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Case Report

Mucopolysaccharidosis Type VII: Sly's Disease About a Case and Literature Review

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Abstract

Mucopolysaccharidosis type VII or Sly disease is a lysosomal storage disease, autosomal recessive, due to an enzymatic deficiency of ß-glucuronidase, responsible for the intra-lysosomal tissue accumulation of glycosaminoglycans. It is a serious disease with a very heterogeneous clinical spectrum. We describe the first Moroccan case of MPS VII in a 9-year-old child, in whom the diagnosis of MPS VII was suspected given a history of recurrent infections, a dysmorphic syndrome, macrocrania, an inguinal hernia, and a growth and cognitive delay. The diagnosis was confirmed on the increased urinary excretion of glycosaminoglycan and on the study of the enzymatic activity of ß-glucuronidase in leukocytes which was collapsed to 0.1 µmol/l/h. in the absence of enzyme replacement therapy in our context, the treatment was only symptomatic.

Keywords: *Beta-glucuronidase; Enzyme Replacement Therapy; Glycosaminoglycans; Sly's Disease; Mucopolysaccharidosis VII*

Introduction

Mucopolysaccharidosis type VII or Sly's disease is a very rare hereditary lysosomal storage disease, discovered by William S. Sly in 1973, secondary to a lysosomal enzyme deficiency (β-glucuronidase), leading to an accumulation of glycosaminoglycans (GAG) in the connective tissue, giving a multi-systemic, progressive attack with progressive cellular dysfunctions in different organs, including respiratory, cardiovascular and nervous [1,2].

We report the first Moroccan case of MPS VII in a 9-year-old child who presented clinical signs characteristic of this disease, having been hospitalized in the pediatric department of the Mohammed V military hospital in Rabat.

Observation

9-year-old male child from an untreated pregnancy, the 7th of eight siblings, of first-degree blood relatives. From the first year of life, progressive development of language delay, mental retardation, growth retardation associated with macrocrania, facial dysmorphism and thoracic deformity, with notion of repeated infections of the upper and lower airways, snoring with noisy breathing. The clinical examination showed a weight of -3DS, a height of -4DS and a PC of +2DS, facial dysmorphism with a pseudo-hurlerian facies, a funnel-shaped thoracic deformity with sternal protrusion, lumbar hyperlordosis without scoliosis, a 2/6th endapexian systolic murmur, bilateral corneal opacity, a right inguinal hernia and a limitation of joint amplitudes (Cf figure 1). The phosphocalcic, hepatic, renal, thyroid assessment as well as the blood count were normal. Skeletal X-ray demonstrated multiple dysostosis (See figure 2), echocardiography showed a slightly remodeled

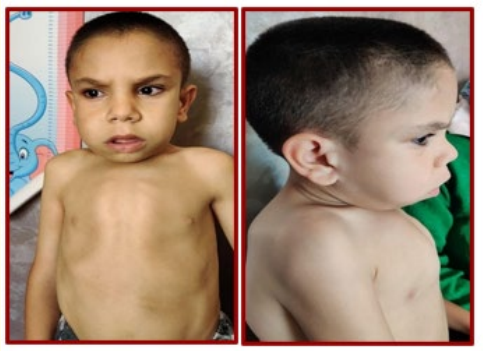

Figure 1: *Dysmorphic syndrome in our patient.*

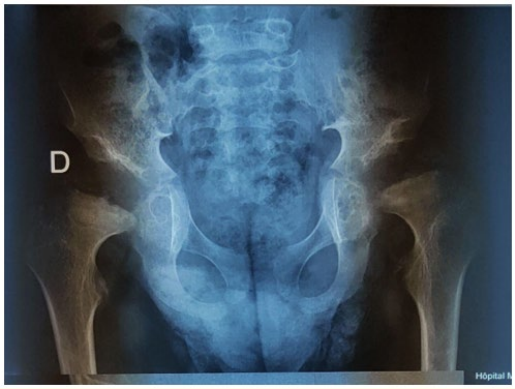

Figure 2: *Frontal X-ray of the pelvis showing a deformation of the 2 femoral heads with a lytic appearance associated with a flared appearance of the metaphyses.*

and moderately leaky mitral valve, abdominal ultrasound was normal, and inguino-scrotal ultrasound showed a right inguinal hernia with a right hydrocele blade. The diagnosis was confirmed on increased urinary excretion of glycosaminoglycan at 30 mg/mmol (dermatan sulfate and heparan sulfate) and on the enzymatic activity of ß-glucuronidase in leukocytes which was collapsed to 0.1 µmol/l/h. In the absence of enzyme replacement therapy in our context, this child benefited only from symptomatic treatment.

Discussion

Mucopolysaccharidosis type VII is a rare disease, with an incidence of < 1/1,000,000 births, transmitted in an autosomal recessive manner. This underlines the importance of genetic counseling for affected families [3]. In Morocco, between 1992 and 2020, 350 cases of MPS were diagnosed, but no cases of MPS VII were identified. Our patient is therefore the first case diagnosed in Morocco.

The deficient enzyme (β-glucuronidase) is encoded by the GUSB gene, located on the long arm of chromosome 7 (7q11.21) [4]. This enzyme is essential for the degradation of glycosaminoglycans: dermatan sulfate, heparan sulfate and chondroitin sulfates. Genetic studies have revealed a wide diversity of mutations, including missense, deletion, and insertion mutations. Deleterious mutations are often correlated with more severe phenotypes, while some point mutations can result in milder forms of the disease. The five most common mutations in MPS VII are mainly exonic point mutations, such as p.L176F and p.R357X [5].

Sly's disease particularly illustrates the heterogeneity of MPS, with phenotypes varying from severe fetal hydrops to milder forms allowing survival into adulthood [6,7]. Typical clinical features include growth retardation, skeletal abnormalities, dysmorphic facial features (pseudo-Hurlerian facies), ophthalmologic abnormalities (corneal opacities), cardiac involvement (valve thickening), hepatomegaly, and respiratory complications. Neurologic involvement, although variable, may include psychomotor delays, hearing and visual disturbances, and abnormalities on brain MRI [8-12] (Table 1).

Prenatal	**At birth**
Hydrops fetalis	Moderate hepatomegaly Bilateral clubfeet
Postnatal and Childhood	
General	Stunted growth retardation Wheelchair use
Dysmorphia Head, Eyes, ENT	Coarse facial features, Macrocrania Short neck, Shaggy hair, Thick eyebrows Recurrent otitis, Macroglossia Snoring, Abnormal teeth, Gingival hypertrophy, Sensorineural hearing loss. Corneal opacification Decreased visual acuity and photosensitivity
Heart attack	Heart valvulopathy Cardiomyopathies
Osteoarticular disorders	Multiple dysostosis Decreased joint range of motion with reduced mobility, joint contractures and stiffness. Scoliosis, Kyphosis, Humpback. Genu valgum, equinovarus feet. Hands in claws Acetabular dysplasia of the hips
Thoracolumbar and abdominal anomalies	Short trunk Pectus carinatum or excavatum Deformations of the rib cage Hepatomegaly/splenomegaly Umbilical and/or inguinal hernias
Neurological damage	Limited vocabulary Mental retardation Hydrocephalus Cervical spinal cord compression No deficit sign
Respiratory impairment	Recurrent respiratory infections Tracheotomy Respiratory arrest

Table 1: *Summary of pre- and post-natal clinical manifestations during MPS VII.*

There are three clinical forms of the disease. Severe forms are detected in utero and present with marked dysmorphisms, hepatosplenomegaly and severe neurological involvement. The classic form, on the other hand, corresponds to Sly's initial description, with an evolution allowing several years of survival; symptoms include hepatosplenomegaly, hernias and progressive kyphoscoliosis. Finally, the moderate form is often diagnosed after the age of 4 years and revealed by bone abnormalities, without significant hepatosplenomegaly.

The biological examinations for orientation include the search for vacuolated lymphocytes in the blood smear and by the study of urinary GAGs. It finds an increased and qualitatively abnormal excretion (presence of dermatan, heparan sulfate and chondroitin sulfates) [13]. The definitive diagnosis is based on the demonstration of β-glucuronidase deficiency in leukocytes, serum or in cultured fibroblasts. This enzymatic activity can also be measured on blotting paper. Confirmation of the diagnosis of MPS VII can also be achieved by studying mutations in the β-glucuronidase gene (GUSB) by molecular biology.

Prenatal diagnosis can be performed by analysis of enzyme activity from chorionic villi or amniotic fluid [14]. This is particularly relevant for families at risk. Differential diagnosis requires a thorough analysis of other types of MPS, including types I, II and IV, and is based on methods of urinary GAG analysis and enzyme profiles.

The management of MPS VII requires a multidisciplinary approach aimed at improving the quality of life of patients, it includes: Enzyme Replacement Therapy: Administration of β-glucuronidase, Vestronidase alfa (Mepsevii™) at a dose of 4 mg/Kg by intravenous (IV) infusion every two weeks has shown positive results. Studies indicate a significant reduction in urinary GAG levels and an improvement in lung function and quality of life of patients [15,16]. Hematopoietic stem cell transplantation (HSCT): Although this option may offer benefits by allowing the transplanted cells to produce the missing enzyme, it carries significant risks, such as rejection and mortality. The effectiveness of this procedure has yet to be evaluated due to the rarity of the disease [17-19].

Symptomatic treatment: Care should also focus on managing complications, such as cardiac, pulmonary, and bone damage, as well as ophthalmologic monitoring to prevent visual complications [20].

Conclusion

MPS VII is a severe, disabling, heterogeneous and degenerative lysosomal, multisystemic disease. Its frequency is underestimated because the symptoms are very heterogeneous. The diagnosis is first guided by the clinic and is based on a dosage of urinary GAGs. Diagnostic confirmation is obtained by the dosage of the enzymatic activity of β-glucuronidase. Specific treatments are hematopoietic stem cell transplantation and enzyme replacement therapy.

Consent

In accordance with international or academic standards, written parental consent was collected and preserved by the authors.

Ethics Approval

In accordance with international or academic standards, written ethical approval was obtained and maintained by the authors.

Correspondence of Interests

The authors declare that they have no conflicts of interest to report.

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