and severe growth failure. This disorder is often lethal within the first decade of life because of secondary infections. Stem cell transplantation (SCT) remains the only curative therapy.

Case Presentation: We report a 4-month old male infant, diagnosed as MIOP while investigating the cause of hepatosplenomegaly.

Conclusion: Malignant infantile osteopetrosis should be kept in mind as a rare cause of hepatosplenomegaly and the patient should be referred for stem cell transplantation before neurologic or visual impairment develops.

Introduction

Malignant infantile osteopetrosis (MIOP) is an autosomal recessive disorder characterized by reduced activity of osteoclasts, resulting in generalized bone osteosclerosis. Abnormal osteoclast activity paired with normal bone formation by osteoblasts leads to the development of densely sclerotic fragile bones. The disease presents in the first few months of life with the manifestations relating to underlying defect in osteoclastic bone resorption. Overgrowth of cranial nerve foramina results in nerve compression, which frequently affects the optic, auditory, and facial nerves. Increased bone density also obliterates the medullary cavity, leading to extra medullary haematopoiesis, hepatosplenomegaly, anaemia, and thrombocytopenia. Growth retardation and recurrent infections are also common. The disease is fatal in infancy and is cured with hematopoietic stem cell transplantation, with a rate of success by 50% and unsatisfactory rescue of growth and visual deterioration. In this article, we report a 4-month old baby, who presented with hepatosplenomegaly and anemia in new born period and is diagnosed as infantile malignant osteopetrosis.

Case Presentation

A 4 month-old male infant was admitted to the department of paediatrics with complaint of severe pallor and hepatosplenomegaly. Past medical history of the patient revealed that he was hospitalized on 20th day of life in the neonatal unit for pyogenic meningitis. He was 1st child born of the triplets after an elective caesarean section performed for triplet delivery after an uncomplicated pregnancy. Delivered at 32 gestation week according to Ballard scoring system with birth weight of 1200 gm. Parental consanguinity was not significant in the past medical history. One son and one daughter of the family died in infancy period with unknown etiology. Systemic examination revealed hepatomegaly with the liver noted to be 4 cm, splenomegaly with the spleen noted to be 3 cm. The patient had a levelled anterior fontanel with 3×2 cm in size. His weight was 2.9 kg (<3rd percentile), his height was 46 cm (<3rd percentile) and head circumference of the patient was 36 cm (50-75 percentile).

Laboratory examination yielded the following: haemoglobin 7.2 g/dl; white blood cell count 4400 cells/mm^3 and platelet count 1.08 lakh /mm^3. Biochemical analysis was normal except for AST 118 U/L, LDH 1150 U/L, parathyroid hormone (PTH) levels were 349 pg/mL, alkaline phosphatase (ALP) was 847 IU/L, acid phosphatase was 16.4 U/L. Peripheral blood smear was significant for leukoerytroblastosis. Serology for toxoplasma, rubella, cytomegalovirus, herpes, and hepatitis virus was negative.

Abdominal ultrasonography detected a marked hepatosplenomegaly. Cranial ultrasonography was normal. Fundoscopic examination revealed optic atrophy bilaterally.A computed axial tomographic scan of orbits demonstrated the narrowing of the optic foramina bilaterally. Skeletal survey revealed diffuse sclerosis of all bones with "harlequin mask appearance" (Fig.1) (sclerosis of sphenoid and orbital bones) "bone within a bone" appearance(Fig.2), and alternating sclerotic and lucent bands in vertebrae "sandwich appearance"(Fig.3). All Figures below case presentation.

Visual evoked potential (VEP) and brain-stem evoked response examination (BERA) showed bilateral profound sensory neural hearing loss. Our initial diagnosis was congenitally acquired infection (TORCH) or a kind of storage disease (like lipid storage or lysosomal diseases) but physical examination and skeletal survey confirmed the diagnosis of osteopetrosis. The disease was presented in new born period and two children of the family had died. Absence of any metabolic acidosis with an alkaline urine pH and the absence of any cerebral calcifications excluded a diagnosis of carbonic anhydrase II deficiency syndrome. The patient was referred for hematologic stem cell transplantation (SCT).

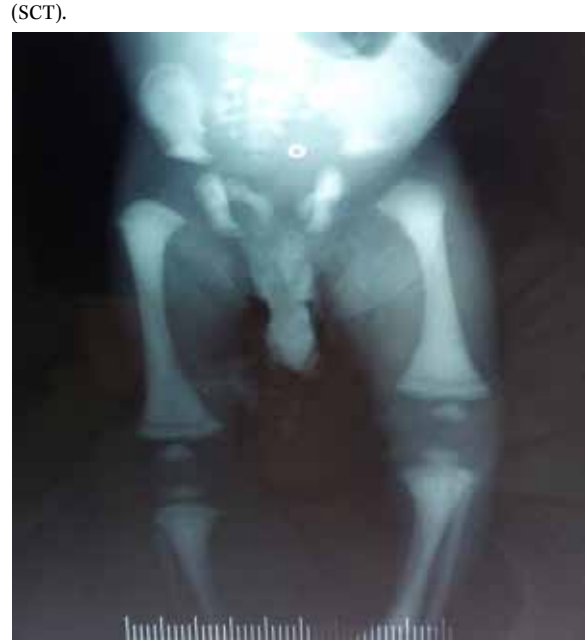

Fig 1: Pelvis and lower limbs radiograph. Note generalized bone density with "bone in bone appearance".

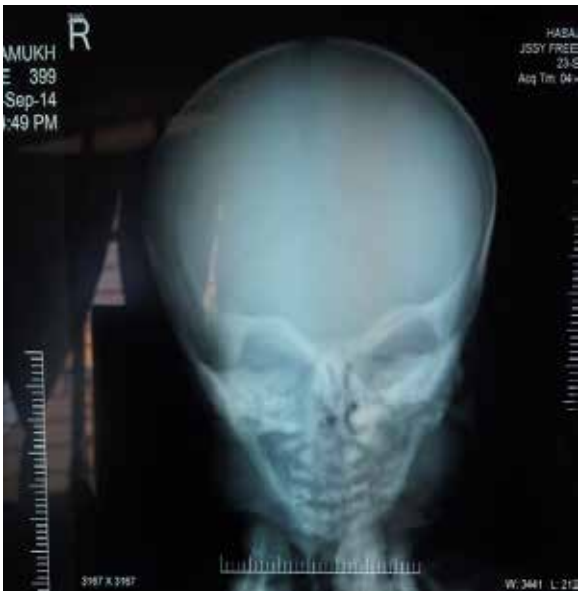

Fig 2: Facial skull radiograph. Note sclerosis of the orbits and sphenoid bones resulting in "Harlequin mask appearance".

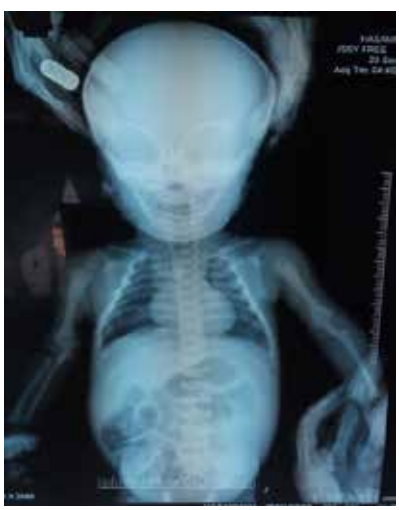

Fig 3: Spine radiograph. Note vertebral sclerosis resulting in "sandwich vertebrae appearance"

Discussion

Osteopetrosis is clinically a highly heterogeneous group of conditions that share the hallmark of increased bone density on radiographs due to abnormalities in osteoclast differentiation or function **[1]**. There are four subtypes of OP (a) malignant or infantile OP, (b) Benign or adult OP, (c) intermediate OP, and (d) carbon anhydrase type II (CAII) deficiency.**[2]**

Malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form of this disease that generally begins in utero **[3]**, it presents at birth **[4,5]**, or within the first year of life and is associated with increased severity compared to the autosomal dominant form **[6]**. Our patient had the symptoms since the age of four months. It has an incidence of 1 in 250,000 births, with a particularly high incidence reported in Costa Rica (3.4:100000) **[7,8]**.

The increase in bone mass leads to phenotypic features such as macrocephaly and frontal bossing. Tooth eruption defects are also common. The longitudinal growth of bones is impaired with a short stature and predisposition to fractures and osteomyelitis.

The abnormal expansion of bone interferes with medullary haematopoiesis, resulting in life-threatening anaemia, thrombocytopenia, increased susceptibility to infections, and extra medullary haematopoiesis sites such as the liver and spleen.

The most commonly observed neurological manifestations of osteopetrosis are secondary to obstruction of the foramina through which the cranial nerves, spinal cord and major blood vessels transverse the skull, resulting in blindness, hearing loss, facial palsy and hydrocephalus **[9,10]**. Distinct from these compressive phenomena, some patients with autosomal recessive osteopetrosis variants (neuropathic ARO) display signs of primary neurodegeneration including primary seizures in the setting of normal calcium levels, developmental delay, hypotonia, retinal atrophy and sensorineural deafness**[9]**.Reported brain MRI findings include significantly delayed myelination and diffuse progressive cortical and subcortical atrophy **[11,12]**. Children with MIOP are at risk of developing hypocalcaemia, with attendant tetanic seizures and secondary hyperparathyroidism**[1,4-5]**. Rickets has been also observed as a complication of MIOP **[13]**. The above patient showed hypocalcaemia and rickets.

Characteristic radiographic findings in osteopetrosis include a marked increase in bone density with defective metaphyseal remodelling, and a ″bone within a bone″ appearance **[7]**. Alternating sclerotic and lucent bands can give the vertebrae a ′sandwich′ appearance. Computerized tomography scan can be used for diagnosis and to determine the effect of the treatment. It is also used to assess auditory and optic canal **[14]**. The skeletal survey and CT scan of our patient was specific for radiologic findings of osteopetrosis.

Genetic testing can be used to confirm the diagnosis and differentiate between different subtypes of osteopetrosis, providing additional information regarding prognosis, likely response to treatment and recurrence risks **[1]**. Bone biopsy can distinguish between osteoclast-poor and osteoclast-rich subtypes of MIOP **[1]**, osteomedullary biopsy of our patient revealed rare osteoclasts.

In our case, storage disease and congenital acquired infection were excluded because laboratory tests findings did not support them. Based on clinical history and radiographic findings, our case was diagnosed as the infantile or malignant type. Management of patients with osteopetrosis requires a comprehensive approach to characteristic clinical problems including haematological and metabolic abnormalities, recurrent infections, bone complications and neurological sequel **[15]**.

At present, Hematopoietic stem cell transplantation (HSCT) offers the only chance of cure for MIOP; it should be performed early before the irreversible neurologic impairment. HSCT replaces abnormal osteoclasts with normal cells, given the high associated morbidity and mortality it's reserved only for the most severe cases of osteopetrosis **[3]**. Successful results have been achieved in patients transplanted with allogeneic donor stem cells **[16]**.Furthermore, non-allogeneic HSCT may be an option to treat MIOP, it showed high survival rate and restoration of haematopoiesis in haploid transplant patients **[17]**.

In our case, HSCT was not performed given its high cost; therefore, treatment was largely supportive and was aimed at providing surveillance and symptomatic management of complications such as antibiotic therapy, calcium and vitamin D supplementation and nutritional measures. Surgical decompression of the optic nerve was also discussed.

Genetic counselling is important. Antenatal diagnosis in families with MIOP may be possible using radiographs **[18]**, thus allowing haematopoietic stem cell transplantation (HSCT) be-

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fore the age of 3 months with the aim of improving neurological outcomes. However, the difficulty in obtaining conclusive results by radiographic evaluation of fetus in utero makes prenatal molecular diagnosis highly desirable **[19]**. Our patient's parents have benefited from a genetic consultation. Prenatal diagnosis is planned for the forthcoming pregnancies.

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