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Case report

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CASE REPORT

Diagnostic Dilemma: Osteopetrosis with superimposed rickets causing Neonatal Hypocalcemia

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SUMMARY

Osteopetrosis is a rare genetic condition of reduced osteoclastic bone resorption which causes defective bone remodeling and skeletal sclerosis during growth, having effects on many organs and tissues. Mutation of T-cell immune regulator 1 (*TCRG1*) gene is the most common genetic defect leading to osteopetrosis, with poor prognosis. The autosomal recessive form presents in the infantile period (also known as malignant infantile osteopetrosis – MIOP), and is characterized by fractures, short stature, hepatosplenomegaly, compressive neuropathies, hypocalcemia and pancytopenia. Being a rare disease with non-specific clinical manifestations, the diagnosis is difficult and usually delayed. Rickets is a characteristic feature of MIOP which results from the defect in osteoclasts to provide a normal Ca/P balance resulting in the poor mineralization of the osteoid. Various treatment options have been suggested for osteopetrosis, but hematopoietic stem cell transplantation still remains the only curative treatment option presently. The authors report the case of a 46-day-old girl with late-onset neonatal hypocalcemia and rickets that was later diagnosed as osteopetrosis. This case report emphasizes that infantile osteopetrosis is an important cause of neonatal hypocalcemia. As irreversible complications develop within the first months of life, immediate diagnosis and early intervention are crucial and may be life-saving.

KEYWORDS: osteopetrosis, rickets, hypocalcemia, osteosclerosis.

INTRODUCTION

Osteopetrosis (OMIM: #259700) is a rare genetic condition of reduced osteoclastic bone resorption which causes defective bone remodeling and skeletal sclerosis during growth. The worldwide incidence is thought to be 1 in 250,000 births [1]. No sex predispositions have been reported. Despite being known primarily as a bone disease, it has many effects on other organs and tissues. Three main clinical forms have been identified, depending on the pattern of inheritance, which are infantile autosomal recessive form, intermediate autosomal recessive form

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and adult autosomal dominant form [2]. Many genetic mutations have been identified as causative in humans, of which T-cell immune regulator 1 (*TCRG1*) gene mutation is the most common in autosomal recessive osteopetrosis (ARO) characterized with poor prognosis [1]. The symptoms may range from asymptomatic to fatal disease. The classic autosomal recessive form (also known as malignant infantile osteopetrosis – MIOP) has poor prognosis. It presents in the infantile period, and is characterized by fractures, short stature, hepatosplenomegaly, compressive neuropathies, hypocalcemia and pancytopenia [3]. Hepatosplenomegaly is caused by anemia due to compensatory extramedullary hematopoiesis. Hemolysis resulting from hypersplenism worsens the anemia and thrombocytopenia. Hematological impairment occurs within the first year of life in about 75% of patients and its presence within 3 months of age is indicative of poor prognosis [4]. Even though it seems paradoxical, rickets may further complicate osteopetrosis. Prompt management of rickets is essential, as the clinical response to hematopoietic stem cell transplantation (HSCT), which is the only curative treatment, is inadequate with rickets underlying osteopetrosis.

We report the case of a 46-day-old girl with late-onset neonatal hypocalcemia and rickets that was later diagnosed as osteopetrosis.

CASE REPORT

A 46-day-old girl was referred to our center owing to refractory hypocalcemia. She was the first child of consanguineous parents. Her mother was dark-skinned and had regular low sun exposure with no history of gestational diabetes or maternal hyperparathyroidism. Severe vitamin D deficiency was detected in the fifth month of her pregnancy and she was treated with oral calcium and vitamin D3 supplements. Control levels of maternal vitamin D were within normal limits. The girl was born at term (weight = 3,435 g) by cesarean section owing to premature rupture of membranes. She had been fed with mother's milk after birth. She was fine until the seventh day of her life, when she had a seizure and was admitted to the pediatric emergency service in another center. Her blood calcium (Ca) level was detected to be 7.5 mg/dl (normal range [NR]: 9–11 mg/dl); she was hospitalized and intravenous (IV) calcium replacement was started. Her magnesium (Mg) level was 1.6 mg/dl (NR: 1.2–2.1 mEq/l), phosphorus (P) level was 3.2 mg/dl (NR: 4.5–6.7 mg/dl), alkaline phosphatase (ALP) level was 375 U/l (NR: 124–341 U/l), parathyroid hormone (PTH) level was 172 pg/ml (15–68 pg/ml) and 25-hydroxy vitamin D (25(OH)D) level was 17.4 ng/ml (30–150 ng/ml). Also, 1,25 vitamin D level was within normal limits. Other hematological and biochemical findings were within normal limits. No X-rays were taken at the time. Hypocalcemia was thought to be secondary to maternal vitamin D deficiency. Calcium levels normalized after replacement therapy immediately (9.3 mg/dl), and she was discharged the day after with oral calcium lactate (75 mg/kg/d elemental calcium) and 1200 U/d vitamin D3 replacement. Oral calcium replacement was discontinued 2 weeks later and afterwards, she had a seizure due to hypocalcemia again (Ca: 6.8 mg/dl). She was hospitalized and IV calcium replacement was initiated. This time, hypocalcemia was refractory for 2 weeks and she was referred to our clinic for further evaluation. On physical examination, her weight was 4 kg (10 p), height 55 cm (50 p) and head circumference 38 cm (25–50 p). Her vital signs were within normal limits. Posterior fontanelle was open, frontal bossing was present, 1/6 systolic cardiac murmur was detected and other findings including neurological examination were normal. Initially, her complete blood count showed anemia (Hb: 6.8 g/dl, MCV: 92.94 fl, RDW: 15.71%). Normal white blood cell count and low platelet count (95,500/µl) were reported. Biochemical findings were normal, other than Ca being 7.79 mg/dl, ionized calcium: 0.63 mmol/L, P: 3.39 mg/dl, ALP: 390 U/L, PTH: 163.8 pg/ml and 25(OH)D: 26 ng/ml. Tubular functions were normal. IV calcium therapy (100 mEq/kg/d) and 400 IU/d vitamin D 3 was started. Her calcium levels ranged around low to low–normal limits when under replacement therapy (7.1–8.4 mg/dl). Skeletal survey was performed where findings compatible with osteopetrosis such as 'space alien' appearance, increased base density of skull and sclerotic long bones were detected (Fig. 1A–D).

Further, 1,25-dihydroxyvitamin D3 ($1,25\text{-}(OH)_2$) treatment was initiated (0.06 µg/kg/d). Genetic analysis for osteopetrosis was performed and

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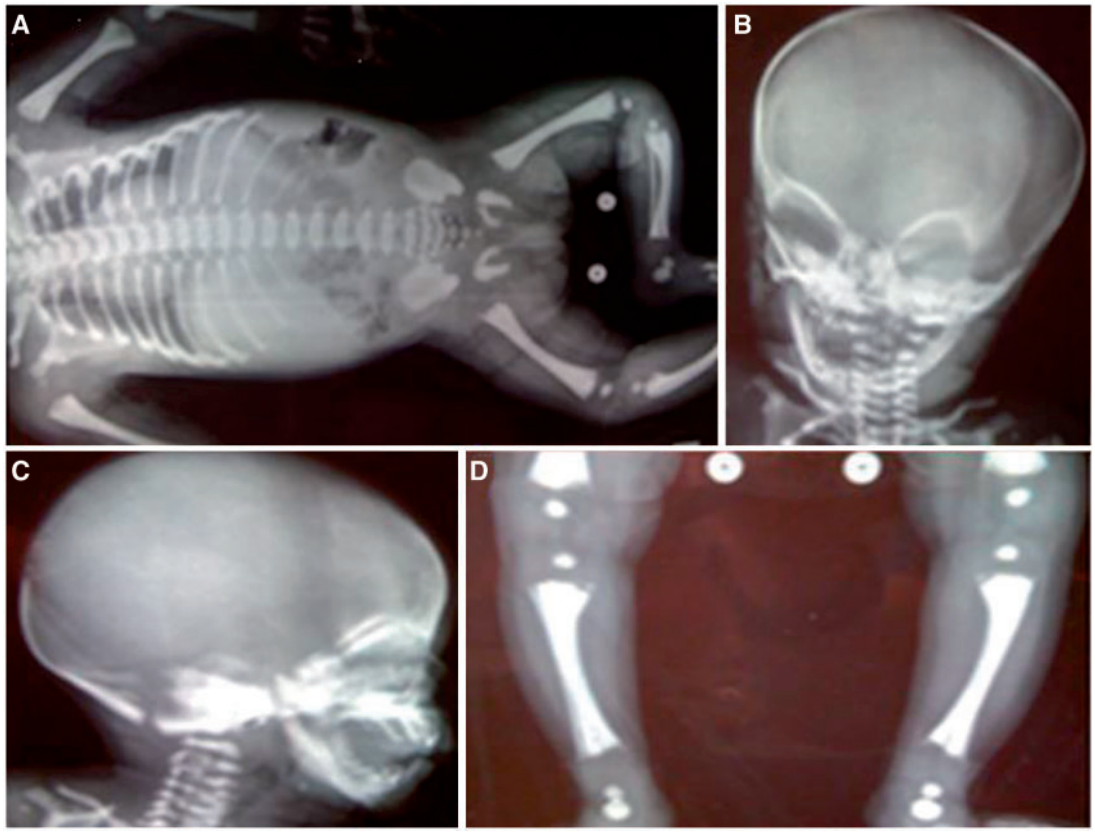


FIG. 1. Roentgenograms showing: (**A**) absence of corticomedullary junctions and sclerosis of long bones, (**B**) typical 'space alien' appearance, (**C**) sclerosis of scull base and (**D**) sclerosis of long bones.

homozygote mutation in *TCRG1* gene *(c.1536C < A(Tyr 512Term)/(c.1536C < A(Tyr 512Term)* was detected. Hypocalcemia recovered soon after 1,25-$(OH)_2$ treatment was started and plasma levels of PTH and ALP normalized. She was discharged on postnatal day 54 and referred to another clinic for HSCT.

DISCUSSION

Osteopetrosis is a rare clinical and genetic group of conditions resulting from increased bone density relating to an underlying defect in osteoclastic function. It is a very rare clinical condition, with the worldwide incidence being 1 in 250,000 births [1]. MIOP has been reported to be more frequent in certain ethnic groups, including inhabitants of Costa Rica (3.4:100,000) [5]. The incidence in Turkey is not exactly known due to lack of studies, but since the disease is inherited autosomal recessively; it is obvious that the incidence is higher than many countries because of the high rate of consanguineous marriages. MIOP classically manifests in the first few months of life, which leads to serious complications if left untreated. Characteristic features are defective immature bone resorption resulting in hypocalcemia, brittle bones, abnormal bone marrow and cranial nerve cavity formation, extramedullary hematopoiesis and optic nerve damage. X-ray findings include the increased density of bones especially of the scull, spine and long bones; bone in bone appearance of the vertebrae and the phalanges; and the space alien-like appearance of the scull. Without treatment, maximum life span in MIOP is 10 years [1, 2].

Mutations known to be associated with osteopetrosis in at least 10 genes have been identified. *TCIRG1* mutations are responsible for MIOP in

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more than 50% of affected individuals and result in poor prognosis [1]. The protein encoded by the *TCIRG1* gene is involved in the proton transport system of the osteoclasts via the vacuolar ATPase channel, where the mineralized phase of the bone matrix is dissolved [3, 6]. The mutation in the *TCIRG1* gene detected in our patient (c.1536C < A(Tyr 512Term)/(c.1536C < A(Tyr 512Term) was a previously defined, well-known mutation for osteopetrosis, and the clinical course of our patient was consistent with other patients previously reported in the literature [7]. Genetic counseling has been given to the family for future pregnancies.

Gonen *et al.* [8] have reviewed 20 children with infantile osteopetrorickets and have detected the mean diagnosis age as 4.7 months (ranging from 2 to 12 months). Mazzolari *et al.* [7] have published a review of 20 cases with MIOP. The mean age at the time of diagnosis was 3.9 months (range 15 days to 9.5 months). Our patient was diagnosed at the age of 49 days, which is earlier than most cases reported in literature.

Del fattore *et al.* have reviewed the clinical findings of 17 MIOP patients and have reported hepatosplenomegaly, macrocephaly and growth retardation to be the most common features [9]. In the study by Gonen *et al.* [8], hepatosplenomegaly was one of the most common finding at the time of presentation. Also 80% of the children had visual impairment, which is also reported to be a common finding in the study by Mazzolari *et al.* [7]. The initial symptom of our patient was seizure due to hypocalcemia. Neurological evaluations were normal at the time of diagnosis. She developed organomegaly later on, after referral to another clinic for HSCT. The fact that our patient did not have organomegaly or visual impairment at the time of diagnosis may be explained by the age of diagnosis, which is quite earlier than the other cases reported in literature [7, 8].

Osteosclerosis was the primary finding of our patient suggestive of osteopetrosis. Other conditions causing osteosclerosis including hypervitaminosis D, hyperparathyroidism, vitamin D-resistant rickets, fluorosis and oxalosis were ruled out by laboratory analyses. Lead poisoning was not considered due to the child's age and history. Intrauterine infections were also ruled out owing to lack of typical findings on physical examination and X-ray examination (irregular 'celery stalk' pattern of metaphyses). Williams–Beuren syndrome was not possible due to lack of hypercalcemia. Robinow–Silverman–Smith syndrome is characterized by osteosclerosis accompanying mesomelic dwarfism and rib anomalies, which were not detected in our patient. Osteosclerosis may also be seen in histiocytic disorders, myelofibrosis, sickle cell disease and melorheostosis (Leri syndrome), but these occur typically in older ages, so they were not considered in our patient [10]. Raine syndrome, also called as lethal osteosclerotic bone dysplasia, is a rare autosomal recessive disorder characterized by exophthalmos, microcephaly, depressed nasal bridge, bilateral choanal atresia/stenosis, gum hyperplasia and osteosclerosis [11]. Although symptoms of our patient were also detected in the infantile period, Raine syndrome was ruled out owing to lack of characteristic features.

Because increased bone density is a characteristic feature of osteopetrosis, the concomitance of rickets and osteopetrosis (also called osteopetrorickets) seems paradoxical. Indeed, rickets is a characteristic feature of MIOP, which results from the defect in osteoclasts to provide a normal Ca/P balance, resulting in the poor mineralization of the osteoid [12]. Coexistence of rickets and osteopetrosis may have adverse effects on clinical response to stem cell transplantation. Therefore, prior to the HSCT, the rickets should be completely treated [13]. The initial findings of our patients suggested neonatal rickets associated with maternal vitamin D deficiency; however, diminished bone density, the characteristic feature of rickets, could not be detected in the X-ray findings. Other conditions related to vitamin D metabolism like 1-α-hydroxylase deficiency were also ruled out because 1,25 (OH)2 vitamin D level was normal. Non-responsiveness to vitamin D3 replacement suggested an underlying pathology other than neonatal vitamin D deficiency. Classical findings of osteopetrosis on skeletal survey led to accurate and early diagnosis.

Mazzolari *et al.* [7] also detected low and unstable levels of serum calcium in 60% of their patient population, which caused neonatal seizures in two of them. They have emphasized that hypocalcemia was more common in patients with *TCIRG1* mutations.

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Srinivasan *et al.* [14] have analyzed six MIOP patients presenting with neonatal hypocalcemia and emphasized that seizure due to hypocalcemia was the first symptom of all these children, starting as early as postnatal day 1, where one of them also had maternal vitamin D deficiency. They have also stated that, although hypocalcemia is an early finding (mean age 12.4 days), other characteristic findings of osteopetrosis like macrocephaly, hepatosplenomegaly and visual failure present later (mean age 6.6 months). Rickets was also reported to be quite frequent in the study population of Gonen *et al.* [8], where 60% of the population was hypocalcemic.

Various treatment options have been suggested for osteopetrosis. High-dose calcitriol, prednisolone, PTH and gamma interferon are being used as supportive agents, while HSCT still remains the only curative treatment option for now [1, 2]. High-dose calcitriol is an important aspect of rickets treatment, as rickets hampers the effects of HSCT [12]. Our patient was responsive to calcitriol therapy. Her Ca and P levels improved soon after the treatment was initiated. Serious complications may be prevented by HSCT if performed promptly, though cranial nerve decompression and growth retardation do not usually reverse [1, 2].

To sum up, our case report emphasizes that infantile osteopetrosis is an important cause of neonatal hypocalcemia. Being a rare disease with nonspecific clinical manifestations, the diagnosis is difficult and usually delayed. As irreversible complications develop within the first months of life, immediate diagnosis and early intervention are crucial and may be life-saving. We suggest performing a leg X-ray in the case of a neonate with refractory hypocalcemia, which may be a low-cost and easy method in the detection of underlying osteopetrosis.

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