Hurler Syndrome: a Biochemically Confirmed Case in Dominican Republic

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Abstract

Mucopolysaccharidosis (MPS) is a group of metabolic disorders caused by the deficiency or complete absence of certain lysosomal enzymes responsible for the breakdown of mucopolysaccharides, causing an accumulation of glycosaminoglycans (GAGs) throughout the body. Mucopolysaccharidosis type I (MPS I), also called Hurler syndrome, is an autosomal recessive lysosomal storage disorder resulting from a deficiency of the enzyme α-L-iduronidase. This report aims to present the clinical findings and diagnosis of a 21-month-old female with no history of similar cases in their previous generations. The diagnosis was considered based on the clinical and radiological characteristics of Hurler syndrome (HS) and confirmed biochemically, becoming the first confirmed case in the Dominican Republic.

Keywords

Mucopolysaccharidosis I, mucopolysaccharide, genetics, lysosomal storage disorder.

Introduction

Mucopolysaccharidoses are a group of diseases within the inborn errors of metabolism characterized by the accumulation of glycosaminoglycans (GAGs) at the lysosomal level as a consequence of the partial or total absence of the enzymes that degrade them. Mucopolysaccharidosis type I (MPS I) is an autosomal recessive lysosomal storage disorder caused by the IDUA gene (4p16.3) resulting from deficiency of the enzyme α-L-iduronidase and a lysosomal accumulation of dermatan sulfate and heparan sulfate [1–2]. This disorder leads to a wide range of clinical manifestations and multiorgan dysfunction with considerable morbidity in most patients.

Throughout history, MPS I has been classified into three clinical syndromes that vary according to the intensity of the symptoms and their age of onset: Hurler syndrome, Hurler-Scheie, and Scheie [3]. Hurler Syndrome (HS), is the most severe form of MPS I, characterized by a significant cognitive and developmental delay with coarse facial features accompanied by respiratory, hepatic, and cardiac diseases. Symptoms make an appearance soon after birth with rapid progress, leading to death in the first decade of life. Hurler-Scheie includes moderate symptoms without cognitive impairment. Patients with Hurler-Scheie syndrome may live to teenage or early adulthood while Scheie manifests with mild symptoms and normal cognitive development living through adulthood [4].

This report presents the clinical findings and diagnosis of a pediatric patient with Hurler syndrome.

Case Presentation

A 21-month-old female, born after a normal full-term pregnancy and a spontaneous vaginal delivery, was referred to endocrinology consultation in the Dominican Republic, by a primary physician who suspected hypothyroidism where examination revealed psychomotor retardation, delayed closure of fontanelles, and retarded dentition along other clinical features including coarse face, enlarged head circumference, depressed nasal bridge (Figure 1-A), low-set ears (Figure 1-D) and corneal clouding (Figure 1-C). The patient had a distended abdomen, with the presence of umbilical hernia and hepatosplenomegaly

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(Figure 2-B), both hands were short with clawed fingers (Figure 2-C) with limitation of joint mobility. Intraoral examination revealed macroglossia and gingival hypertrophy with no signs of dentation (Figure 1-B). Radiological findings included thoracolumbar kyphosis (Figure 2-A) and a barrel-shaped chest (Figure 2-B). Therefore, the Department of Genetics was notified, and the diagnosis of Hurler syndrome was considered based on clinical and radiological findings.

Echocardiographic evaluation was made by the Department of Pediatric Cardiology indicating interventricular septal thickness, asymmetric hypertrophic cardiomyopathy, and 17mm dilated aortic root (z-score: 5.23) and trivial aortic regurgitation.

Dried blood spots were sent to the molecular diagnostic laboratory in Greenwood Genetic Center, South Carolina. Genomic DNA from the patient was used to amplify all 14 coding exons of the IDUA gene (chromosome 4p16.3). Specifically, this essay showed a homozygous mutation in exon 9 where a nucleotide change occurred from Guanine1205 to Adenosine, producing an amino acid change to tryptophan 402. Quantitatively, a total deficit (0 nmol/ml) was found (normal range 2.02-16.1), leading to confirm the diagnosis of Hurler syndrome.

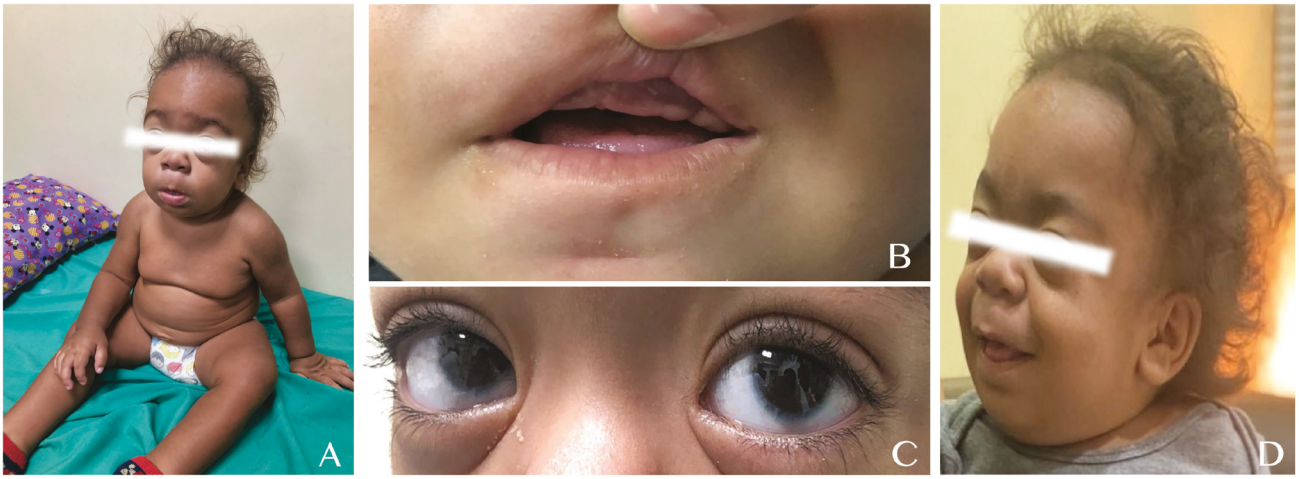

Figure 1. Clinical features of Hurler Syndrome. (A) Coarse face. Enlarged forehead, depressed and broad nasal bridge, ocular hypertelorism, thick eyelids. (B) Gingival hypertrophy with no signs of dentation. (C) Corneal Clouding. (D) Low-set Ears.

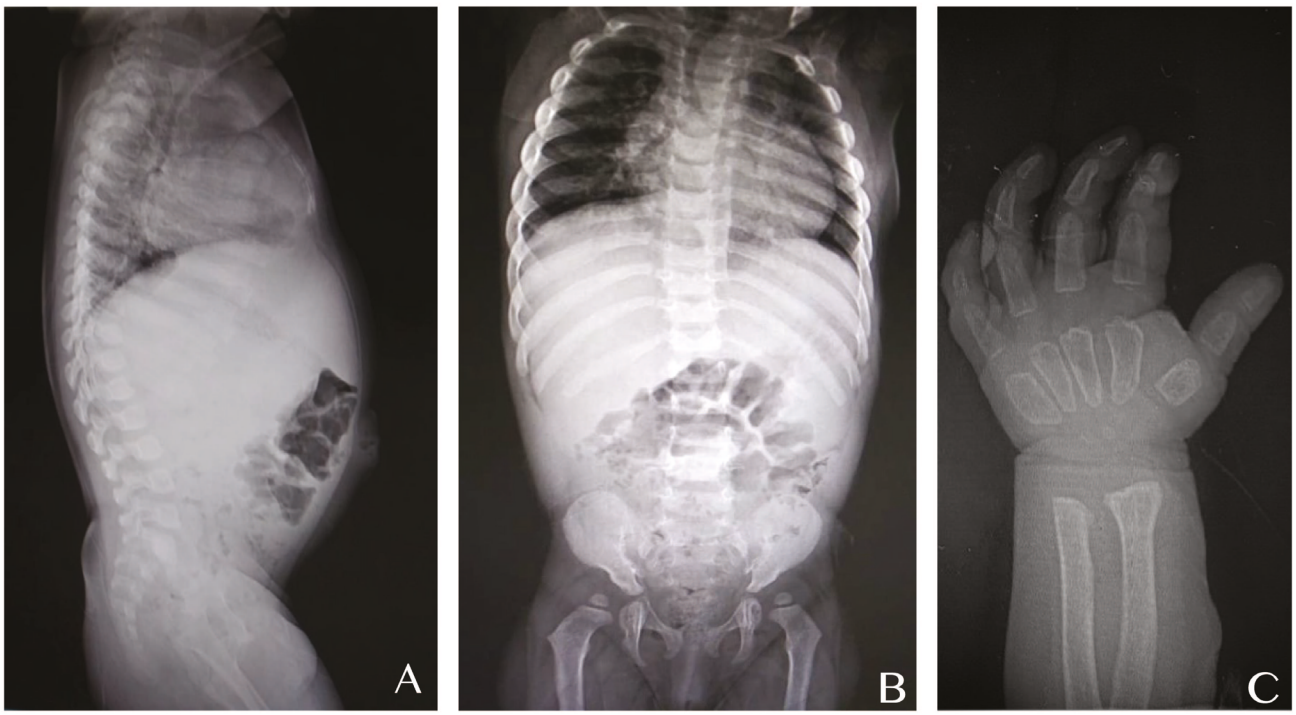

Figure 2. Radiological findings in a Hurler Syndrome patient. (A) Lateral view of the spine. Thoracolumbar kyphosis (B) Barrel-shaped chest. Hepatosplenomegaly. (C) Short hands with clawed fingers.

The treatment was based on supportive care, including vitamins and mucolytic medications. The patient's family was advised by a geneticist to further manage to improve the quality of life of the patient and family. An anonymous charity foundation recently authorized the provision of 78 vials of Aldurazyme as the beginning of therapy for six months. The patient will receive the enzyme as promptly as possible after the permission to transport the medication into the country is completed.

Discussion

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive lysosomal storage disorder resulting from deficiency of the enzyme α-L-iduronidase characterized by a variety of diseases with different organ involvement, onset, and progressive ages [1]. The buildup of these GAGs leads to progressive and multisystem organ damage. Patients with the most severe phenotype, which is often fatal by the age of 10, endure progressive degeneration of the musculoskeletal, cardiorespiratory, and central neurological systems if untreated [5]. The best long-term prognosis for patients with MPS I depends on early symptom detection and diagnosis. Therefore, pediatricians and other experts must be aware of the clinical signs and consider MPS as a differential diagnosis. Due to the degree of complexity of this disease, the follow-up of these patients must be carried out by a multidisciplinary team at least once a year [6].

Early manifestations include the presence of umbilical and inguinal hernias and coarse facial features which are the most prevalent symptom in patients with Hurler and Hurler-Scheie phenotypes [5]. Corneal opacity is commonly present in all patients with MPS, leading to vision loss. Acute blindness may occur in the presence of untreated communicating hydrocephalus. Consequently, severe MPS I phenotype patients should receive a non-contrast computed tomography or MRI every 1 to 2 years, along with neurological and ophthalmologic examination [6]. Recurrent upper respiratory tract infections, chronic recurrent rhinitis, and frequent ear infections are commonly present in these patients resulting in airway compromise and hearing loss, respectively. Ear, nose, and throat examinations should be performed at least once a year.

Pulmonologists are also crucial in routine examinations for MPS I. Both attenuated and severe MPS I phenotypes are at risk of severe respiratory insufficiency because of restrictive lung disease, obstructive sleep apnea, and asthma. Patients with attenuated MPS I should have sleep tests upon diagnosis and annually after that if respiratory insufficiency is found, as should patients with severe MPS I after the age of 2 to 3 years [6].

Serious cardiac manifestations are frequent as well and aggravate with time. This may include pulmonary and systemic hypertension, cor pulmonale, valvular disease, arrhythmia, cardiomyopathy, congestive heart failure, coronary artery disease, and cardiomyopathy. Echocardiography and 12-lead electrocardiography should be performed at the time of diagnosis and monitored regularly. The use of pharmaceutical management has not been decided. Nevertheless, one of the treatments typically carried out on MPS patients is cardiac valve surgery [7]. Other clinical features include growth retardation, hepatosplenomegaly, progressive skeletal dysplasia, macroglossia, short stature, cardiomyopathy, and gum, tooth, and enamel abnormalities.

When the diagnosis of HS is suspected, urinary screening tests can be carried out to determine the urinary excretion of GAGs. Since September 2022, Berry Spot Test, a urine semiquantitative GAGs analysis, is available at the public healthcare level in Santiago, Dominican Republic. Although this is an easy and cheaper alternative, it is a nonspecific screening test for MPS I with a sensitivity and specificity of 93.6% and 53.9%, respectively [8]. Deficient α-L-iduronidase activity in fibroblasts, leukocytes, serum, or blood spots is the basis for a conclusive diagnosis of MPS I [9]. Once MPS I is confirmed, patients should be referred to professionals with a background in genetics for specialized care and family counseling, including reproduction [10]. However, the Dominican Republic has 5 trained geneticists, with only 4 available in the public health care system making their participation in the patient's clinical care team very rare.

Among the available treatments are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). Enzyme replacement therapy with iduronidase, a GAG that doesn't cross the blood-brain barrier, is considered to relieve non-neurological symptoms, and delay and prevent the development of some clinical features. On the other hand, HSCT can prevent and even reverse many features of MPS I prolonging survival, preserving neurocognition, and improving some somatic characteristics, especially in the early form of the disease (<2.5 years) and >70 developmental quotients [11]. Both treatments' success depends on how early they are administered, the severity of clinical manifestation, and the cardiopulmonary and neurological status of the patient [12].

The present case represents the first confirmed case of Hurler Syndrome in the Dominican Republic. A few cases of mucopolysaccharidoses have been suspected, but not genetically established. Despite there being a few methods available to diagnose MPS, early diagnosis of rare diseases has been a challenge for countries in Latin America and the Caribbean [13]. In 2021, the Senate of the Dominican Republic approved legislation that orders the performance of neonatal screening for the early detection of congenital and metabolic diseases in the infant population with an obligatory basic screening covering the most important pathologies from the clinical and epidemiological point of view including congenital hypothyroidism, phenylketonuria, galactosemia, cystic fibrosis, congenital adrenal hyperplasia, biotinidase deficiency, and hemoglobin defects. Nevertheless, this agreement hasn't been implemented yet. The lack of newborn screening programs delays the diagnosis of many diseases, affecting early interventions and impacting the morbidity and mortality associated with these disorders [14].

Conclusion

The importance of early diagnosis of MPS I, especially HS, to guarantee the effectiveness of treatments is evident. However, the lack of availability of neonatal screening programs for inborn errors of metabolism and the limited access to diagnostic tools make timely initiation difficult. On the other hand, access to MPS treatments is another limiting factor to assure these patients a good quality of life while only MPS IV therapy is available through the high-cost program controlled by the country's Ministry of Health. MPS I enzyme is exclusively available through private organizations. To date, the patient continues without enzyme replacement therapy treatment due to the unavailability of the corresponding medication and the limitation of not having specialized centers for stem cell transplantation for children in the country. However, the initial treatment was donated by a charitable foundation, and the administration of the enzyme is expected to begin as soon as it gets into the country.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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