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WHEN BONES TURN TO BRITTLE STONE: CLINICAL AND GENETIC INSIGHTS INTO INFANTILE OSTEOPETROSIS CAUSED BY A HOMOZYGOUS TCIRG1 MUTATION- A CASE REPORT

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ABSTRACT Infantile malignant osteopetrosis (IMO) is a rare autosomal recessive skeletal dysplasia caused by defective osteoclast-mediated bone resorption, resulting in generalized osteosclerosis, bone marrow failure, cranial nerve compression, and early mortality if untreated. Mutations in the TCIRG1 gene account for nearly 50–60% of autosomal recessive cases and are associated with severe clinical manifestations. [1–3]We report a 10-month-old female child born to non-consanguineous parents who presented with developmental delay, recurrent respiratory infections, poor visual fixation, and hypotonia. Examination revealed pallor, frontal bossing, coarse facial features, left lower motor neuron facial palsy, hepatosplenomegaly, roving nystagmus, and bilateral optic atrophy. Laboratory evaluation showed anemia with mild pancytopenia. Skeletal survey demonstrated diffuse osteosclerosis with classical bone-within-bone appearance and sandwich vertebrae. Whole exome sequencing identified a homozygous nonsense variant in TCIRG1 (c.969G>A; p. Trp323Ter) confirming autosomal recessive infantile osteopetrosis. Despite supportive care, the child succumbed to severe respiratory infection at 18 months of age. This case highlights the importance of early clinical recognition, characteristic radiological findings, and molecular confirmation for prompt referral for hematopoietic stem cell transplantation, the only curative treatment currently available. [1–4]

KEYWORDS : Infantile malignant osteopetrosis, TCIRG1, Whole exome sequencing, Osteoclast dysfunction, Hematopoietic stem cell transplantation.

INTRODUCTION

Osteopetrosis, commonly known as marble bone disease, is a genetically heterogeneous disorder characterized by failure of osteoclast-mediated bone resorption leading to generalized skeletal sclerosis. Although the bones become radiologically dense, they remain structurally abnormal and brittle due to defective remodeling. [1]

The infantile or malignant autosomal recessive form is the most severe phenotype with an estimated incidence of approximately 1 in 250,000 live births. Without definitive treatment, most affected children die during early childhood because of bone marrow failure, recurrent infections, or neurological complications. [2, 4]

The disease results from mutations affecting genes involved in osteoclast differentiation or acidification of the resorption lacuna. Among these, mutations in TCIRG1, encoding the a3 subunit of vacuolar H^+-ATPase, account for nearly half of all autosomal recessive cases. [3,5]Defective proton pump function prevents acidification of the osteoclast resorption lacuna, resulting in impaired dissolution of hydroxyapatite and failure of normal bone remodeling. [6]

Early diagnosis is crucial because hematopoietic stem cell transplantation (HSCT) performed before irreversible cranial nerve damage offers the only curative treatment. [7, 8]

We describe a genetically confirmed case of infantile malignant osteopetrosis due to a homozygous TCIRG1 mutation with classical clinical, radiological, and molecular findings.

CASE REPORT

A 10-month-old female child, second-born to healthy non-consanguineous parents, presented with complaints of developmental delay, poor visual response, recurrent respiratory tract infections, and generalized hypotonia since early infancy. She was born at term by normal vaginal delivery with a birth weight of 2.8 kg following an uneventful antenatal and perinatal period. There was no history of birth asphyxia, neonatal seizures, prolonged neonatal intensive care admission, or significant family history of similar illness.

Developmental assessment revealed marked delay in both gross and fine motor milestones. The child had poor head control, was unable to sit without support, and had poor visual fixation.

On examination, the child appeared pale with coarse facial features, frontal bossing, thick skin, and left lower motor neuron facial nerve palsy. Hepatosplenomegaly was present, with both liver and spleen palpable approximately 4 cm below the costal margin. Neurological examination revealed generalized hypotonia and roving nystagmus. Fundus examination demonstrated bilateral optic atrophy, consistent with compressive optic neuropathy secondary to narrowing of the optic canals. No congenital cardiac or renal anomalies were identified. The constellation of developmental delay, recurrent infections, anemia, hepatosplenomegaly, and cranial nerve involvement raised the suspicion of an inherited metabolic bone disorder, particularly infantile malignant osteopetrosis. [1-4]

Investigations

Laboratory investigations revealed hemoglobin of 9 g/dL with mild pancytopenia. Peripheral blood smear demonstrated normocytic normochromic anemia. Serum alkaline phosphatase was elevated, reflecting increased but ineffective bone turnover.

Bone marrow aspiration resulted in a dry tap, suggesting obliteration of the medullary cavity due to excessive sclerosis. Bone marrow failure in infantile osteopetrosis occurs because progressive deposition of dense bone replaces normal hematopoietic tissue, leading to anemia, thrombocytopenia, leukopenia, and compensatory extramedullary hematopoiesis. [2, 6]

A skeletal survey demonstrated diffuse generalized osteosclerosis involving the axial and appendicular skeleton.

Characteristic radiographic findings included:

Diffuse increase in bone density Bone-within-bone appearance involving long bones Sandwich vertebrae (rugger-jersey spine) involving vertebral bodies These findings are considered highly suggestive of osteopetrosis and reflect defective osteoclastic bone remodeling. [2, 9]

To establish the molecular diagnosis, whole exome sequencing was performed. It identified a homozygous nonsense variant in exon 9 of the TCIRG1 gene (c.969G>A; p. Trp323Ter), classified as likely pathogenic (ACMG: PVS1, PM2). The mutation introduces a premature stop codon resulting in truncation of the a3 subunit of the vacuolar H -ATPase, thereby impairing acidification of the osteoclast resorption lacuna and preventing normal bone resorption. No clinically significant copy number variants were detected. The findings confirmed autosomal recessive osteopetrosis type 1 (OMIM #259700).

Management

The child received comprehensive supportive care, including packed red blood cell transfusions for symptomatic anemia, broad-spectrum intravenous antibiotics for recurrent respiratory infections, nutritional

rehabilitation, physiotherapy, and early developmental stimulation. Multidisciplinary management involving pediatricians, neurologists, ophthalmologists, and rehabilitation specialists was instituted.

Ophthalmological evaluation confirmed bilateral optic atrophy, indicating irreversible optic nerve damage. Neurological assessment documented developmental delay and hypotonia secondary to cranial nerve compression and progressive skeletal disease.

The family was counseled regarding the diagnosis, prognosis, autosomal recessive inheritance pattern, and the 25% recurrence risk in future pregnancies. Genetic counseling and parental mutation analysis were advised. Hematopoietic stem cell transplantation (HSCT), the only definitive treatment capable of restoring normal osteoclast function through donor-derived hematopoietic cells, was discussed. However, definitive transplantation could not be performed before irreversible neurological involvement had occurred. [7,8]

The unfortunate outcome reflects the aggressive natural history of untreated TCIRG1-associated infantile malignant osteopetrosis, emphasizing the need for early diagnosis and timely hematopoietic stem cell transplantation before irreversible cranial nerve damage and life-threatening complications develop. [2,7,8]

DISCUSSION

Infantile malignant osteopetrosis (IMO) is the most severe form of osteopetrosis, characterized by failure of osteoclast-mediated bone resorption leading to progressive skeletal sclerosis, bone marrow failure, and cranial nerve compression. Although the bones appear radiologically dense, they are mechanically weak because of defective remodeling. Without definitive treatment, most affected children die during infancy or early childhood due to bone marrow failure, recurrent infections, or neurological complications. [1,2]

The present case demonstrated the classical phenotype of autosomal recessive infantile osteopetrosis with developmental delay, recurrent respiratory infections, anemia, hepatosplenomegaly, cranial nerve involvement, and characteristic radiological findings. These manifestations can be explained by the underlying pathophysiology. Failure of osteoclast-mediated bone resorption causes progressive narrowing of the medullary cavity, leading to pancytopenia and compensatory extramedullary hematopoiesis, resulting in hepatosplenomegaly. [1,2,6]

Cranial nerve compression is one of the most debilitating complications of malignant osteopetrosis. Progressive sclerosis of the skull base narrows neural foramina, resulting in optic nerve compression, optic atrophy, blindness, hearing impairment, facial nerve palsy, and developmental delay. Our patient exhibited bilateral optic atrophy, roving nystagmus, and left lower motor neuron facial palsy, all of which are well-recognized manifestations of severe TCIRG1-associated disease. [2,6]

Radiological evaluation remains an essential component of diagnosis. The bone-within-bone appearance, observed in our patient, results from defective remodeling of primary spongiosa during endochondral ossification. Similarly, sandwich vertebrae (rugger-jersey spine) result from sclerosis of the vertebral end plates while the central portion remains relatively lucent. These findings are highly characteristic of osteopetrosis and often suggest the diagnosis even before molecular confirmation. [2,9]

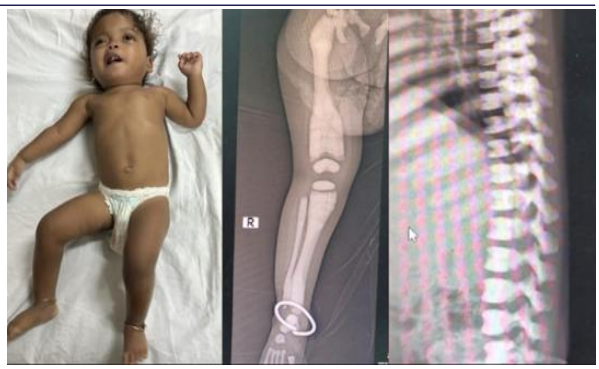
Whole exome sequencing confirmed a homozygous nonsense mutation in the TCIRG1 gene (c.969G>A; p. Trp323Ter). The TCIRG1 gene encodes the a3 subunit of the vacuolar H -ATPase proton pump located in the osteoclast ruffled border. This proton pump is essential for acidification of the resorption lacuna, allowing dissolution of hydroxyapatite crystals and degradation of bone matrix. Premature truncation of the protein caused by the p. Trp323Ter mutation results in complete loss of proton pump activity and severe impairment of osteoclast function. [3,5,6] the genetic findings in our patient correlated well with the severe infantile phenotype, early neurological involvement, and poor clinical outcome

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene[4] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[5]
TCIRG1 (+) (ENST00000265686.8)	Exon 9	c.969G>A (p.Trp323Ter)	Homozygous	Osteopetrosis, autosomal recessive 1 (OMIM#259700)	Autosomal recessive	Likely Pathogenic (PVS1,PM2)



The differential diagnosis included pyknodysostosis, carbonic anhydrase II deficiency syndrome, fluorosis, hypoparathyroidism, and other sclerosing bone dysplasias. However, the combination of generalized osteosclerosis, bone marrow failure, cranial nerve compression, hepatosplenomegaly, and molecular confirmation of a TCIRG1 mutation established the diagnosis of autosomal recessive infantile malignant osteopetrosis. [2,6]

Currently, hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for TCIRG1-associated osteopetrosis because osteoclasts originate from hematopoietic stem cells. Successful transplantation restores normal osteoclast function, improves hematopoiesis, and halts progression of skeletal disease. However, irreversible neurological deficits such as optic atrophy usually do not recover after transplantation, highlighting the importance of performing HSCT before permanent cranial nerve damage occurs. [7,8,10]

Despite aggressive supportive management, our patient succumbed to severe respiratory infection at 18 months of age. Recurrent infections remain a major cause of mortality in infantile osteopetrosis because of progressive bone marrow failure, neutropenia, impaired immune function, and respiratory compromise secondary to craniofacial abnormalities. This unfortunate outcome underscores the aggressive natural history of untreated disease and the necessity of early diagnosis and timely referral for transplantation. [2,7]

This case contributes to the limited literature on genetically confirmed TCIRG1-associated infantile malignant osteopetrosis from India. It highlights the diagnostic value of combining clinical examination, characteristic radiological findings, and molecular genetic testing. Early recognition by pediatricians is essential because prompt referral for HSCT before irreversible neurological damage offers the best chance for long-term survival and improved quality of life.

CONCLUSION

Infantile malignant osteopetrosis should be suspected in infants presenting with developmental delay, recurrent infections, anemia, hepatosplenomegaly, and visual impairment associated with diffuse skeletal sclerosis. Classical radiological findings such as bone-within-bone appearance and sandwich vertebrae provide important diagnostic clues. Molecular confirmation by whole exome sequencing not only establishes the diagnosis but also facilitates genetic counseling and prenatal diagnosis in future pregnancies. Early hematopoietic stem cell transplantation remains the only curative treatment and should be undertaken before irreversible neurological complications develop. Our case further emphasizes the aggressive clinical course and poor prognosis associated with untreated TCIRG1-related infantile malignant osteopetrosis.

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