CASE REPORT

MALIGNANT INFANTILE OSTEOPETROSIS

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Two main forms of osteopetrosis are recognized, a severe autosomal recessive form (MIM 259700) with an incidence of approximately 1 in 250,000 births and a mild autosomal dominant form (MIM166600) with an incidence of 1 in 20,000 births. Intrinsic disturbances of osteoclastic function due to mutations in genes encoding osteoclast-specific subunits of the vacuolar proton pump (TCIRG1, CLCN7) are found in most patients with recessive form. Mutations of CLCN7 are observed in dominant form of osteopetrosis .The recessive form of ostreopetrosis, i.e, malignant infantile osteopetrosis (MIOP) presents early in life with extreme sclerosis of the skeleton and reduction of marrow space. Signs/symptoms of MIOP appear as early as neonatal age. As there is defect in bone marrow children present with deficiency of red blood cells, white blood cells and platelets. There is extramedullary haemopoiesis, cranial nerve compressions and severe growth failure. The condition also presents with early and late onset neonatal sepsis and is often lethal in the first decade of life due to secondary infections. Treatment is mainly supportive. The only curative treatment is stem cell transplantation. This is a case report of a new-born who was admitted in nursery of Ayub Teaching Hospital initially with complains of neonatal jaundice and sepsis , and a second time with lower respiratory tract infection. Death was eventually due to sepsis .Workup led to diagnosis of Malignant infantile osteopetrosis.

Keywords: Malignant infantile osteopetrosis; Neonatal sepsis

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INTRODUCTION

Malignant infantile osteopetrosis (MIOP) is a rare inherited bone disease characterized by reduced or dysregulated activity of osteoclasts, resulting in generalized osteosclerosis.[1,2] (Figure-1) Overgrowth of cranial nerve foramina and the foramen magnum results in nerve compression progressively affecting the optic, facial, oculomotor, and auditory nerves and hydrocephalus.[3,4] Other problems include irritability, hypocalcemic seizures, snuffling because of disruption of nasal architecture, hepatosplenomegaly (the result of extramedullary haemopoiesis)[5,6] and eventually hypersplenism. Failure to thrive and increased infections because of an unexplained defect in neutrophil superoxide function are also characteristic features.

Two main types of osteopetrosis have been recognized, a severe autosomal recessive form (OMIM 259700) with an incidence of 1/250,000 births and a mild autosomal dominant form (OMIM1666000) with an incidence of 1/20,000 births. Both types of mutations lead to disturbances of acidification needed for normal osteoclast function. The severe form is usually detected during infancy or early childhood due to macrocephaly, hepatosplenomegaly, deafness, blindness and severe anemia.[2]

CASE REPORT

A new born 3 days old male weighing 3.5 kg born to a mother $G_3P_3Ab_0Alive_2$ with one healthy female child who is 3 years old, one previous male child died at 3 months' age and diagnosis was unknown. The patient had D.O.B = 20.09.14, T.O.B was 3.00 am was brought to Paediatrics' out patient with chief complaint of irritability and excessive crying, on examination child was jaundiced, dehydrated and had strabismus. He was referred to nursery for Liver function tests and rehydration. After 3 hours of phototherapy child was shifted to home. 0n 25th day of life child was brought to OPD with respiratory distress and breathing difficulty. According to the mother child was crying constantly and was unable to take feeds. Baby looked wasted, tachypnoeic. He was febrile with temperature up to 101 °F. Baby was admitted as late onset neonatal sepsis, and was started on iv cefotaxime, Tazocin and amikacin. Along with iv fluids and calcium gluconate.

On examination child was febrile, had tachypnea and was constantly crying. liver and spleen were enlarged. During admission, he was having spikes of fever up to 103 °F and 104 °F. After 72 hours of admission fever was still not settling. Clinically baby showed some improvement. Blood samples were sent for culture and sensitivity. Lumbar puncture was considered. A complete blood picture showed leucocytosis with 80% lymphocytes. The blood culture report showed growth of Klebsiella that was resistant to cefotaxime and sensitive to ciprofloxacin, meropenem, Tazocin and partially sensitive to Amikacin. Intravenous cefotaxime, Tanzo and amikacin continued and baby was started on meropenem.

After starting meropenem fever started to subside and baby was sent home after 14 days without any new complications. Three days after being discharged baby was brought again with stuffy nose and difficulty in breathing. Upon examination of chest there were no added sounds. A chest x-ray was advised. (Figure-1) It showed signs of rickets and bones showed typical features of osteopetrosis.

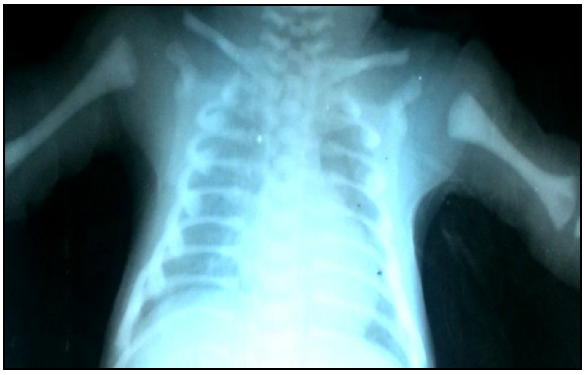

Figure-1: Chest X-Ray showed signs of rickets and bones showed typical features of osteopetrosis

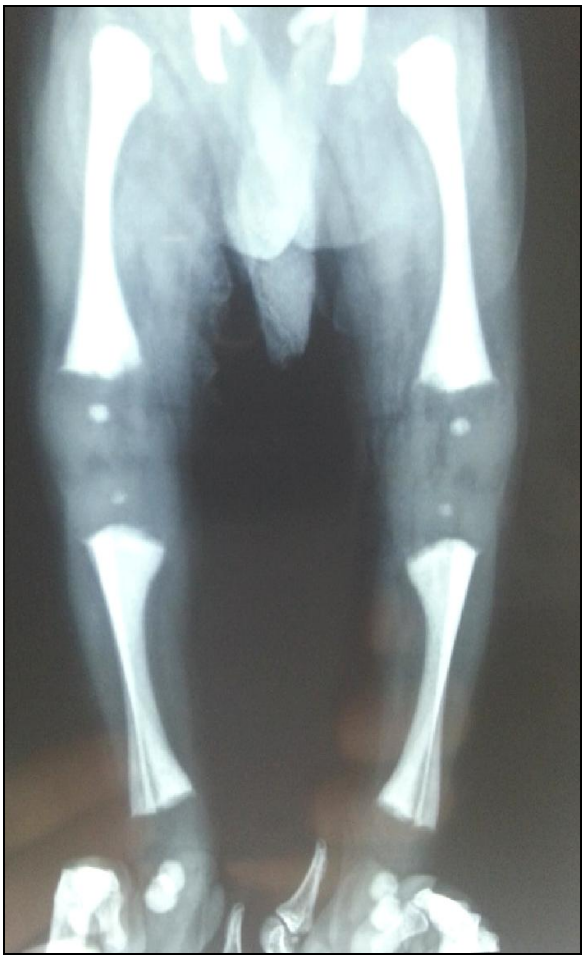

Figure-2: (Sclerotic bones: bone inside bone appearance)

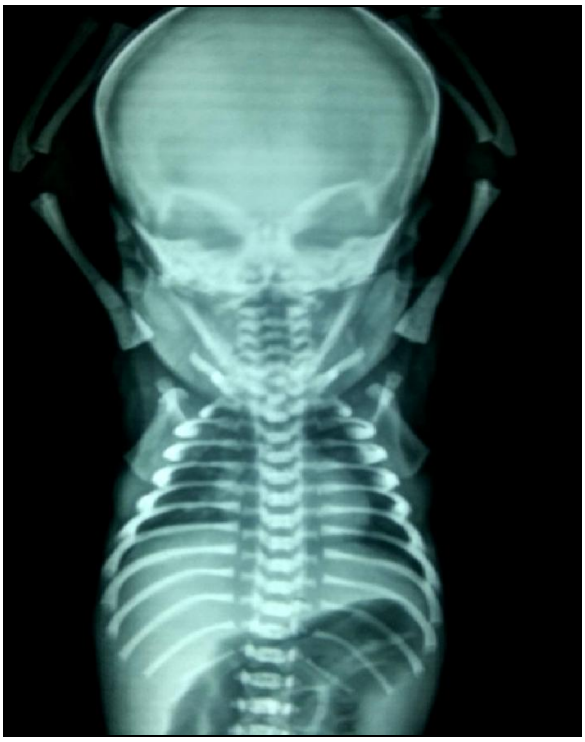

Figure-3: Bone sclerosis

Digital X-rays were done to confirm the diagnosis. A diagnosis of malignant infantile osteopetrosis was made. After the third admission, the child did not survive and expired 3 days after the second admission due to sepsis and cardiorespiratory failure.

DISCUSSION

Infantile malignant osteopetrosis (IMO) includes various genetic disorders that affect osteoclast development and or function. It is one of two sub types and the more severe form that tends to present earlier. Hence, it is referred to as "infantile" and "malignant" compared to its autosomal dominant mate.[3] Genotype-phenotype correlation studies in IMO have been hampered by the rarity and heterogeneity of the disease and by the severity of the clinical course, which often leads to death early in life. In the natural course of the disease, 70% of children die within the first six years.[7] Most of the remainder have a very poor quality of life and die by the age of 10 years.[8]

With the exception of a very small proportion of cases characterized by primary neurodegenerative disease.[9–11] Bone marrow transplantation (BMT) is curative, as osteoclasts are derived from bone marrow precursors. About two thirds of children are cured by BMT from matched sibling donors. Historically, the use of alternative (non-sibling) donors has yielded very poor results because of a combination of high

rejection rates and other transplant complications. However, there are now encouraging signs that the use of high dose, highly T lymphocyte depleted, parental marrow or peripheral blood stem cell transplants can improve outcome for those lacking a family donor.[12]

The commonest presentations result from optic nerve compression in the first year of life. This may result in failure to establish fixation and nystagmus, or slightly later development of strabismus. Unfortunately, one of the most disappointing aspects of transplantation is the rarity of reversal of these symptoms.[13] Therefore, it is crucial to identify affected children at the earliest possible stage and to perform BMT with relative urgency. This is particularly true now that suitable donors (either sibling or haploidentical) can be found for all patients with only minimal delay. Some patients with severe osteopetrosis have responded to bone marrow transplantation.[14] Calcitrol and interferon-γ have also been used with equivocal results.[15] Symptomatic care, such as dental care, transfusion for anaemia, and antibiotic treatment of infections is important for patients who survive infancy.[2]

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