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CASE REPORT

Hurler syndrome: diagnostic journey in a orphan disease - case report

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Abstract

Objectives: Promote the early detection of the disease through pertinent clinical findings in patients with mucopolysaccharidosis. **Case Report:** Patient with MPS I with typical clinical signs of the disease from a very early age were diagnosed only at 22 months old and will begin enzymatic replacement therapy. **Discussion:** The disease, the earlier it is detected, the better and more effective the treatment, which may be enzyme replacement therapy, or, in the last case, transplantation of hematopoietic stem cells.

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INTRODUCTION

Are lysosomal storage diseases caused by the accumulation of mucopolysaccharides (long sugar molecules), more modernly called glycosaminoglycans (GAGs). The accumulation is due to the deficiency of the enzyme α-L-iduronidase and its type of inheritance is autosomal recessive origin . They are rare metabolic diseases , currently presented in seven different types (I, II, III, IV, VI, VII and IX). Type I is also referred to as Hurler syndrome, Hurler-Sheie syndrome and Sheie syndrome (varying according to the severity of the patient's involvement)[1-5].

With the progressive accumulation of GAGs, essential components of the structure of bones, cartilage, skin, tendons and other tissues of the body, several organs can be compromised, particularly the brain[4,5].

Its incidence is around 1 affected every 130,000 live births in some statistics. It is an autosomal recessive genetic disorder characterized by a defect in the alpha-iduronidase enzyme causing accumulation of glycosaminoglycans[2,5,6].

The most common signs and symptoms of MPS I are recurrent airway infections , inguinal and/or umbilical hernia, enlarged liver and spleen, obstructive sleep apnea, joint stiffness, and corneal opacity . In the most severe presentation of the disease (Hurler syndrome), central nervous system (CNS) involvement is common, with patients presenting neuropsychomotor delay and intellectual disability[8,9].

Hurler syndrome comprises enzyme replacement therapy (ERT), which consists of the periodic application of a recombinant enzyme intravenously, and hematopoietic stem cell transplantation (HSCT), which must be carried out, preferably, even before two years. The success of these current therapies can be influenced by several factors and should be monitored with clinical evaluation and the use of biomarkers (such as the measurement of urinary GAGs)[9,10,14-16].

CASE DESCRIPTION

Patient, female, Caucasian, was referred for evaluation due to delayed motor development. Patient was born on 11/29/2016 by cesarean section (by maternal option), at term, weighing 3450g, length 51cm, head circumference 36cm, chest circumference 36cm, with an APGAR score of 9 in the 1st minute and 10 in the 5th minute. Her gestational history did not reveal complications, prenatal examinations did not reveal any abnormalities. Mother reported good fetal movement (from the 4th month of pregnancy).

Neuropsychomotor developmental history did not reveal significant delay in motor milestones, although speech delay was already observed in the patient. Although the patient had recurrent airway infections and had been followed up with an otorhinolaryngologist since one month of life, there was no diagnosis of her underlying disease. The mother reports that the patient has nocturnal snoring with frequent apnea, undergoing polysomnography that showed severe obstructive sleep apnea.

Her family history does not present a similar case or any other hereditary pathologies, parents were young at the time of conception and not consanguineous. There was no maternal exposure to teratogenic agents during pregnancy.

Assessed by several medical specialties (such as orthopedics, pediatric cardiologist, neuropediatrician), the patient was referred to the medical genetics service.

Her clinical-genetic examination revealed: height below the 3rd percentile; weight between the 50th and 75th percentiles; head circumference between the 50th and 75th percentiles, easy infiltration, short nasal dorsum, more flat nose, thick lips, joint contracture and stiffness, claw hands, thick skull hair, hepatosplenomegaly, grade 1 osteotendinous reflexes in lower limbs and upper limbs, no signs of spinal cord compression.

Due to the suspicion of lysosomal storage disease due to facial dysmorphisms (Figure 1), complementary exams were requested aimed at this diagnostic hypothesis (Table 1).



Figure 1. Typical face of a patient with MPS-I.

Deficiency of the alpha-iduronidase enzyme associated with a significant increase in urinary GAGs confirmed the diagnosis of type I mucopolysaccharidosis in the patient (now 22 months old). Due to the age of presentation and neurological involvement, the patient is classified as Hurler's syndrome. The therapeutic possibilities were discussed

Table 1. Complementary tests performed by the patient and results obtained.

EXAM	RESULT
Thoraco-lumbar spine radiography	Anomalies of vertebral bodies
Hand X-rays	Tapered metacarpal bases with widening of metacarpals (distal portion) and phalanges
Foot X-rays	Irregular metatarsal metaphysis; enlarged metatarsals and phalanges
Abdominal ultrasound	Presence of hepatosplenomegaly
Echocardiogram	Within normality
Glycosaminoglycans (urine)	1,432 µg/mg creatinine (VN = < 2 years 79-256)
Enzyme assay of alpha-iduronidase in leukocytes	0.7 nanomoles/hour/mg prot (VN=32 – 56)
Plasma beta-glucuronidase enzyme assay	213 nanomoles/hour/mg prot (VN= 30 – 300)
Iduronate sulfatase enzyme assay in leukocytes	97 nanomoles/4 hours/mg prot (NV=31 – 110)
Beta-galactosidase enzyme assay in leukocytes	125 nanomoles/hour/mg prot (VN = 72 – 280)

Legenda: VN: Valor normal.
Fonte: Os autores (2018).

with the parents: parents declined hematopoietic stem cell transplantation due to the associated mortality risk and chose to start ERT.

DISCUSSION

MPS I (CID E76.1) used to be divided into two large groups (hard and soft). Currently, it can be classified into MPS I-classical form (Hurler syndrome), MPS Intermediate (Hurler-Scheie syndrome) and MPS I-mild (Scheie syndrome), according to the magnitude of symptoms presented by patients[1,4-6,8].

The worldwide incidence of MPS I is quite variable, being estimated between 0.69 to 1.66 per 100,000 people; however, neonatal screening data have shown that the incidence may be higher, ranging from 1:7,353 (Washington state, USA)[13] to 1:14,567 (Missouri, USA). In a study by Pastores et al. (2007)[4], in which clinical data from patients with MPS I were captured in order to characterize the natural course of the disease, the distribution of MPS I between males and females was similar, as expected for a disease autosomal recessive[2,7].

There are rare epidemiological studies on MPS I in Brazil. According to the Brazilian registry of the disease, which is part of an international registry, in 2010, 891 patients with MPS I were registered worldwide, of which 82 were in Brazil. . Another Brazilian study reported 225 diagnosed cases of MPS I between 1982 and 2015 and, considering the period between 2000 and 2013, the prevalence of MPS I at birth was 1/322,580 live births[6,7].

The vast majority of patients with the Hurler form of the disease show signs of disease during the first 6 months of life, such as recurrent airway infections and otitis media (as presented by our patient) (Table 2). Other symptoms, such as kyphosis, corneal clouding , heart disease , joint restrictions, and increased head circumference , appear slightly later (mean age 8 to 10 months). During the first 12 months, motor development is affected, and a significant number of patients also have language delay (as in the case of the patient reported)[4,9-11].

Table 2. Warning Signs for MPS.

Age	Signals
Up to 6 months	Airway infections; Repetitive otitis.
Up to 8 and 10 months	Kyphosis; corneal clouding ; heart disease ; _ joint restrictions; increase in cephalic perimeter.
Up to 12 months	Motor development is affected ; language delay.
Other findings	Chronic ear infections; _ vision and hearing problems; joint stiffness; heart disease ; h is inguinal and umbilical kidneys; carpal tunnel syndrome; communicating hydrocephalus and sleep apnea.

Source: The authors (2018).

Individuals with MPS I form Hurler have progressive developmental delay and more severe physical problems. They often have other medical problems that require multidisciplinary care, such as chronic ear infections, vision and hearing problems, joint stiffness, heart disease (both hypertrophic heart disease and valvular heart disease involving the aortic and mitral valves), inguinal and umbilical hernias , carpal tunnel syndrome, communicating hydrocephalus and sleep apnea (momentary cessation of breathing during sleep)[4,11,13].

Corneal opacification is a common finding in patients with MPS I, which can lead to visual difficulties, and periodic evaluation with the ophthalmologist is important. Recurrent otitis media is common and contributes to the hearing loss that these patients may experience[11,13].

Symptoms presented by the patient with severe obstructive sleep apnea, leading to constant respiratory arrest, also contribute to the worsening of cardiac function. Cardiorespiratory dysfunction in patients with mucopolysaccharidosis are signs of the severity of the disease, being, in the case of the patient, an important risk factor for sudden death, particularly during sleep itself due to repeated apneas and the increased risk of cardiorespiratory arrest in these episodes[4,9,11].

The delay in diagnosis can further compromise the patient's condition, which reiterates the importance of the clinician in recognizing the early symptoms of this disease[10,15,17].

Enzyme replacement therapy for MPS type I (Laronidase enzyme, Aldurazyme ®) constitutes an effective therapeutic modality to combat the accumulation of GAGs and, consequently, control the adverse implications of the deposit of this substance in different human tissues, however it is unable to pass the blood-brain barrier, therefore it does not prevent the involvement of the CNS in this disease[10,11,16,17].

Hematopoietic stem cell transplantation (HSCT) is effective in preserving the mental and cognitive function of patients, but it is associated with a higher risk of mortality, and its use is indicated for patients with the Hurler form of the disease. Preferably, it should be performed before two years of age, which is often impossible, since diagnostic delay in this disease is common . As a result, there is a need to include MPS I in neonatal screening programs, in order to obtain an early diagnosis of the disease and enable the performance of the HSCT in a timely manner[3,11-13,16,17].

Regardless of which therapy is performed, long-term periodic multidisciplinary follow-up of the patient is essential to assist in the early detection and resolution of problems associated with the disease (particularly in the management of carpal tunnel syndrome, signs of hydrocephalus, and treatment of sleep apnea) . Furthermore, as it is an autosomal recessive genetic disorder, there is a 25% risk of recurrence in the couple's future offspring, and it is important to carry out genetic counseling for the patient's parents[1,14,15].

The patient in question will start treatment with ERT, which also needs to be performed as soon as possible, since several complications associated with the deposit of GAGs can have their impact reduced with the use of the recombinant enzyme, in particular, improvement of the respiratory condition. of the patient, organomegaly and obstructive sleep apnea. Unfortunately, the patient's diagnosis required a 22-month journey, from the first respiratory symptoms at one month of life to the emergence of complications such as obstructive sleep apnea and joint contractures, a delay that is not uncommon for patients with MPS I, even in countries considered "developed"[1,2,4,14,16].

Thus, early diagnosis of the disease is crucial for the patient's quality of life and consequent increase in survival, in addition to reducing the impact of irreversible sequelae of the disease[9,11,16,17].

FINAL CONSIDERATIONS

Thus, the urgency for the diagnosis of this disease requires recognition of the initial signs and symptoms of the disease which, although nonspecific at first, may, as a whole, point to a lysosomal storage disease as the cause of the patient's condition. While neonatal screening for MPS I is not implemented, only clinical evaluation and careful observation of unusual signs in children (such as severe obstructive apnea) will lead the health professional to suspect the disease and allow an early diagnosis[15,17].

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