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DENGUE HAEMORHHAGIC FEVER WITH OSTEOPETROSIS

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ABSTRACT
Osteopetrosis, also known as marble bone disease belongs to a group of disorders in children associated with increase in skeletal density. Osteopetrosis is caused by defect in bone resorption by osteoclasts leading to hyperostosis. At least 9 types of Osteopetrosis have been described, with variations in clinical and radiological features. Hall BD [1]. The autosomal dominant form is usually asymptomatic and diagnosed incidentally in late childhood/adulthood. We report a case of dengue hemorrhagic fever who was incidentally found to have osteopetrosis manifesting in early childhood.

CASE REPORT

A six year old female daughter of a govt employer resident of Jhansi, presented with history of fever (8 days), generalized bodyache (8days), epistaxis (2 days), appearance of bluish spots on body (2days). The patient was born full term by normal vaginal delivery at home. Birth weight was not recorded. There was no known antenatal illness in mother. There were no immediate postnatal complications and breast feeding was established. At 2 years of age, she was noted to have lack of visual activity from her left eye along with deviation of eye. Developmental history was normal. The patient was immunized for age and a product of non-consanguineous marriage and elder sibling aged 4 years was healthy. There was no family history of neurological illness. Patient had one episode of fracture of right lower limb following a fall while walking on high heel sandal. Fracture healed in 6-8 weeks following successful plaster application.

At admission the infant weighed 13.5 kg (67% of expected). Height 98 cm (84 % of expected). Pallor was present. Two 2×2.5 cm bluish colour maclur lesions presently over cheek were present. On per abdominal examination liver 3.0 cm below costal margin, soft to firm, non-tender, well defined margin, with span 10 cm, spleen 2 cm below costal margin non tender, firm, was present. Neurological examination revealed, higher mental status, motor, sensory, normal with left second nerve palsy and left optic disc pallor present. No dysmorphic features or neurocutaneous markers were present. Respiratory and Cardio-vascular examination was normal.

Investigations revealed: Hb 6.4 gm%, TLC 5400/cu mm, platelet count 18000/cu mm. Peripheral blood smear showed 4 premature myeloid cells per 100 cells examined. Blood sugar, liver function tests, urea, creatinine, sodium and potassium were within normal limits. Serum calcium was 7.4 mg%. Serum phosphorus 3.1mg%, alkaline phosphatase was 146u/l, acid phosphatase 1.74, serum was positive for IgM and IgG of dengue and rapid malarial antigen test was negative for p.vivax and p.falciparum. Blood culture was sterile. HIV spot test was negative. Radiographs of limbs showed generalized increase in bone density and 'bone within bone' appearance. Radiographs of skull showed sclerosis and thickening of orbital rims and anterior cranial fossa. Sella was small. Ultrasonography

abdomen showed hepatosplenomegaly with no other whole blood, 9 units PRP, 2 units FFP,I/V Fluids and inj monocef.Parents refused bone marrow biopsy. Based on the clinical presentation, classical radiological findings and haematological picture a diagnosis.

Figure 1. AP view of the pelvis showing expanding osteosclerosis of the pelvic bone and the iliac wings.

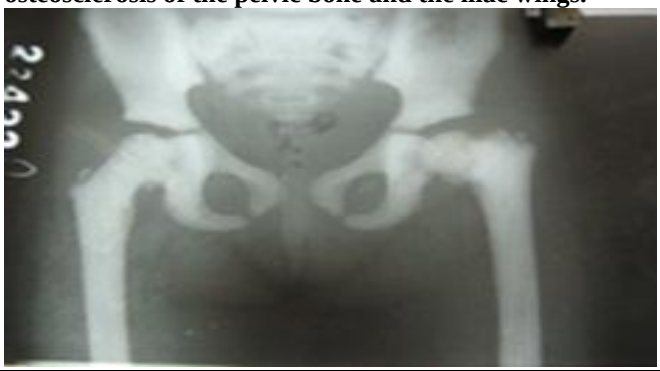


Figure 2. PA chest showing generalised osteosclerosis in the thoracic cage and both clavicular bones.

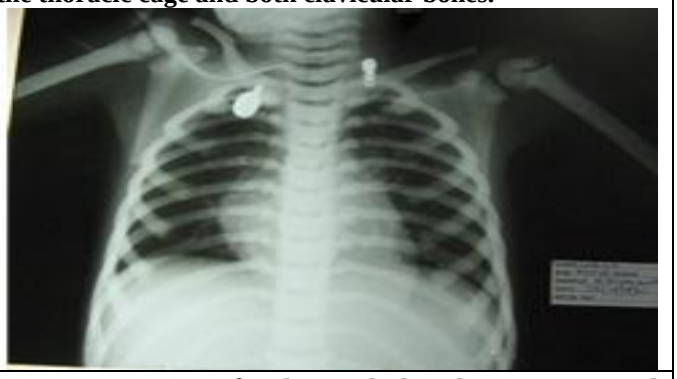


Figure 3. AP view wrist showing cylindrical appearance of the metacarpals.

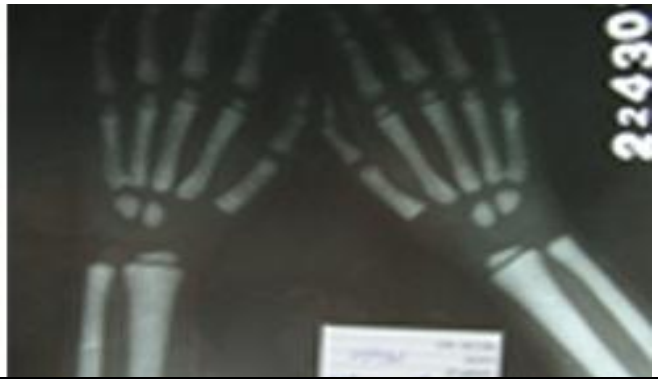
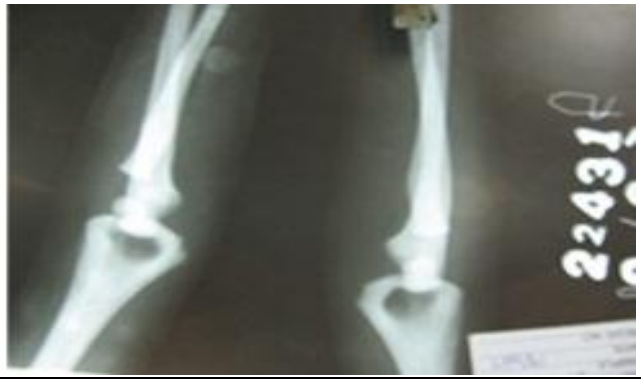


Figure 4. AP view of radius and ulna showing increased radiodensity in all the bones, smoothening of the bone surfaces



DISCUSSION AND CONCLUSION

Malignant recessive osteopetrosis or osteopetrosis with precocious manifestations is a rare disorder occurring with an incidence of 1:200000 population. Johnson CC et al [2]. It is an autosomal recessive condition presenting in neonatal period or early infancy. Its various manifestations are a result of hyperostosis. The initial presentation of these patients may be with pallor, failure to thrive, nasal obstruction or visual impairment. Lorea Cortes et al found nasal obstruction as an early symptom in their series of 26 patients over a period of 10 years. Loria Cortes R et al [3], whereas Gerritsen EJ et al reported ocular manifestations as an early symptom in their series of 33 patients over 16 years Gerritsen EJA et al [4]. Our patient was brought with symptoms of nasal obstruction aggravated by recurrent upper respiratory infection. He was also noted to have impaired vision.

Haematological findings are due to obliteration of bone marrow cavity by bone, causing myelophthisic anaemia, which manifests as a leukoerythroblastic picture on peripheral blood smear (neutrophilia, immature granulocytes, nucleated RBCs). Hepatosplenomegaly is due to extra medullary haematopoiesis. Thrombocytopenia, leukopenia and haemolytic anaemia may occur due to hypersplenism. Alter BP et al [5]. In our case, haemoglobin level was relatively preserved as a result of compensatory haematopoiesis. However, many patients of malignant recessive osteopetrosis become transfusion dependant. Wilson CJ et al [6].

The radiological findings are increase in bone density with defective metaphyseal remodelling. A 'bone within bone' appearance is characteristic and diagnostic and was seen in the above case. The finding differentiates osteopetrosis from other sclerosing dysplasias. This is due to the cyclical nature of the disease, so that the dense shadow of bone at the time of formation of abnormal bone is seen within the outline of the current normal or abnormal shadow. Irregular condensation of bone at metaphysis may produce parallel plates of dense bone at the end of long bones, a finding that is normally seen in older children. Base of skull is dense, with or without involvement of vault and sella is small. Orbital margins are markedly increased in density. Sphenoid, mastoid and frontal sinuses are under or non-pneumatised. Jacobs P et al [7].

Visual impairment is seen due to bony encroachment on optic foramina. It is a common initial symptom as reported by Gerritsen EJA et al [4]. Optic atrophy is present in a significant number of cases. In the series reported by Phadke et al [8], optic atrophy was present in 3 out of 6 cases. Visual impairment is responsible for lack of acquisition of certain early development milestones like social smile, as seen in our case. Early visual impairment in combination with haematological impairment is associated with a poor outcome. Gerritsen EJA et al [4]. Hearing impairment may be due to bony encroachment on auditory nerve, sclerosis of middle ear ossicles and/or middle ear effusion. Various other cranial nerve palsies can similarly be present due to bony encroachment on foramina. Wilson CJ et al [6]. Our patient had clinical evidence of hearing impairment.

Spastic quadriparesis and pseudobulbar palsy were present in our case. This may be due to associated neurodegenerative disorder, which has been reported to occur in osteopetrosis. Wilson CJ et al [6]. Other neurological manifestations described in osteopetrosis are macrocephaly, seizures, hydrocephalus, psychomotor retardation and strabismus. Loria Cortes R et al [3].

Hypocalcemia, low serum phosphorous levels and elevated serum alkaline phosphatase levels are known to occur in osteopetrosis. Hall BD et al [1] .Serum calcium was marginally lower in our case. In the series of cases reported by Phadke et al, serum calcium levels were normal. Phadke SR et al [8]. Hypocalcemia is related to decrease in osteoclastic activity and can be the cause of seizures occasionally.

Infants with malignant osteopetrosis also suffer from recurrent infections as a result of defect in macrophage function. Hall BD [1]. Chronic anaemia, recurrent infections, feeding problems due to bulbar nerve involvement and nasal congestion lead to failure to thrive in these children. Fractures are common and one of the classical features of osteopetrosis. They are usually transverse and heal with normal callus. They occur after moderate trauma and are thus rare in infancy. Skeletal maturation is normal.

The course of illness in autosomal recessive osteopetrosis is progressive and these children do not survive long. Survival at 6 years is about 30%. Gerritsen EJA et al [4].The cause of death is usually severe anaemia, bleeding or overwhelming infection. Mortality is higher in first two years of life. Children who are not transfusion dependent and alive at 2 years have a relatively favourable prognosis.

The definitive treatment is bone marrow transplantation. Recipients of HLA identical bone marrow transplant have 79% 5-year survival. Vossen JM et al [9]. Supportive treatment includes treatment of anaemia, thrombocytopenia and infections. Prednisolone may arrest progress of anaemia and thrombocytopenia. Oral cellulose phosphate, low calcium diet, recombinant human interferon gamma may also be beneficial. Hall BD et al [1] .Neurosurgical unroofing of optic foramina has been tried.

Genetically, recessive osteopetrosis is a heterogenous disease and a number of genetic loci are likely. Recently mutations in the gene coding for an osteoclast specific vacuolar pump have been found in a subset of affected children. The near future will see other genes being mapped, cloned and mutational analysis hopefully made available. Wilson CJ et al [6]. Appropriate genetic counselling could then be offered.

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