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CASE REPORT

Sanfilippo syndrome: The challenges of early diagnosis for pediatricians - Case report

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Abstract

Mucopolysaccharidosis type III, also known as Sanfilippo syndrome, is an autosomal recessive disorder, caused by deficiency in one of the four enzymes involved in the lysosomal degradation of one type of glycosaminoglycan: heparan sulfate. There are four subtypes of MPS: A, B, C, and D. Here we report a female patient with language delay, behavioral issues (increasing agitation and hyperactivity) and fine motor incoordination. After evaluation in a reference center for rare diseases, Sanfilippo syndrome was suspected, however her first urinary screening was not informative for mucopolysaccharidosis. Nevertheless, since there was a strong suspicion of MPS III, further enzymatic studies were performed for Sanfilippo syndrome, confirming Sanfilippo type B diagnosis. Correct diagnosis allowed proper genetic counselling for the family and better patient clinical follow-up. The authors reinforce the importance of raising suspicion of Sanfilippo syndrome in children with neurodevelopmental delay, abnormal behavior and language regression/stagnation.

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INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of diseases of accumulation of glycosaminoglycans (GAGs) such as dermatan sulfate, heparan sulfate, keratan sulfate and chondroitin. There are 8 types of MPS, listed I through IX, caused by a deficiency in one of the eleven different enzymes involved in the catabolism of GAGs[1]. Patients with MPS present progressive accumulation of GAGs in different tissues, leading to the clinical picture of the disease.

Although they are typically multisystemic diseases, some forms of MPS[1], such as type IX, the rarest of all forms of MPS, do not present a neurological, visceral or cardiovascular condition, being only osteo-articular, reminiscent of rheumatoid arthritis. childish. Others, such as type III (Sanfilippo syndrome), present predominantly central nervous system involvement with fewer somatic findings when compared to other subtypes such as type I (Hurler syndrome), type II (Hurler syndrome) and type VI (Hurler syndrome). Marateaux-Lamy)[1,2].

Mucopolysaccharidosis type III (MPS III), also known as Sanfilippo syndrome, is an autosomal recessive genetic disease characterized by the accumulation of glycosaminoglycans in lysosomal cells. It is caused by a deficiency in one of the four enzymes necessary for the breakdown and recycling of heparan sulfate[1].

There are four human-proven subtypes of MPS III, which are type A (heparan-N-sulfatase deficiency, OMIM #252900), type B (alpha-N-acetylglucosamidase deficiency, OMIM #252920), type C (acetyl deficiency -CoA-alpha-glucosamine acetyltransferase, OMIM #252930) and type D (N-acetylglucosamine 6-sulfatase deficiency, OMIM #252940)[1]. The most common are types A and B, the others being rarer. Recently, another subtype, E, was identified in an animal model, however, to date, there are no human patients diagnosed with this form of disease[2,3].

The prevalence is 1 in 70 000 live births, being, therefore, the most frequent subtype of MPS when compared to the others[4]. Clinical symptoms begin between 2 and 6 years of age[1,4] and the life expectancy of these patients is around three to four decades[5]. The clinical manifestations of Sanfilippo syndrome are mainly neurological[1,4] (hyperactivity, sleep disturbances, aggressiveness, delay in neuropsychomotor development, dyslalia, "autistic-like" behavior, etc.) and somatic (repeated ear and nose infections). , hearing loss, scoliosis, lordosis, hepatomegaly, etc.)[4].

This article reports the case of a patient diagnosed with MPS III – B, whose early diagnosis allowed rehabilitation interventions, which impacted the patient's quality of life, and genetic counseling for her parents.

CASE REPORT

Patient, female, 5 years old, daughter of young and non-consanguineous parents, was referred for evaluation of behavioral disorder and language delay.

She was born by elective cesarean section, at term (39 weeks), with a length of 51 cm and a weight of 2.7 kg, with no reports of complications in the gestational and neonatal period. The parents deny other health problems or clinical complications of the patient; they also deny other family members with symptoms similar to hers; the patient has two healthy older siblings.

From the age of 2, the parents noticed that the child had difficulty formulating complete sentences, agitated behavior, apparently without showing fear in dangerous situations (such as crossing a street with heavy traffic of cars) and motor incoordination. The patient, however, demonstrated adequate motor development. The parents reported that the pediatrician observed hepatomegaly in the patient (confirmed by ultrasound), which subsequently regressed.

The patient had adequate height and weight for his age, without evident dysmorphic signs, however, comparing the evolution of the patient's facies at different ages, it can be considered that there was the appearance of more infiltrated facial features ("coarsening facial features") (Figure 1).

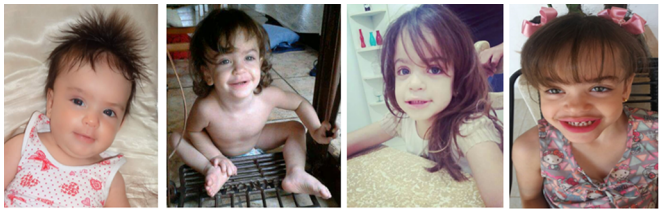


Figure 1. Evolution of the patient's facial phenotype.

Patient attended normal school and was in the competent year for his age, however, in view of the patient's language changes, the school's pedagogical department advised the family to seek speech therapy for the patient. She was evaluated by a speech therapy service, which suggested evaluation by a neuropediatrician.

The evaluation with the neuropediatrician suggested the diagnosis of a genetic syndrome, questioning a form of Sanfilippo (type III mucopolysaccharidosis). However , only the urinary test was requested to search for GAGs, whose result was within the normal range (Table 1).

Subsequently, the patient was referred to the medical genetics service, and the hypothesis of "mild/attenuated" form of Sanfilippo was raised. Pharmacological treatment was started for the patient's hyperactivity with clonazepam, and urinary and blood tests (enzyme tests) were requested for the patient. Urinary screening for the presence of GAGs and total dosage of GAGs was again within the normal range (Table 1). However, given the clinical suspicion, an enzymatic study of the four enzymes involved in Sanfilippo syndrome was carried out and a deficiency of the enzyme alpha-N-acetylglucosamidase (type B) was observed, confirming the diagnosis of Sanfilippo (Table 2).

Table 1. Urinary screening.

Quantitative tests	Sample	Result	Reference value
Glycosaminoglycan electrophoresis	Urine	Normal pattern	Normal pattern
Glycosaminoglycans	Urine	123 ug/mg creatinine	< 5 years 64 - 127

Source: The authors (2018).

Table 2. Enzymatic study.

Enzyme Assays	Sample	Activity	Reference value
Heparan sulfamidase (MPS IIIA)	Leukocytes	9.2 nmol/17h/ mg protein	5,5-24
N-Acetylglucosaminidase (MPS IIIB)	Leukocytes	not detectable	10-34
N-Acetylglucosamine-6- -Sulfatase (MPS IIID)	Leukocytes	9.1 nmol/24h/ mg protein	7-22

Source: The authors (2018).

At the moment, the patient presents challenging behaviors, such as loss of fear and hyperactivity, with difficulty focusing, even for a few minutes, on a single game or activity. There were no signs of self-aggression, but the patient sometimes exhibited more aggressive behavior (such as biting) towards his mother, when he felt contradicted by her. In addition, until now, he has presented an adequate growth rate for his age, although with evident stagnation of his neuropsychomotor development, without, however, showing signs of neurological regression. Parents deny any current or previous sleep disorders.

DISCUSSION

As Sanfilippo syndrome is a disease that courses with neurological stagnation/regression in childhood, it must always be present as a differential diagnosis in children who develop behavioral disorders[5].

Traditionally, the course of the disease is divided into 4 stages:

- Pre-clinical phase: the child has a normal neuropsychomotor development. On average, this phase occurs from birth to two years of age[1,4,6].
- In stage 1, children have both neurological disorders (delayed neuropsychomotor development or speech delay) and somatic problems. It starts around the first to the fourth year of life[4,7].
- In phase 2, the presence of developmental delay associated with sleep disturbances and challenging behaviors ('autistic-like' behavior, loss of fear, aggression, hyperactivity) is observed. It starts around the third to the seventh year of life[4,6,7].
- In stage 3, the child is usually less agitated, actually reflecting the dementia process associated with the disease. There is a clear regression, albeit slowly. It starts around eight to ten years of age[4,6,8].

Compared to other mucopolysaccharidoses that have a more multisystemic character, MPS III can present as a purely neurological disease in many patients. This is due to the type of GAG that accumulates in this disease, in this case heparan sulfate (figure 2). Heparan sulfate accumulates in the individual's body globally in all organs, however, unlike other MPSs, this GAG is toxic mainly to the cells of the central nervous system, leading to the process of neurodegeneration[4,9-11].

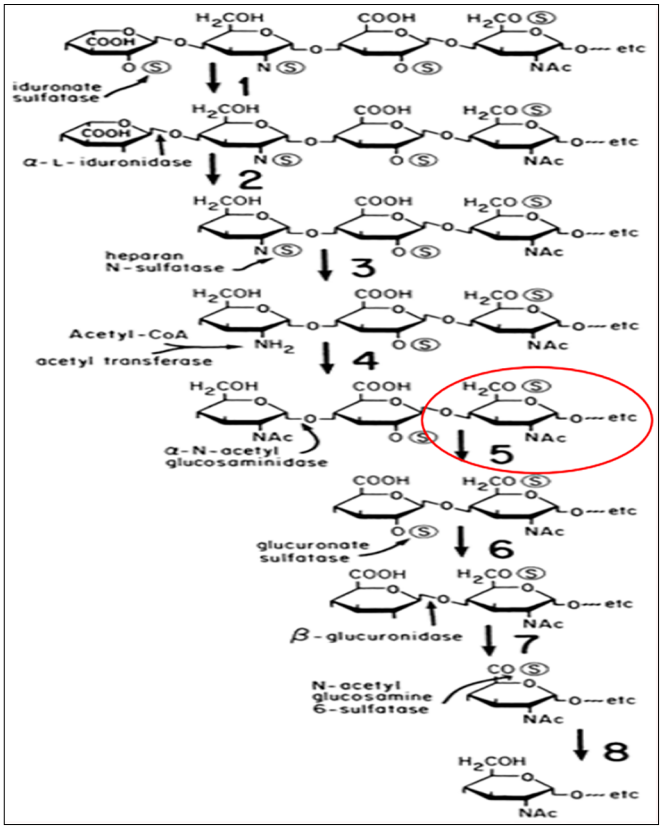


Figure 2. GAG metabolic pathway - Gradual degradation of heparan sulfate. Deficiency diseases correspond to the numbered reactions: 1 = MPS II, Hunter Syndrome; 2 = MPS I, Hurler, Hurler-Scheie and Scheie syndromes; 3 = MPS III A, Sanfilippo Syndrome type A; 4 = MPS III C, Sanfilippo Syndrome type C; 5 = MPS III B, Sanfilippo Syndrome type B; 6 = no known deficiency disease; 7 = MPS VII, Sly Syndrome; 8 = MPS III D, Sanfilippo Syndrome type D. The drawing represents all known structures that occur within heparan sulfate, not implying that they occur stoichiometrically.

In MPS III, the accumulation of heparan sulfate in lysosomal cells generates an extensive brain inflammatory process. This process occurs because heparan sulfate released by lysosomes is phagocytosed by microglia. The same happens with neurons engulfed and damaged by the excess of this glycosaminoglycan, initiating a process of metabolic changes in neural cells (when there is an increase in other glycosphingolipids such as gangliosides with neurotoxic potential) that culminates in the activation of apoptosis (programmed cell death), leading to neurodegeneration[12-14].

What this case teaches:

✔ In the investigation of Sanfilippo syndrome, attention to the details of the clinical history and physical examination is essential;

✔ In MPS III, if the urinalysis does not show an increase in GAGs and/or the presence of heparan sulfate, but clinical suspicion persists, it is essential to order the enzyme test for the four forms of the disease;

✔ Patients diagnosed with agitation, autistic-like behavior or ADHD with neurological delay/regression, should have Sanfilippo as a differential diagnosis.

Despite constituting the most common subtype of MPS, there is still a lot of underdiagnosis of this disease, because patients with Sanfilippo do not present the classic multisystem phenotype with "rough facies" observed in other MPSs, such as type I, type II and type VI[15].

When MPS III is suspected, some tests are essential to define the presence or absence of the disease and, if confirmed, which subtype. The first complementary test to be performed is, usually, the urinalysis (chromatography of glycosaminoglycans to define the type of GAG present in the urine and the total dosage of GAGs in the quantitative urine), which will tell you in a quantitative way the dose of heparan sulfate. present in the patient's urine. [1,15] In Sanfilippo syndrome, it is not uncommon for the urinalysis to be negative, however, if the patient's clinical condition is very suggestive, the clinician should order the enzyme test (made from a blood sample) for the four enzymes of MPS III to confirm or rule out this diagnosis[1,15].

In addition, it is interesting to note that children who have acquired autistic or hyperactive behavior, but who do not meet diagnostic criteria for autism or ADHD should be investigated for MPS III as a possible organic cause[16-18].

MPS III is a disease that still has no cure, but there are rehabilitation therapies that aim to slow down the progression of the disease and provide a better quality of life for the patient[19,20].

Thus , the benefit of an early recognition of MPS III includes genetic counseling for the parents, early initiation of rehabilitation therapies and better quality of life for the patient and his/her family[21,22].

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