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Case Report

Cardiac disease as the presenting feature of mucopolysaccharidosis type IIIA: A case report

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ABSTRACT

Severe cardiac involvement is a common feature of mucopolysaccharidoses (MPS), but occurs only rarely in MPS III (Sanfilippo syndrome). We report herein a case of MPS III-A having cardiac involvement as its first manifestation. Analysis of the *SGSH* gene showed homozygosity for the novel mutation p.G80V. We propose that MPS disorders, including MPS III-A, should be included in the differential diagnosis of every case of cardiomyopathy presenting during the first year of life.

1. Introduction

Mucopolysaccharidoses (MPS) are a group of rare inherited disorders characterized by abnormal accumulation of glycosaminoglycans (GAGs) in various tissues. A common feature of several of these disorders is cardiac involvement, which often includes anatomic and functional abnormalities of the heart valves. MPS types I–IX each results from a deficiency of enzymes that are involved in the stepwise degradation of GAGs such as dermatan, keratan, heparin and chondroitin sulfates.

MPS III comprises four related inborn errors of lysosomal degradation of heparan sulfate, known as MPS III types A, B, C, and D. All of them are characterized by progressive mental deterioration and behavioral problems, with only mild facial dysmorphism and mild somatic disease [1]. The onset and severity of the disease are highly variable, but symptoms rarely appear during the first year of life. MPS III-A, or Sanfilippo syndrome type A (OMIM#252900), arises when the activity of the enzyme N-sulfoglucosamine sulfohydrolase (heparan N-sulfatase or sulfamidase; EC 3.10.1.1) is lost. The sulfamidase gene (*SGSH*;605270) is 11 kb long, comprises 8 exons, and is located on chromosome 17q25.3. To date, around 140 different mutations associated with MPS III-A have been identified (HGMD 2014) (http://www.hgmd.org).

Cardiac compromise, including anatomical and functional abnormalities of the cardiac valves, myocardial hypertrophy, thickened chordae tendineae, and narrowing of the coronary arteries, develops in most patients with MPS [2–6]. Involvement of the mitral valve, often associated with an aortic valve anomaly and/or left ventricular hypertrophy, is the most common presentation [7]. Cardiomyopathy has been reported in MPS I and VI [4,6,8]. However, cardiac involvement in MPS III is generally mild [2,9].

We report a case of a patient with MPS III-A who presented cardiac symptoms in the first year of life, ultimately requiring mitral valve replacement surgery in childhood.

2. Case report

A 6-month-old girl was admitted to a tertiary public children's hospital in Northeast Brazil for evaluation of signs and symptoms of cardiac insufficiency. She was the first child of consanguineous and healthy parents. Gestation and delivery were normal. The weight and length at birth were 2900 g and 49 cm respectively. According to her mother, the patient had exhibited cyanosis since age 1 month. The remainder of the physical examination was normal. An echocardiogram showed

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cardiomyopathy, left ventricular dilatation, and mild mitral insufficiency. The patient responded to medical therapy and was lost to follow-up until age 6 years, when she returned with anasarca and pneumonia. On physical examination, she had coarse facial features, with thick hair, a low hairline, thick eyebrows with synophrys, a wide and flat nasal bridge, thick lips and full cheeks; generalized hirsutism; short neck; a cardiac murmur; and hepatosplenomegaly. No limitation of joint movement was present. Neurological examination showed clumsiness of fine movements, a waddling gait and autistic behaviors. The patient was able to walk only if aided. Severe mental retardation was also present, with complete loss of speech.

An echocardiogram showed dilated cardiomyopathy, rupture of the mitral chordae tendineae, severe mitral insufficiency, and mild tricuspid insufficiency. A CT scan of the chest revealed right apical pneumonia and left atelectasis in the lingula. Ophthalmic examination was normal. Abdominal CT scan confirmed hepatosplenomegaly. The diagnosis of MPS was confirmed by increased urinary excretion of heparan sulfate and deficient sulfamidase activity on leukocytes. The patient underwent cardiac surgery for mitral valve repair (placement of biological prosthesis), which was completed successfully with an uneventful postoperative course. A control echocardiogram showed mild aortic regurgitation and normalization of left ventricular function. Unfortunately, the patient died at the age of 13 due to aspiration pneumonia.

2.1. DNA analysis

Genomic DNA was extracted from peripheral blood sample using a standard salting-out procedure [10]. All coding exons of *SGSH* gene and intron-exon boundaries were amplified by polymerase chain reaction (PCR) as per Beesley et al. [11]. PCR fragments were sequenced using a standard protocol and submitted to capillary electrophoresis on a 3500 Applied Biosystems DNA analyzer. cDNA and protein numbering were based on the reference sequences NM_000199.3 and the nomenclature used for reporting sequence variants was according to [12].

After bidirectional sequencing of all exons of the *SGSH* gene, we were able to identify three different alterations in homozygosis: c.239 G > T (p.G80V), c.1337 A > G (p.H446R) and c.524 T > C (p.Y174Y). These variants have not been previously described in the Single Nucleotide Polymorphism database (dbSNP; http://www.ncbi.nlm.nih.gov/) and the Human Gene Mutation Database (HGMD) (http://www.hgmd.org). According to PolyPhen (http://genetics.bwh.harvard.edu/pph2/) algorithm [13], c.239 G > T (p.G80V) is predicted to be probably damaging, with a score of 1.00, and c.1337 A > G (p.H446R) is predicted to be a benign mutation, with a score of 0.

3. Discussion

Cardiac involvement is detected early in life in more than half of all patients identified as having MPS [2], but it is rarely the first presenting feature of MPS III, as the case presented herein [7]. Cardiomyopathy and cardiac valve insufficiency develop as GAG accumulates in the myocardium, expands the spongiosa of the cardiac valves, and proliferates within the myointima of the epicardial coronary arteries. In the most severe cases of MPS I and MPS VI, congestive heart failure and death occur in the first decade of life [3–6,8]. In MPS III, however, severe cardiac manifestations are extremely rare [9], although a report of cardiomyopathy in a 53-year-old patient with MPS III-A patient has been published in the literature [14]. Besides that, in one patient with severe mitral valve stenosis, the detection of unexplained hepatomegaly led to further metabolic studies and, ultimately, a diagnosis of MPS III-A [15]. In another case of MPS III-C, a 39-year-old patient presented conduction disturbances, mitral regurgitation and diastolic dysfunction [16].

Fesslová et al. [7] studied 57 cases of MPS regarding cardiac symptoms, and found that only four had such symptoms as the presenting feature (MPS I, age 1.2 years; MPS II, age 3 years; MPS III, age 9 years; MPS IV, age 0.3 years). In the case presented herein, there was no initial suspicion of MPS during the first year of life because the patient did not exhibit dysmorphic features or neurological impairment. In the literature, there are few cases of MPS III in which developmental delay was noted from birth; in the majority of cases, symptoms were first noted at a median age of 2.5 years, and consisted of developmental delay and/or behavioral problems [15,17].

Dangel [9] examined 20 patients with MPS III and found that 50% had a normal echocardiogram, but one 8-year-old girl had congestive cardiomyopathy with severely impaired left ventricular function. Our patient presented these symptoms during the first year of life.

Regarding genotype–phenotype association as the pathogenic mutation described here is novel, we are not able to predict if this is associated with a higher risk of development of cardiac disease.

We propose that MPS, including MPS III-A, should be suspected and added to the differential diagnosis of all patients presenting with cardiomyopathy during the first year of life, even without somatic feature characteristic of MPS. We do not know whether severe cardiac involvement in MPS III-A is rare or simply underdiagnosed. However, the finding that MPS III is also associated with secondary storage of dermatan sulfate [18] suggests that other organs, in addition to those of the nervous central system, can be severely affected by this disorder. Furthermore, the rapidly lethal course of cardiomyopathy may hinder diagnostic investigation of MPS in affected patients.

Disclosure statement

Erlane Marques Ribeiro, Ida Vanessa Schwartz, Ana Carolina Brusius-Facchin, Sandra Leistner-Segal and Carlos Antônio Bruno da Silva declare that they have no conflicts of interest.

Informed consent

All procedures were conducted in accordance with the ethical standards of the institutional and national committees on human experimentation and with the 1975 Declaration of Helsinki, as revised in 2000. Informed consent was obtained from parents.

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