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GM1 Gangliosidosis Revealed by Fetoplacental Hydrops Syndrome: A Case Report

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Abstract **Case Report**

GM1 gangliosidos is describes a family of disorders that result from deficient activity of the lysosomal hydrolase, β-galactosidase, and which manifest varying degrees of neurodegeneration, retinal cherry-red spots, and visceromegaly. The three traditional subgroups of infantile, juvenile, and adult GM1 gangliosidosis show phenotypic overlap, although in general, the earlier the onset, the more severe the manifestations. This article gives an overview of the clinical signs in a patient with GM1 type 1 gangliosidosis revealed by fetoplacental hydrops syndrome.

Keywords: GM1 gangliosidosis, GLB1, Lysosomal storage disorders, Fetoplacental hydrops syndrome.

BACKGROUND

GM1 gangliosidosis is a lysosomal storage disorder due to deficiency of the β-galactosidase enzyme characterized by the accumulation of ganglioside GM1 (glycosphingolipid), both in the central nervous system (CNS) and the viscera. It is a rare autosomal recessive genetic disease that affects the GLB1 gene located on chromosome 3.

Here we aim to expand the clinical and genetic spectrum of infantile form GM1 gangliosidosis (type 1) by reporting a case with hydrops fetalis syndrome, in which whole-exome sequencing (WES) given to make the diagnosis the rare neurodegenerative disease entity with clinical atypical presentation.

CASE REPORT

A 2-month-old infant, the second child of first-degree consanguineous parents. Pregnancy and delivery were normal. His brother died at the age of 1 year from a psychomotor developmental delay with an edema-ascites syndrome associated with hepatomegaly of unidentified cause.

The infant was admitted at the age of 1 month to the pediatric department for management of a hydrops fetalis syndrome diagnosed on antenatal ultrasound of 27 weeks.

The clinical examination finds a hypotonic infant, without dysmorphic syndrome, presenting a oedemato-ascites syndrome (Fig. 1) associated with hepatomegaly, without splenomegaly, or signs of respiratory distress, the cardiac examination was normal.

Fig. 1: Our patient with a oedemato-ascites syndrome

The biological assessment was normal, in particular the blood count, transaminases, renal function, thyroid assessment, 24-hour proteinuria as well as the cytobacteriological and biochemical study of the ascites puncture fluid.

TORCH, HIV, HVA, B, C, EBV and parvovirus B 19 serologies were all negative.

For radiological examinations (abdominal ultrasound, cerebral CT, and skeletal X-ray) were unremarkable apart from hepatomegaly with ascites on ultrasound. The ophthalmological examination does not show the cherry red spot.

After eliminating the most frequent causes of fetal anasarca syndrome, a lysosomal storage disease was suspected. The sequencing of the whole exome of our patient reveals the presence of the variant NM_000404.4(GLB1): c.1577dup p.(Trp527Leufs*5) in the homozygous state. coming back in favor of a GM1 gangliosidosis.

DISCUSSION

Non immunologic hydrops fetalis (NIHF) was first described by POTTER in 1943 [1]. It has an incidence of 1/1.600-1/37.000 of live births according to different series [2, 3]. In spite of that, the mortality rate is still higher than 80% [2, 4].

The most common etiologies for NIHF described in different reviews were chromosomal abnormalities (15%), cardiac anomalies (11-20%), recognizable genetic disorders (20%) and congenital infectious diseases (4%). Lysosomal storage disorders have been identified in 1% of NIHF [5].

GM1 gangliosidosis is an ultra-rare lysosomal storage diseases caused by defects in the degradation of glycosphingolipids in the lysosome, characterized by neuro-viceral, ophthalmologic and dysmorphic signs. The causative gene, GLB1, encodes the enzyme, acid ß-galactosidase, the mutations of which result in increased lysosomal accumulation of GM1 ganglioside in the brain and of oligosaccharides in the visceral tissues [6].

The estimated incidence of GM1 gangliosidosis is 1/100,000–200,000 live births [7]. The disease is classified into types I, II, and III according to the age of onset, and clinical course or severity. Although the severity or onset of GM1 gangliosidosis is correlated with residual enzyme activity in general, there can be wide phenotypic variability [8].

The juvenile form (type II) develops between 7 months and 3 years of age, with a slower evolution. There is generalized central nervous system involvement with psychomotor regression, convulsive seizure and localized skeletal abnormalities [9], without hepatosplenomegaly, oedemato-ascitic syndrome or retinal involvement [10].

The adult form (type III) occurs between the ages of 3 and 30, manifesting as dystonia, language and gait disorders. The progression of symptoms is slow, but the intellectual disability is accentuated [9].

Our patient represents type 1 (infantile form) which is the most severe form of autosomal recessive transmission due to biallelic mutations of the GLB1 gene. The risk of recurrence is 25% for the parents of a patient for any new pregnancy. This type is established during the first 3 months of life. The first signs may be very early, in the form of fetoplacental hydrops syndrome. In the state phase, the child has a facial dysmorphia: The skull is often large, the features coarse, the forehead high and wide, the base of the nose flattened and the ears have low implantation. The mouth is small, with a hypertelorism.

The psychomotor delay, of progressive evolution, is constant. The child is hypotonic and hyporeactive. Hepatomegaly is practically constant, splenomegaly is frequent. Blindness and deafness are often observed. The fundus shows a cherry red spot in half of the cases [11]. Cardiomyopathy and cardiac hypertrophy are less frequent signs. Death is rapid in the first two years due to severe respiratory infections [9].

Our patient did not present certain clinical features that are typical of type 1 gangliosidosis: dysmorphic syndrome, cherry red macular spots, skeletal deformities, which made the clinical diagnosis difficult. However, he presented with feto-placental hydrops syndrome and hepatomegaly. Cardiac hypertrophy, which can be observed, and which has not been reported in other infants with gangliosidosis type 1 like our patient's case.

Radiologically, early spinal abnormalities are the most consistent. They result in hypoplasia of the anterosuperior part of one or two lumbar vertebrae, an appearance comparable to that of Hurler's disease. The long bones are often stocky, as well as the metacarpals and phalanges.

In the peripheral blood, the lymphocytes are vacuolated. The histological study shows a poly visceral overload in the form of voluminous vacuoles, containing a granular material not very dense to electrons. In nerve cells, there are cytoplasmic membranous bodies.

B galactosidase deficiency is demonstrated in serum, leukocytes, fibroblasts, and amniotic cells [11].

However, the diagnosis of GM1 gangliosidosis is sometimes a challenge, because of not specific

neurodegenerative symptoms, was eventually diagnosed using WES [12]. A prenatal and preimplantation diagnosis is possible by searching the fetus for the mutation identified in the family.

CONCLUSION

The search for lysosomal diseases is particularly important in cases of hydrops fetalis because of the high risk of recurrence of these diseases, mainly autosomal recessive, and because for most of them a prenatal diagnosis can be proposed during the first trimester of the pregnancy.

GM1 Gangliosidosis is a rare lysosomal storage disorder whose clinical diagnosis is difficult and relies on genetic study. The treatment is symptomatic and relies mainly on genetic counseling.

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