Ann Hematol (2003) 82:64–67
DOI 10.1007/s00277-002-0578-9

CASE REPORT

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Malignant infantile osteopetrosis initially presenting with neonatal hypocalcemia: case report

Received: 13 June 2002 / Accepted: 20 October 2002 / Published online: 11 December 2002

Abstract Autosomal recessive "malignant" osteopetrosis is a rare congenital disorder relating to bone resorption abnormalities. It is believed to arise due to the failure of osteoclasts to resorb immature bone. This leads to abnormal bone marrow cavity formation and, clinically, to the signs and symptoms of bone marrow failure. Impaired bone remodeling associated with dysregulated activity of osteoclasts for such a condition may typically result in bony narrowing of the cranial nerve foramina, which typically results in cranial nerve (especially optic nerve) compression. Abnormal remodeling of primary woven bone to lamellar bone results in "brittle" bone that is prone to fracture. Thus, fractures, visual impairment, and bone marrow failure are the classical features of this disease. We describe the case of a 23-day-old boy in whom neonatal hypocalcemia was present initially after birth. Malignant infantile osteopetrosis (MIO) was diagnosed for the patient at 4 months of age based on evidence of anemia, thrombocytopenia, leukoerythroblastosis, sclerotic bone, hepatosplenomegaly, and visual deficit from a bony encroachment by the cranial nerve foramina. Although only occasionally reported previously, MIO remains essentially unrecognized by clinicians as a cause of neonatal hypocalcemia, which often results in diagnostic confusion and delay. This is important in the context of curative hemopoietic stem cell transplantation where preservation of sight may depend upon early intervention.

Keywords Malignant infantile osteopetrosis · Neonatal hypocalcemia · Visual impairment

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Introduction

Malignant infantile osteopetrosis (MIO) is a rare autosomal recessive disorder characterized by presentation within the first few months of life with manifestations relating to an underlying defect in osteoclastic bone resorption [4]. For such a condition, abnormal osteoclast activity paired with normal bone formation by osteoblasts leads to the development of densely sclerotic fragile bones [6]. The encroachment of hyperostotic bone upon the marrow cavities results in profound anemia and thrombocytopenia, typically associated with extramedullary hematopoiesis and hepatosplenomegaly [6]. Deficits in immune function can lead to patient presentation with overwhelming sepsis during the newborn period, while a narrowing of the optic and auditory foramina can lead to progressive blindness and hearing loss [6]. Until recently, the prognosis for this disorder had been uniformly dismal with death usually occurring within a few months of diagnosis [6].

Case report

A male infant was born after an uncomplicated first pregnancy and delivery by a 30-year-old woman. There was no history of parental consanguinity.

The infant was admitted to our ward at 23 days of age suffering from complaints of generalized tonic-clonic seizure since the patient's 19th day of life. Upon examination the child was irritable but generally alert. Systemic examination revealed bulging and a widening of the anterior fontanelle by approximately 6 cm. Whole blood cell count revealed no significant abnormal findings including hemoglobin 12.0 g/dl, leukocyte count 14,900/μl, and platelet count 172,000/μl. Suspecting neonatal sepsis, we performed a septic work-up including a lumbar puncture. Empiric antibiotics were given which included ampicillin and gentamicin sulfate. Hypocalcemia featuring a serum-free calcium level of 2.76 mg/dl (normal: 4.8–4.92 mg/dl) was an incidental finding and was treated

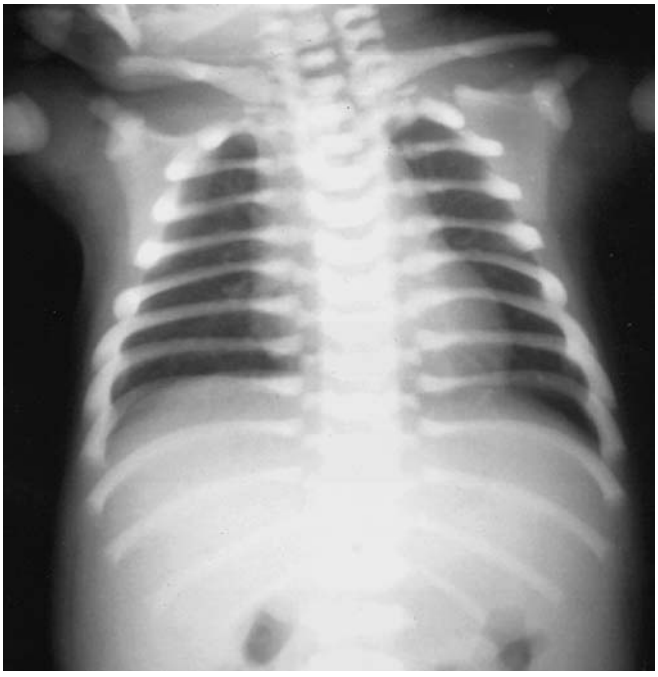

Fig. 1 Roentgenogram demonstrating uniformly dense, homogeneous, and sclerotic bone with an absence of corticomedullary junctions

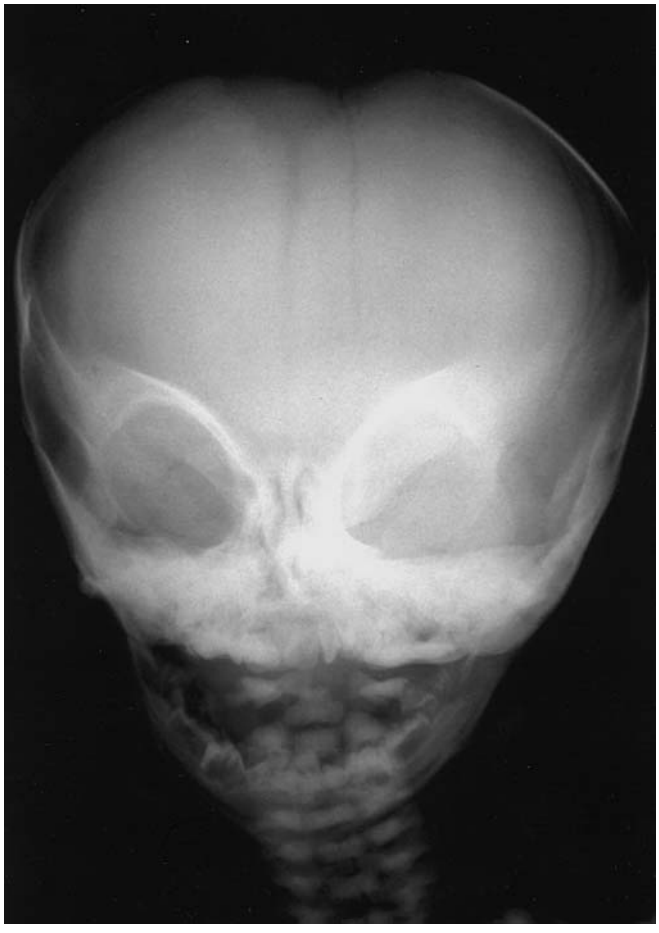

Fig. 2 Frontal radiograph depicting osteopetrosis-associated enlargement of the calvaria and upward slanting of the greater sphenoid alae, the typical "space alien" face

with infusions of calcium gluconate. A brain magnetic resonance imaging (MRI) scan proved to be normal and a CSF study negative. The patient was discharged 2 weeks subsequently without evidence of any further seizure activity.

Unfortunately, 3 months subsequently, wandering eye movements were noted by the patient's mother, and a subsequent physical examination revealed sunset eye, a sluggish pupillary response to light, and hepatosplenomegaly with the liver noted to be 2 cm and the spleen 4–5 cm below the costal margin. Funduscopic examination revealed pale optic nerve heads, and laboratory findings demonstrated thrombocytopenia, low hemoglobin level, and leukoerythroblastic anemia. Whole body roentgenogram investigation demonstrated uniformly dense, homogeneous, and sclerotic bone with an absence of corticomedullary junctions (Fig. 1). A frontal radiograph revealed the enlargement of the calvaria and upward slanting of the greater sphenoid alae, the typical "space alien" face (Fig. 2). A computed axial tomographic scan of the patient's orbits demonstrated the narrowing of the optic foramina bilaterally (Fig. 3). An MRI scan of the patient's brain at this time revealed that bilaterally the optic nerves appeared to become very thin and be arranged in an abnormally vertical fashion (Fig. 4). An attempt to evoke a visual response proved unfruitful. An auditory brain stem-evoked response demonstrated normal peripheral auditory sensitivity on the right side and only mild impairment to the left. Extramedullary hematopoiesis was also noted upon ^{99m}Tc-microcolloid bone marrow scintigraphy. Such summary findings were quite characteristic of MIO, which was our determination at the time. The 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, while the family history and the observed severe clinical manifestations excluded a dominant pedigree for the patient's condition.

Discussion

While numerous molecular defects have been described for rodent models of MIO, the human genetic defect(s) responsible for this malady remain(s) unclear. It is thought by Felix et al. that the defect could be intrinsic to the osteoclasts or to the mesenchymal cells that constitute the microenvironment supporting the development and activation of the osteoclasts [4]. Some patients do experience associated renal tubular acidosis and cerebral calcification, and for this specific group of patients, the defect has been identified as carbonic anhydrase II inhibitor deficiency. For another subgroup

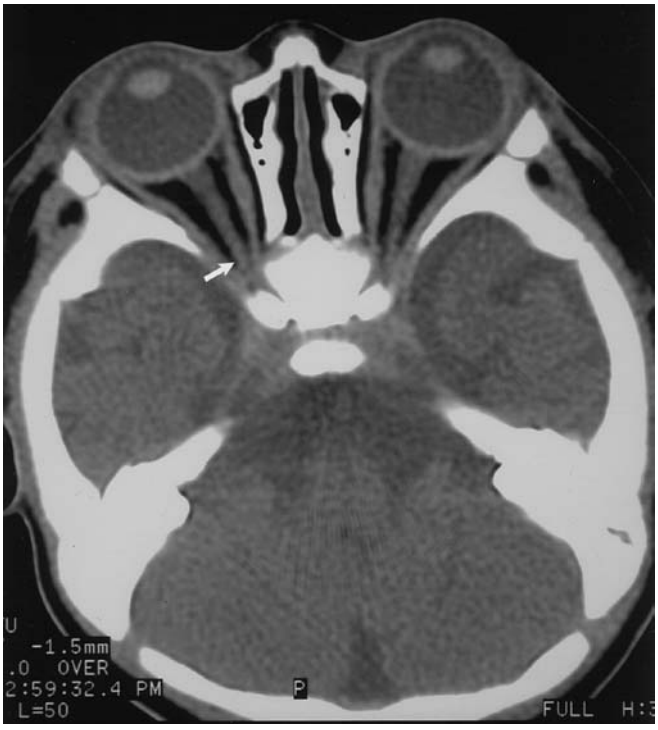

Fig. 3 Computed axial tomographic scan of the orbits demonstrating narrowing of optic canals bilaterally (*arrows*)

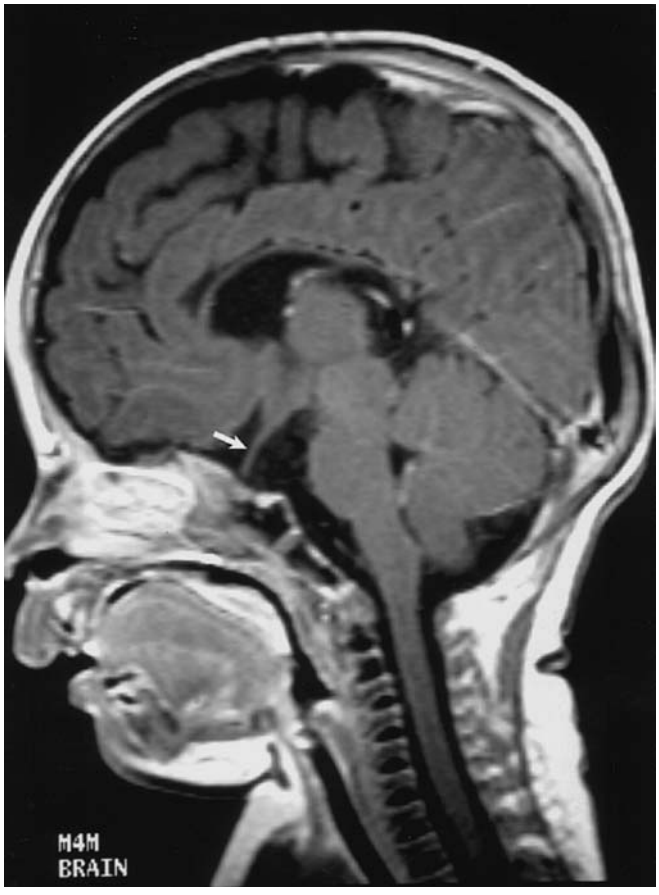

Fig. 4 Sagittal T1-weighted MRI image revealing atrophy and abnormal arrangement of optic nerves in a vertical fashion (*arrows*)

of patients, osteoclast dysfunction due to lack of expression of the vacuolar protein pump has been associated with craniometaphyseal dysplasia [4]. A defect in leukocyte superoxide formation related to defective bone resorption is present among patients suffering from MIO [9].

Disturbance of calcium homeostasis mechanisms has been well described in MIO previously, the first such reference possibly having been described by Avery et al. in 1969. These authors referred to a baby born with MIO in 1956 who was described as being "a bit twitchy" at 6 days of age [1]. Subsequently, in a large survey of European patients in 1994, Gerritsen et al. reported on the conditions of 23 children with MIO for whom the serum calcium level was measured at the time of patient presentation. Three of these children (from separate families) presented with convulsions at less than 1 month of age and revealed serum calcium levels of <6 mg/dl (normal: 8.8–10.8 mg/dl). Seven other patients demonstrated levels of 6–8 mg/dl [6].

According to Srinivasan et al., eight children from six families presented with symptomatic hypocalcemia during the 1st month of life. The diagnosis of MIO was quickly established in five of these cases. One was diagnosed by routine X-ray examination on day 2 of life because of the previous family history. However, in the remaining children, diagnosis was delayed by 50, 68, and 200 days, by which time all three had developed visual failure [12].

In the neonatal period, children are, functionally, relatively hypoparathyroid, such that in such a setting, normal osteoblast function, unbalanced by compensatory osteoclast function, pushes some osteopetrotic children into hypocalcemia [12]. Previously reported treatment modalities for MIO patients include supportive care measures, dietary regimens to reduce calcium and increase phosphate intake [3], parathyroid hormone [7], and calcitonin infusions in order to induce bone resorption. Such measures have all proven to be largely unsuccessful [3, 7, 10]. High-dose calcitriol [13] and prednisolone [3, 10] administration have been attempted for this disorder on previous occasions, just as we attempted to use such a protocol for our patient for the duration of the wait for bone marrow transplantation (BMT). However, the response was both minimal and transient as has been reported elsewhere [8]. The use of interferon-gamma enhances bone resorption and leukocyte function, but the effects upon patient morbidity and survival remain unclear at present [9]. The only curative therapy for MIO at this stage would appear to be allogeneic BMT [2, 11], such a treatment modality retaining the potential to lead to immune recovery, bone remodeling, improved bone growth, and longer-term patient survival [5].

Early visual and hematological impairment, especially that arising before 3 months of age, typically carries a very poor prognosis for survival [6]. Although having been occasionally reported previously, MIO remains essentially unrecognized as a cause of neonatal hypocalcemia, the condition often resulting in diagnostic confusion and delay. This is important in the context of curative hemopoietic stem cell transplantation where preservation of sight may depend upon early medical intervention.

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