CASE REPORT

Hurler syndrome. Case report

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ABSTRACT

Introduction: Hurler syndrome belongs to a group of diseases called muco polysaccharidosis and is a rare disease in pediatric age.
Patient information: 12-year-old male adolescent, product of normal delivery, who at the age of two years started with loss of speech and constant drooling. He was evaluated by the Genetics Specialist who, due to his phenotypic characteristics, suspected a possible Hurler syndrome. We present an interesting case, not commonly seen in medical practice, with the aim of informing students and health professionals about the physical characteristics of the patient, who has survived more than 10 years of life.
Conclusions: the diagnosis was confirmed by mucopolysaccharide chromatography study performed at the National Genetics Center. Patients often die in the first decade of life due to respiratory and cardiac complications, hematopoietic precursor transplantation and enzyme therapy with alpha-L-iduronidase can improve life expectancy.
Key word: mucopolysaccharidosis I; Hurler syndrome; alpha-L-iduronidase

RESUMEN

Introducción: el síndrome de Hurler pertenece a un grupo de enfermedades llamadas muco polisacaridosis y es una rara enfermedad en la edad pediátrica.
Información del paciente: adolescente masculino de 12 años de edad, producto de parto normal, que a los dos años comenzó con pérdida del habla y babeo constante. Fue valorado por el Especialista en Genética que, debido a sus características fenotípicas, sospechó un posible síndrome de Hurler. Se presenta un caso interesante, no comúnmente visto en la práctica médica, con el objetivo de dar a conocer a estudiantes y profesionales de la salud las características físicas del paciente, que ha tenido una supervivencia mayor de los 10 años de vida.
Conclusiones: el diagnóstico se confirmó por estudio de cromatografía de mucopolisacáridos realizado en el Centro Nacional de Genética. Los pacientes a menudo mueren en la primera década de la vida debido a complicaciones respiratorias y cardíacas, el trasplante de precursores hematopoyéticos y la terapia enzimática con alfa-L-iduronidasa pueden mejorar la esperanza de vida.
Palabras clave: mucopolisacaridosis I; síndrome de Hurler; alfa-L-iduronidasa

INTRODUCTION

Mucopolysaccharidosis type I (MPS-1) is a lysosomal metabolic disease due to an enzymatic deficiency of alpha-L-iduronidase, which results in an accumulation of dermatan and heparan sulfate glycosaminoglycans (GAGs) in organs and tissues and increased urinary excretion. It is a rare disease, with an incidence of approximately one in every 100,000 live newborns. It is inherited in an autosomal recessive manner and more than 80 different mutations of the IDUA gene (locus 4p16.3) have been described.(1) It was described in 1919 by Gertrud Hurler, who published the clinical history of patients with corneal opacity and mental retardation. In 1952 Brant isolated the mucopolysaccharide dermatan sulfate in the liver of two patients with Hurler's syndrome; the disease was named mucopolysaccharidosis (MPS). The other two forms of the disease are Sheie syndrome, which is the milder form of MPS, and Hurler Sheie syndrome, which is less severe. Hurler syndrome is the most severe of the MPS-1 subtypes, the child presents with neurodevelopmental delay before the first year of life and stops between the ages of two to four years. This is followed by progressive deterioration and loss of mental and physical abilities. Language may be limited due to hearing loss and macroglossia; they also have corneal opacity and carpal tunnel syndrome. Affected children may be very large at birth, but at one year of age stature begins to lag and stops at three years of age, they have a short trunk, facial features include prominent forehead, flat nasal bridge, bushy eyebrows, open mouth and ogival palate.(2) Cardiomyopathy and valvular anomalies, organomegaly, hernias and hirsutism are common in some cases. Early diagnosis is difficult, based on the determination of alpha-L-iduronidase enzyme deficiency, detection of increased heparan and dermatan sulfate in urinary excretion and confirmatory genetic testing for the IDUA gene mutation.(3) The prognosis is poor, children with this disease have nervous system problems and may die at an early age from respiratory and cardiac complications.

PATIENT INFORMATION

The patient is a 12-year-old male adolescent with a history of being the product of a low-risk obstetric pregnancy, euthecological delivery at 39.5 weeks, institutional, with a birth weight of 7.10 pounds, who presented neonatal hypocalcemia, without other complications.

He walked at one year and started the infant circle, at two years of age the educator noticed that he stopped talking and had constant drooling. He was taken to the consultation of a Neurology Specialist of the University Pediatric Hospital "José Luis Miranda" of Santa Clara City, Villa Clara Province, who requested an interconsultation with the Diagnosis and Orientation Center and he was diagnosed with a possible severe mental retardation. The Neurology Specialist indicated as treatment levomepromazine, ½ tablet every 12 hours, carbamazepine, one tablet every eight hours and vitamin B6, three tablets a day.

The Neurology and Genetics Specialists, due to her phenotypical characteristics and her neurodevelopmental delay, suspected a possible Hurler syndrome and

indicated the corresponding studies. When he finished pre-school he was diagnosed with attention deficit and was transferred to the Home for the Physically Handicapped, where he stayed until he was nine years old; his mother decided to leave him at the home when he stopped walking. Physical examination revealed coarse fascia, elongated face, broad forehead, thick eyebrows, thick lips, ogival palate, tendency to open mouth, constant drooling, depressed nasal bridge and hypertrichosis on the back (Figures 1 and 2). In the osteomyoarticular system: thoracolumbar scoliosis, knee deformity and joint stiffness, in the genitourinary system: macroorchidism, on abdominal palpation: hepatomegaly and splenomegaly, height/age percentile: 90-97 and normal ocular fundus.

Figure 1. Shows coarse fascia, broad forehead, bushy eyebrows, thick lips and broad nasal bridge

Figure 2. Displays open mouth, elongated face, joint stiffness

Studies performed:

- Brain stem and brainstem evoked potentials: mild hearing loss in the right ear and moderate in the left ear
- Electroencephalogram: normal

- Computerized axial tomography (CAT) scan of the skull: cortical atrophy
- Abdominal ultrasound: hepatomegaly of 5 cm and splenomegaly of 2 cm
- Echocardiogram normal
- Mucopolysaccharide chromatography: presence of dermatan and heparan sulphate
- Hemogram and blood chemistry within normal limits.

The diagnosis was confirmed by mucopolysaccharide chromatography study performed at the National Genetics Center.

DISCUSSION

This condition is a congenital metabolic disease. An autosomal recessive disorder resulting from mutations in the gene encoding the enzyme alpha-L-iduronidase, it causes an accumulation of the GAGs heparan sulfate and dermatan sulfate in all tissues of the body and causes a wide variety of physical symptoms as well as organ-damaging abnormalities, including the heart. These mucopolysaccharide molecules are found throughout the body, often in mucous secretions and in the fluid surrounding joints. The rate of accumulation is variable in each affected individual and this makes for great diversity in clinical manifestations; symptoms become more apparent as the accumulation progresses. Both parents need to transmit the defective gene in order for their child to develop this syndrome.[4]
Among the differential diagnoses of this disease are:

1. **Hurler-Scheie syndrome:** represents the intermediate phenotype of an alpha-L-iduronidase deficiency. These patients present with short stature, dental problems and high risk of complications associated with anesthesia. Severe joint involvement and respiratory infections and chronic otitis, small thorax, hepatosplenomegaly, coarse facial features and corneal opacity, umbilical and inguinal hernia, dysmorphic fascies, developmental delay, hearing loss, gastrointestinal problems, skeletal deformities and cardiac defects (caused by accumulation of dermatan sulfate), among others; however, their nervous system is normal.[5]
2. **Scheie's syndrome:** it is the mildest form of an alpha-L-iduronidase deficiency, it occurs more frequently in children from five years of age. Unlike the other types, it has a higher incidence rate of glaucoma. These patients usually have normal stature and their hepatosplenomegaly is very mild. Joint stiffness may not be evident, they are not retarded and do not have coarse features. Dysostosis multiplex is very mild. Carpal tunnel syndrome or other manifestation of joint stiffness is what brings these patients to the physician; cardiac problems are associated with mucopolysaccharide accumulation in the veins and arteries. Ocular impairment, such as corneal opacity and retinal degeneration, may lead to suspicion of mucopolysaccharidosis.[5]
3. **Hunter syndrome:** it is determined by a mutation in the X chromosome, in the region Xq25-q27, which affects the normal function of the enzyme iduronate sulfatase, essential for the fragmentation of two mucopolysaccharides, dermatansulfate and heratansulfate, causing

cytoplasmic accumulation of mucopolysaccharides. The clinical features progressively settle in. They consist of coarse fasciitis, thickened skin, umbilical hernia, hepatosplenomegaly, hump, broad nasal base, short stature and joint stiffness.[6]

Diagnosis of the disease can be made prenatally by measuring enzyme activity in chorionic villus or amniocyte culture, through a genetic test if the mutation responsible for the disease is known. Another method is based on the detection of increased heparan and dermatan sulfate in urinary excretion and is confirmed by demonstrating enzymatic deficiency of alpha-L-iduronidase.[3]

The definitive diagnosis is established by molecular genetic study of the IDUA gene mutation type,[1] not available in Cuba. It is inherited as an autosomal recessive genetic trait, the chromosomal alteration has been identified and is located on the short arm of chromosome 4, close to the gene that regulates the expression of Huntington's disease. Numerous mutations with different degrees of expression have been described, which explains the great variability of clinical forms in this disease.[7] Another study is based on the demonstration of deficient activity of the lysosomal enzyme alpha-L-iduronidase in peripheral blood leukocytes, cultured fibroblasts or plasma. Urinary excretion of glycosaminoglucan (heparan and dermatan sulfate) is a useful preliminary test.[8]

To determine the involvement of other systems, studies such as brain stem and brainstem evoked potentials, echocardiogram, electroencephalogram and abdominal ultrasound, among others, should be performed as deemed necessary.

The management of the disease is multidisciplinary. Hematopoietic precursor transplantation is the treatment of choice for patients with Hurler syndrome under two and a half years of age because it can prolong survival, preserve neurocognition and improve some somatic features. Enzyme replacement therapy with alpha-L-iduronidase is recommended for all patients and is a lifelong therapy that alleviates non-neurological symptoms. Additional management of this disease is largely supportive and includes surgical interventions (adenotonsillectomy, hernia repair, ventriculoperitoneal shunt and heart valve replacement) and medication to alleviate gastrointestinal symptoms.[3]

Hurler syndrome is the most severe form of the mucopolysaccharidoses. Its progressive course usually leads to death before the age of 10 years from cardiorespiratory causes,[1,2,3,8] but hematopoietic precursor transplantation can improve life expectancy, as can enzyme therapy with alpha-L-iduronidase.[3]

MPS are a large group of infrequent diseases, but with a very high impact on the patient, family and society. It is important to recognize their characteristics in order to establish a timely diagnosis and offer appropriate treatment.[9]

Genetic testing and counseling, as well as a complete family history profile, are important for prospective parents with a family history of Hurler syndrome.

An interesting case was presented, not commonly seen in medical practice, with the aim of informing students and health professionals about the physical characteristics of the patient with this syndrome, who has survived more than 10 years of life, thanks to multidisciplinary care and management.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.