

A RARE CASE OF FAILURE TO THRIVE IN INFANTS: MALIGNANT INFANTILE OSTEOPETROSIS

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Abstract

Background: Malignant infantile osteopetrosis (MIOP) is a rare autosomal recessive bone disease, characterized by reduced or dysregulated osteoclastic activity and increased bone mass. Major consequences include bone marrow failure and nerve compression. Chronic anemia, feeding problems caused by bulbar nerve involvement and recurrent infections as well as bone growth in diameter and not length leads to failure to thrive (delayed growth, weight gain, and development), seen in many osteopetrotic children. The pericentric inversion of chromosome 9 is the most frequently found in general population and has a role in abnormal phenotype development. **Material and methods:** Case report of a 6 months old boy with 3 admissions, first at the age of three months for hypocalcemic seizures. Based on the dysmorphic phenotype, presence of anemia, severe hypocalcemia, hepatosplenomegaly, failure to thrive, mental retardation, ventriculomegaly, optic nerve atrophy and the typical radiological images diagnose of MIOP complicated by rickets was established. Failure to thrive was defined based on persistent weight and waist below the 5th percentile. Genetic evaluation for chromosome abnormalities revealed apericentric inversion of chromosome 9. **Conclusions:** MIOP is a rare disease which can present with nonspecific symptoms; therefore it has to be considered in case of craniofacial bones abnormalities, severe hypocalcemia, anemia and early onset failure to thrive. The association of osteopetrosis complicated by rickets and chromosome 9 inversion led in our case to severe dysmorphic features and severe growth restriction.

Key word: osteopetrosis, failure to thrive, chromosome 9 inversion

Introduction

Osteopetrosis, also referred to as ‘marble bone disease’, is an inherited disease characterized by failure of osteoclasts to resorb bone making bones abnormally dense and prone to fracture. Impaired bone modeling and remodeling and defect in bone turnover result in skeletal fragility despite increased bone mass and may also lead to insufficient hematopoietic activity. The disease was firstly described by Albers-Schönberg in 1904 [1]. To date, researchers have described at least eight types of osteopetrosis in humans distinguished by their pattern of inheritance and by the severity of their signs and

symptoms [4]. Autosomal dominant osteopetrosis (ADO), also called Albers-Schönberg disease, with onset in late childhood and adolescence. It is the most common form with good prognosis [5] and an incidence of 1: 20-500.000 children. Autosomal recessive osteopetrosis (ARO) or malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form. This form has an early onset, during infancy, and a poor prognosis. In this case the incidence is 1: 200.000 children. Although rare, MIOP should be considered in children with failure to thrive. A cause of short stature in children with MIOP is abnormal bone development, bone grows in width and not length.

Case report

The patient M.T., 6 month old male infant, with repeated admissions in our clinic, presented at the age of 3 months seizures due to severe hypocalcemia. At the first hospitalization, at the age of three months, during the physical examination, a dysmorphic phenotype was observed: plagiocephaly (bilateral parietal and temporal flattening with prominent frontal and occipital regions), high forehead, frontal bossing, head circumference > 97th percentile, microretrognathia, asymmetry of the ears, the left ear inserted below, bulging anterior fontanelle with a diameter of 4.5 / 4 inches, sunsetting eyes sign, ogival palate. Further inspection detected a slightly flared thorax, distended abdomen, the liver with the inferior margin palpable at 4 cm below the costal margin and the spleen palpable at 2 cm below the costal margin. Based on the presence of anemia, hypocalcemia, hepatosplenomegaly, failure to thrive, mental retardation, ventriculomegaly, optic nerve atrophy and the typical radiological images diagnose of MIOP complicated by rickets was established.

Failure to thrive was defined based on persistent weight and waist below the 5th percentile. (Fig.1) Genetic evaluation revealed a pericentric inversion of the chromosome 9. Treatment with high doses of calcium (50 mg / kg / day) and active vitamin D (calcitriol-0, 3 ug / kg / day) showed a slow biological improvement. After 1 month of treatment, the vitamin D levels normalized while the PTH levels remained high.

Paraclinical findings showed abnormal hypocalcemia, anemia, low vitamin D levels and high PTH levels. 25-OH Vitamin D3 = 19.4 ng/l - 3 months; = 36,4 ng/l – 3 months 2 weeks; - .NV. > 30 ng/l (fig. 2, 3,4, 5, 6, 7)

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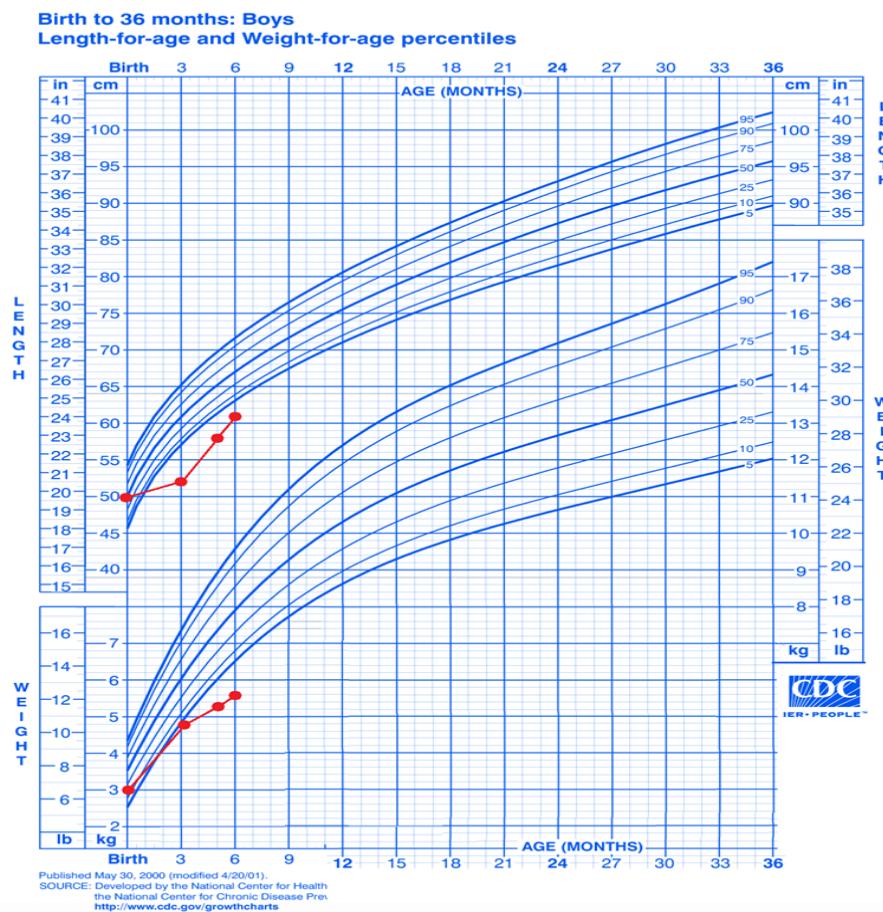


Fig. 1 Length and weight evolution of the patient at 3, 5 respectively 6 months.

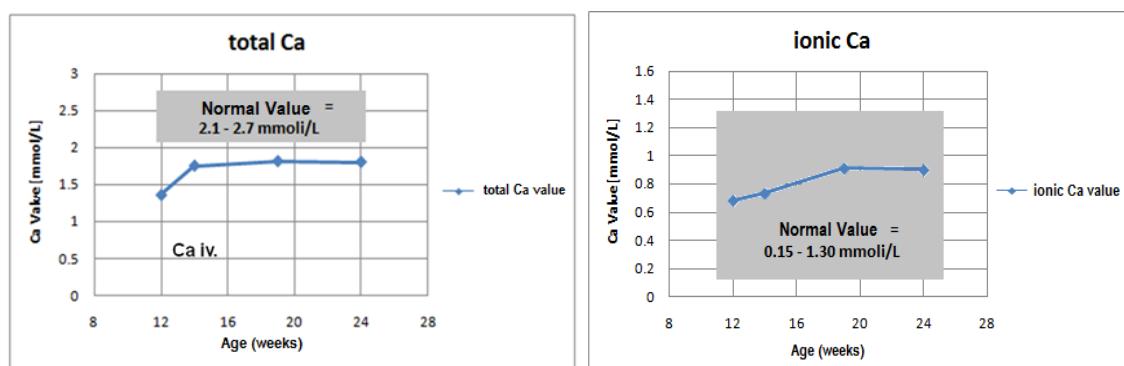


Fig. 2 Evolution of the calcium levels

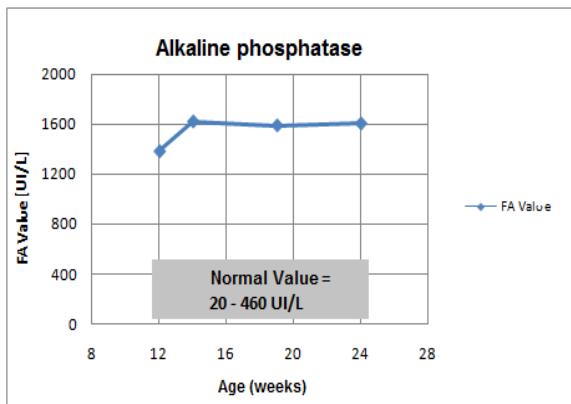


Fig. 3 Levels of alkaline phosphatase

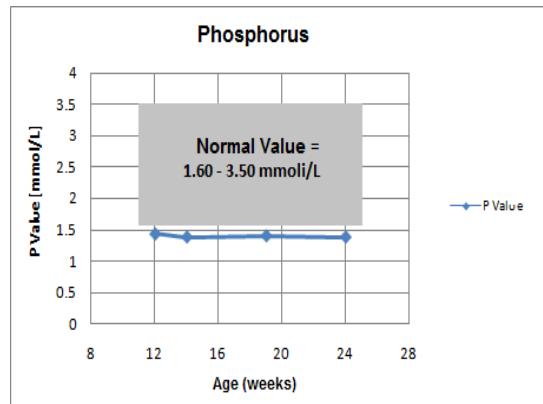


Fig. 4 Phosphorus values

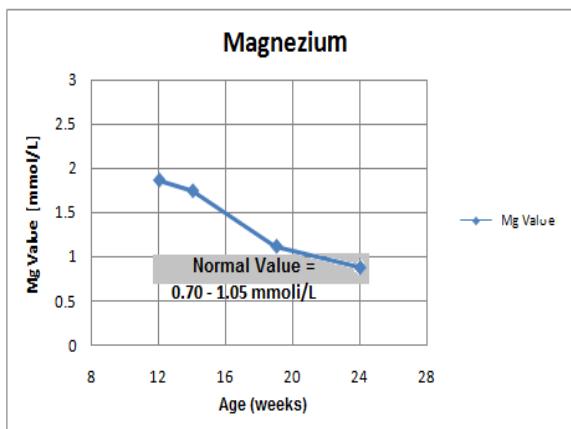


Fig. 5 Magnesium values

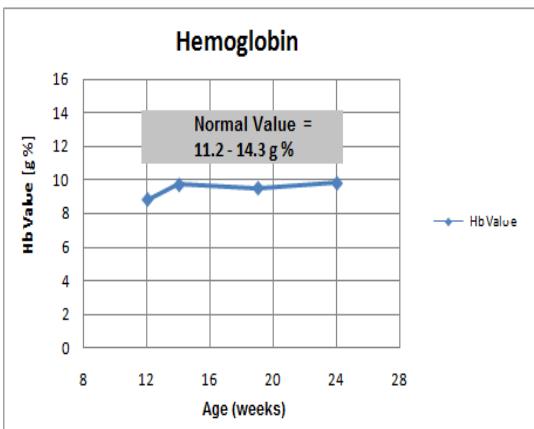


Fig. 6 Hemoglobin values

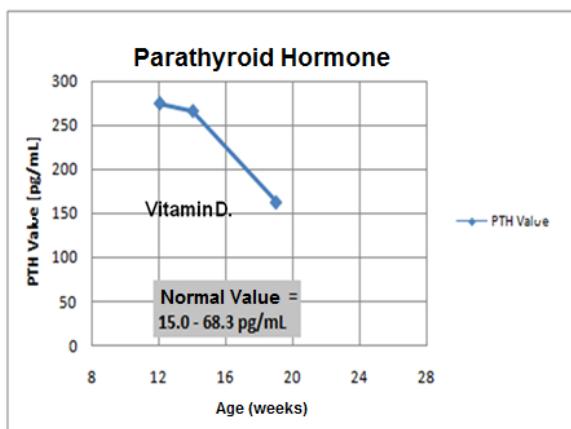


Fig. 7 Parathyroid hormone level



Fig. 8 transfontanelar ultrasound: Bilateral Ventriculomegaly



Fig. 9 Transfontanelar ultrasound: Mild cerebral atrophy

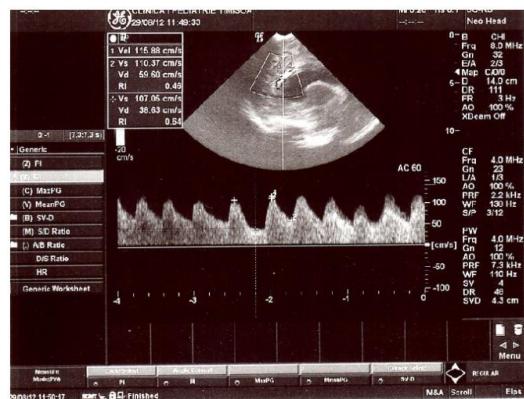


Fig. 10 Transfontanelar Doppler: Anterior cerebral arterial resistivity index (RI)



Fig. 10 MRI: Hypertrophy of the cranial bones

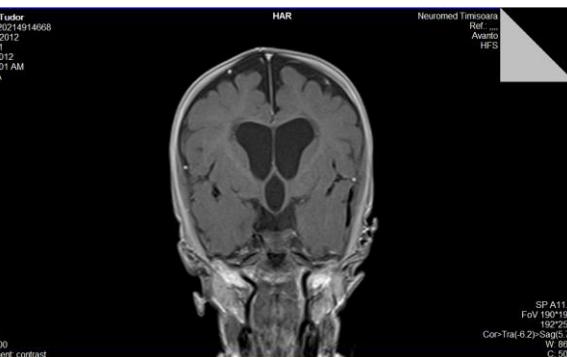


Fig. 11 MRI: Tricameral ventriculomegaly

Thoracic X-Ray showed rachitic cupes on the ribs and proximal humerus.

Imaging, transfontanelar ultrasound revealed ventriculomegaly and cerebral atrophy without signs of increased intracranian pressure (Δ RI < 15) (Fig. 8, 9, 10)

MRI: Moderate tricameral ventriculomegaly, without signs of activity. Homogenous hypertrophy of the cranial bones, more pronounced at the bones of the base of the skull with secondary volume reduction of the cranial cavities. (Fig. 11, 12)

Discussions

High Calcitriol doses stimulate the bone resorbing function of the osteoclasts, with slow biological improvements.

Levels of parathyroid hormone and alkaline phosphatase were raised in our patient. Elevated alkaline phosphatase is a sign of defective bone mineralization, while high serum levels of parathyroid hormone are caused by decreased calcium levels. Defectuous bone resorption due to damaged osteoclasts and vitamin D deficiency lead to severe hypocalcemia.

Vitamin D dosage and bone X-Ray images have revealed signs of rickets. The PTH levels decreased after the correction of the vitamin D deficiency, remaining at elevated levels.

Failure to thrive occurs due to the dysfunctional osteoclasts resulting in bony overgrowth, bones that are abnormally dense and brittle. This defect prevents the normal development of marrow cavities, the normal tubulation of long bones and the enlargement of osseous foramina.

Conclusions

MIOP has a poor prognosis unless treated early with hematopoietic stem cell transplantation. It remains essentially unrecognized as a cause of neonatal hypocalcemia and often leads to diagnostic delays and confusion. MIOP should be considered in the differential diagnosis of idiopathic neonatal hypocalcemia refractory to treatment or requiring correction doses.

While it may seem a paradox, osteopetrosis and rickets, cases in literature are described as a complication, resulting from the inability of osteoclasts to maintain a balance of Ca-P in the extracellular fluid.

The association with chromosome 9 inversion accentuates the severe dysmorphic features, with no clinical significance in the disease progression.

Although rare, MIOP should be considered in children with failure to thrive. A cause of short stature in children with MIOP is abnormal bone development, bone grows in width and not length.

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