



## Malignant Infantile osteopetrosis

### Osteopetrosis infantil maligna

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Received: 22-11-2018; Approved: 11-03-2019

#### Abstract

**Introduction:** Malignant Infantile Osteopetrosis (MIOP) is a rare and severe genetic disorder due to abnormal osteoclast activity. **Objective:** To report an infant who presented Malignant Infantile Osteopetrosis, reviewing the most relevant diagnostic and therapeutic aspects. **Clinical case:** A ten-month-old male infant with diagnosis of MIOP confirmed after presenting thrombocytopenia and visceromegaly. He was the first child of non-consanguineous parents, and among the findings, he presented severe hepatosplenomegaly, thrombocytopenia, and anemia; visual and hearing impairment, and repeated infections. The diagnosis was confirmed by genetic study, which identified two heterozygous mutations in the TCIRG1 gene. Hematopoietic stem cells were transplanted without hematological recovery. The patient died due to occlusive venous disease. **Discussion:** MIOP is a rare, severe, and early-onset disease, with a high rate of suspicion necessary in the presence of hepatosplenomegaly and bone marrow failure. Early diagnosis and hematopoietic stem cells transplantation are the only potentially therapeutic interventions of this lethal entity.

#### Keywords:

Malignant Infantile Osteopetrosis;  
Thrombocytopenia;  
Bone Marrow Failure;  
Osteosclerosis;  
Hepatosplenomegaly

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## Introduction

Osteopetrosis is a set of genetic disorders that produce sclerosis of the skeleton<sup>1</sup>. It is also known as Albers-Schonberg Disease, who made the first description of the benign form in 1904<sup>2,3</sup>. At least 10 varieties of Osteopetrosis are known with different modes of inheritance and severity, ranging from asymptomatic to fatal forms<sup>1,2</sup>. The most severe presentations are inherited in an autosomal recessive form and appear in childhood, called Malignant Infantile Osteopetrosis (MIOP), while the milder forms appear in adults and are of autosomal dominant inheritance<sup>2,4,5</sup>. It has an estimated incidence of 1 in 250,000 newborns in the autosomal recessive form and 1 in 20,000 in the autosomal dominant one<sup>2,6</sup>.

MIOP is a disorder caused by defects in bone resorption<sup>6</sup>, its pathogenesis lies in the alteration in differentiation or osteoclastic function, which prevents normal bone resorption and remodeling<sup>1,2,4,6-9</sup>. This causes an excess of osteoid substance, leading to a progressive bone marrow space reduction, where hematopoiesis occurs<sup>6,8,10</sup>. X-rays show diffuse bone sclerosis<sup>4</sup>. The gradual reduction in blood production determines the appearance of anemia, thrombocytopenia, immature leukocytes and erythroblasts in peripheral blood, with the consequent progressive hepatosplenomegaly due to compensatory extramedullary hematopoiesis<sup>2,4,8,9</sup>.

The diagnosis is based on clinical and radiological findings, and its confirmation is carried out through genetic and molecular analysis, which allows, in addition to characterizing the specific functional alteration, defining therapeutic strategies<sup>1,2,11</sup>. The only curative treatment is allogeneic bone marrow transplantation, which should be early in order to avoid severe marrow failure and severe sensorineural sequelae of progressive osteosclerosis<sup>2,7,8,12</sup>.

## Objective

The objective of this work is to report the clinical case of an infant with a diagnosis of Malignant Infantile Osteopetrosis, reviewing the most relevant diagnostic and therapeutic aspects.

## Clinical Case

Male infant, the first child of a 23-year-old, healthy, non-consanguineous couple, with no pathological family history. The pregnancy had no complications, a child was born at term, of adequate weight for the gestational age, and he presented nasal stridor.

At 15 days of age, he was hospitalized due to acute bronchiolitis and was admitted to the Intensive Care Unit since he developed acute respiratory failure. He received prolonged mechanical ventilation and tracheostomy. The patient stayed in this unit for five months, suffering from multiple invasive bacterial infections.

Hematologically, he presented severe thrombocytopenia (minimum levels of 16000/ $\mu$ L) since his admission, adding later normocytic normochromic anemia and massive hepatosplenomegaly. The patient received multiple red blood cell and platelets transfusions. The myelogram showed normal bone marrow density and polymorphous appearance, with significantly increased bone puncture resistance. Skull and long bones X-rays were taken showing a marked increase in the bone density of the diploe, and sclerosing involvement of the base (Figures 1A and 1B). The head and ocular orbit CT scan showed an increase in the skull bone density (Figure 1C). In the metabolic measures, the patient presented symptomatic hypocalcemia requiring supplementation. Neurological evidence included global hypotonia and visual and auditory sensory involvement. The ocular fundus showed bilateral papillary atrophy, and the visual evoked potentials did not identify cortical potentials corresponding to the retino-geniculo-calcarine pathway. The auditory potentials showed mild bilateral hearing loss. Head MRI identified bone malformation at the skull base.

Laboratory analysis showed normocytic normochromic anemia (Hb 6.75 g/dl), thrombocytopenia 47.700/ $\mu$ L, 6% erythroblasts, and 21% relative reticulocytosis. The immunoglobulins and lymphocyte populations quantification were normal.

In the presence of hematological failure associated with visceromegaly and skeletal sclerosis, a diagnosis of probable bone resorption defect was made and, considering the severe and early clinical presentation, a MIOP was proposed. A DNA sample was sent to the Molecular Biology Laboratory of the Universitätsklinikum Ulm in Germany, World Reference Centre for the study of this pathology, finding two mutations in the TCIRG1 gene (11q13.2), in compound heterozygosity: c.797delA (p.Glu266GlyfsX12), and c.1387ins (GCTTCATCTACAACGfs) (p.Glu463Glyfs), confirming the proposed diagnosis. A hematopoietic progenitor cell transplantation (HPCT) was performed at 10 months of age. Since the patient was an only child, he received a haploidentical HPCT (donor mother), with T lymphocyte deletion (CD3+ negative selection with CliniMacs technology), and myeloablative conditioning using Busulfan, Fludarabine, and Thiotepa. The patient died due to hepatic veno-occlusive disease, with multiple organ failure, without any hematological recovery.



**Figure 1.** **A)** Lateral x-ray of the skull showing sclerosis of the skull base. **B)** Radiography of long bones showing increased density and absence of medullary cavity. Vertebrae and pelvic bones with increased density. **C)** Computed tomography of the skull, where a significant increase in bone density is noticeable.

## Discussion

We are facing an infant with thrombocytopenia, which in the evolution develops bone marrow failure and visceromegaly, associated with skeletal sclerosis. It was suggested MIOP as a diagnosis, which was confirmed by the molecular study.

The main manifestation of the disease is hematological. The remodeling failure of the growing bones determines the medullary cavity invasion by osteoid substance excess. As a consequence, progressive bone marrow failure syndrome leads to severe anemia, thrombocytopenia, and leukoerythroblastosis. Hepatosplenomegaly is a manifestation of compensatory extramedullary hematopoiesis<sup>2,4,5,8</sup>.

Clinically, these patients can present a particular phenotype, given by wide forehead and fontanelles, flat nose, and thick gums. They may also associate craniosynostosis, progressive macrocephaly with frontal bossing, exophthalmos, and hypertelorism<sup>2,3,4,8</sup>.

A significant element is the presence of nasal stridor since birth. Noisy breathing is observed, caused by the involvement of skull base bones, choanae, and jaw, which define an upper airway obstruction<sup>4</sup>. It may be an element of diagnostic suspicion in the first month of life in a patient with normocytic normochromic anemia or unexplained thrombocytopenia<sup>3</sup>. Sensorineural impairments are frequent due to narrowing of the cranial nerve foramina, which cause vascular and nerve compression<sup>4,5,6,8,11</sup>. The optic nerve is the main affected nerve, resulting in partial or total vision loss. The patients may have abnormal eye movements or nystagmus<sup>3</sup>. More rarely, the auditory, facial, and olfactory nerves may be affected<sup>4,2</sup>.

The patient manifested symptomatic hypocalcemia since birth. This phenomenon is frequent, due to the defective osteoclastic function, which determines disturbances in the calcium homeostasis<sup>4</sup>. It is usually

symptomatic, of early-onset, with high body reserves of calcium<sup>4</sup>. In severe cases, it can cause tetany and secondary hyperparathyroidism<sup>2</sup>.

The high incidence of infections is characteristic. They are caused by alterations in the cellular immunity. It is common to find monocyte and neutrophil dysfunctions and decreased natural killer activity<sup>8</sup>.

Facing a clinical picture suggestive of MIOP, radiological studies should be made<sup>1,3</sup>. The characteristic findings are uniformly dense, sclerotic and radiopaque bones; bone within a bone appearance, especially in vertebrae and phalanges, and focal sclerosis of the skull base, pelvis, and vertebrae. In the long bones metaphysis, radiolucent bands and disappearance of the medullary cavity can be observed<sup>2,5,8</sup>.

Confirmatory diagnosis is made through molecular studies, which has therapeutic, prognostic and genetic counseling implications<sup>2,11</sup>. The TCIRG1 and CLCN7 genes were sequenced, and the presence of two transacting mutations in the TCIRG1 gene (compound heterozygous) was observed: an exon 8 deletion that leads to a change in the reading frame, generating a premature stop codon (truncated protein), and a 15-base pair insertion in exon 12, which causes a change in the reading frame in the codons that flank the insertion and addition of four amino acids. Although both mutations have not been previously described, they should probably be considered pathogenic, as they severely alter the protein structure and can be associated with gene function loss.

Mutations in the TCIRG1 gene determine 50% of MIOP cases<sup>1,4,10</sup>. This gene encodes a specific subunit of the osteoclasts proton pump; its dysfunction generates alterations in acidification, necessary for the correct function of bone resorption<sup>4,5</sup>. Carriers of mutations in this gene are candidates for urgent bone marrow transplantation, due to the severity of the condition and the potential response to this treatment, since they

are dysfunctional osteoclasts in a normal bone matrix. Although this mutation is not accompanied by neurodegenerative disease, international guidelines recommend neurological assessment, EEG, and MRI<sup>1</sup>.

The natural evolution is to progression, with death generally in the first decade of life<sup>2,6</sup>, where survival without treatment after two years of age is rare<sup>1</sup>. Among the most frequent causes of death are infections, hemorrhages, and severe anemia<sup>3,8</sup>. So far, there is no curative medical treatment, it is only supportive and aimed at treating complications: transfusions for the anemia and thrombocytopenia treatment<sup>2</sup>. The results of treatment with corticosteroids, vitamin D, and calcium or HPCT are disappointing<sup>1,2</sup>. The use of recombinant human interferon-gamma-1b has shown to improve bone resorption and decrease infections<sup>2,4</sup>, however, since the effects are partial and require frequent subcutaneous treatment, it is currently discouraged<sup>4</sup>.

Early hematopoietic stem cell transplantation is the only effective treatment to halt the progression of the disease, reserving it for the most severe forms<sup>2,3,7-10</sup>. It corrects bone, hematological, and immune anomalies by providing stem cells capable of producing mature osteoclasts of normal functioning<sup>8,10</sup>. The patient was a carrier of mutations in a gene that does not associate neurodegenerative disease and presented severe hematological failure, constituting an absolute indication for transplantation. Since the disease is lethal without treatment, HPCT is accepted with haploidentical HPCT donors and unrelated donors<sup>8</sup>. In the case of haploidentical family donors, survival is lower (13-24%) and it is associated with high risks such as implant failure, toxic and infectious complications<sup>1,4,7,8</sup>. Age at the time of transplantation is an important prognostic factor. Children under the age of two have a lower incidence of peri-transplant complications and less neurosensory involvement<sup>8</sup>.

Genetic counseling was carried out since it is an autosomal recessive inherited disease. In this couple, prenatal or preimplantation diagnosis can be made

since the mutations are known. In case the fetus is affected and they decide to continue with gestation, it is possible to schedule an early HPCT with a better prognosis<sup>2</sup>.

## Conclusions

A multidisciplinary MIOP approach is a priority. It is essential that the pediatrician recognizes this entity to achieve a correct and timely diagnosis.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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