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GM1 gangliosidosis: a case report

Gangliosidose GM1: um relato de caso

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ABSTRACT

GM1 gangliosidosis is a lysosomal disease characterized by the accumulation of GM1 ganglioside (glycosphingolipid) in the visceral and central nervous system (CNS), due to the deficiency of the beta-galactosidase enzyme (lysosomal hydrolase). It mainly affects the CNS and viscera and produces important skeletal abnormalities, often occurring with the presence of vacuolated lymphocytes in the peripheral blood or bone marrow sample. It has three forms of presentation, which makes its identification even more challenging due to the wide clinical spectrum. The present study aims to describe a case of GM1 gangliosidosis in a male patient, born at 38 weeks. To date, there is no effective treatment for GM1 gangliosidosis, that is, the carrier of the disease only receives symptomatic and palliative care. Therefore, early diagnosis of the disease is extremely important, as its only form of prevention, currently, is through genetic counseling.

Key words: GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.

RESUMO

A gangliosidose GM1 é uma doença lisossômica caracterizada pelo acúmulo de gangliosídeo GM1 (glicoesfingolipídeo) no sistema nervoso visceral e central (SNC) devido à deficiência da enzima betagalactosidade (hidrolase lisossômica). Afeta, sobretudo, o SNC e as vísceras e produz anormalidades esqueléticas importantes, ocorrendo frequentemente com a presença de linfócitos vacuolizados no sangue periférico ou na amostra de medula óssea. Possui três formas de apresentação, o que torna sua identificação ainda mais desafiadora por conta do amplo espectro clínico. O objetivo do presente estudo é descrever um caso de gangliosidose GM1 em um paciente do sexo masculino, nascido com 38 semanas. Até o momento, não existe tratamento eficaz para a gangliosidose GM1, ou seja, o portador da doença recebe apenas medidas sintomáticas e paliativas. Portanto, o diagnóstico precoce é extremamente importante, pois sua única forma de prevenção, atualmente, é por meio do aconselhamento genético.

Unitermos: *gangliosidose GM1; doença por armazenamento dos lisossomos; betagalactosidase.*

RESUMEN

La gangliosidosis GM1 es un trastorno lisosomal caracterizada por la acumulación de gangliósido GM1 (glucoesfingolípido) en el sistema nervioso central (SNC) y visceral, debido a la deficiencia de la enzima beta-galactosidase (hidrolasa lisosomal). Afecta principalmente al SNC y las vísceras y produce importantes anomalías esqueléticas, que a menudo ocurren con la presencia de linfocitos vacuolados en la muestra de la sangre periférica o médula ósea. Tiene tres formas de presentación, lo que dificulta aún más su identificación debido al amplio espectro clínico. El presente estudio tiene como objetivo describir un caso de gangliosidosis GM1 en un paciente masculino, nacido a las 38 semanas. Hasta el momento, no existe un tratamiento efectivo para la gangliosidosis

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GM1, es decir, el portador de la enfermedad solo recibe medidas sintomáticas y paliativas. Por tanto, el diagnóstico precoz de la enfermedad es de suma importancia, ya que su única forma de prevención, actualmente, es a través del consejo genético.

Palabras clave: *gangliosidosis GM1; trastorno por almacenamiento lisosómico; beta-galactosidasa.*

INTRODUCTION

GM1 gangliosidosis is a lysosomal disease characterized by the accumulation of GM1 ganglioside (glycosphingolipid), both in the visceral and central nervous system (CNS), due to a deficiency of the enzyme betagalactosidase (lysosomal hydrolase). It is a rare recessive genetic disorder that affects the *GLB1* gene located on chromosome 3. Its incidence is estimated to be 1:100,000-200,000 live births. It mainly affects the CNS and viscera, in addition to producing important skeletal abnormalities. It often occurs with the presence of vacuolated lymphocytes in the peripheral blood or bone marrow sample. It has three forms of presentation, which makes its identification even more challenging due to the wide clinical spectrum[1].

The disease is divided into three types (type I, II, and III), and the severity of the phenotype is associated with the degree of enzyme deficiency. The infantile form (type I) is the most severe; establishes in the first 6 months of life with generalized CNS involvement, hypotonia, delay in neuropsychomotor development, apathy, weak sucking, subnormal weight gain, hepatosplenomegaly, facial dysmorphism, macular cherry-red spot, skeletal dysplasia, repeated respiratory infections, and early death (usually before 2 years of age). The early and extensive involvement of the CNS leads to a marked delay in neuropsychomotor development (NPMD), which gradually progresses to generalized hypotonia and seizures. Cardiomyopathy and cardiac hypertrophy are less frequent findings[1, 2].

The juvenile form (type II) develops between 7 months and 3 years of age, with a slower course. It has generalized CNS involvement with psychomotor deterioration (NPMD regression), seizures, and localized skeletal involvement. With this form, the child usually survives only until childhood, since convulsive conditions and recurrent infections, especially pneumonia, are usually the causes of death[1].

The adult form (type III) manifests from 3 to 30 years of age; the involvement of the CNS is more localized, presenting with dystonia, speech and gait disorders. The progression of symptoms is slow, but the intellectual disability is accentuated[1].

This study aims to describe a case of GM1 gangliosidosis in a male patient, born at 38 weeks.

CASE REPORT

Male patient, born and resident in Joinville, Santa Catarina, Brazil, born at 38 weeks, weighing 2880 grams, was admitted for the first time to Dr. Jeser Amarante Farias Hospital with pneumonia at 11 months of age. The mother reported a diagnosis of intrauterine growth restriction in the last trimester of pregnancy, with no changes in the neonatal period. He received exclusive breastfeeding for up to six months. The child presented developmental delay, accompanied by hypotonia and non-acceptance of solid foods, a condition of progressive evolution noticed by the parents from 6 months of age.

Physical examination on admission showed severe muscle hypotonia, neuropsychomotor development delay, absence of resistance to passive movements, and absence of bilateral patellar reflex. The patient also had a large forehead and fontanelle, edema in the lower limbs and face, low weight-for-age and height below the 3rd percentile, in addition to a head circumference between the 15th and 50th percentiles.

During hospitalization, we found an evolving neurological condition with progression of hypotonia, loss of visual contact, dysphagia, focal seizures, and apnea.

Among the laboratory tests initially requested, we noticed the presence of 35% of vacuolated lymphocytes in the peripheral blood (**Figure 1**). The fundus examination revealed the presence of a cherry-red spot. Cranial computed tomography (CT) showed prominence of sulci between the gyri and fissures and prominence of the bilateral frontal and parietal space filled with CSF (cerebrospinal fluid) density material, suggesting benign external hydrocephalus of childhood. Cranial nuclear magnetic resonance (NMR) showed hypomyelination and signal alteration in the basal ganglia and thalamus (**Figure 2**). The echocardiogram showed left ventricle at the upper limit of normal (dilation), signs of increased pulmonary resistance, and preserved anatomy

and function. Abdominal ultrasound and long bone radiography showed no changes.

Following the investigation, cytogenetic studies indicated a typical male karyotype. The hexosaminidase enzymatic assays were normal, excluding GM2 gangliosidosis. Normal alpha-galactosidase and beta-galactosidase values were found. The results of qualitative tests in analysis of urinary oligosaccharide (**Figure 3**) and sialyl-oligosaccharide (**Figure 4**) by chromatography resulted in the GM1-gangliosidosis pattern. This was diagnosed by beta-galactosidase activity deficiency 1.5 mmol/h/ml [reference value (RV) 35-126] in a blood sample soaked into filter paper.

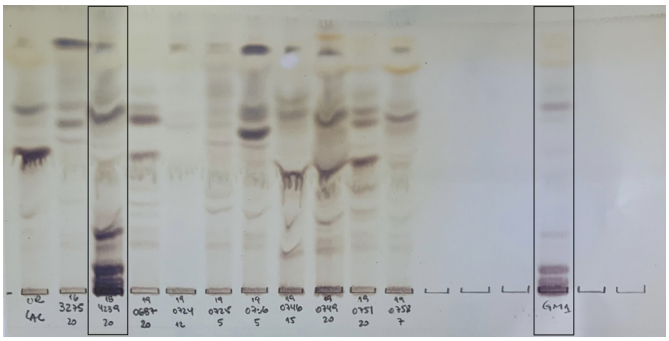

FIGURE 3 – *Analysis of urinary oligosaccharide by chromatography showing GM1-gangliosidosis pattern*

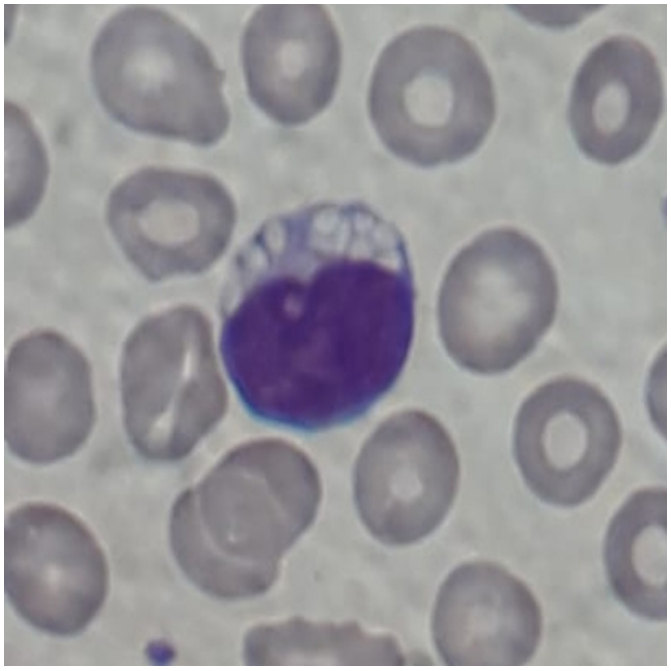

FIGURE 1 – *Lymphocyte showing multiple vacuole-like cytoplasmic inclusions*

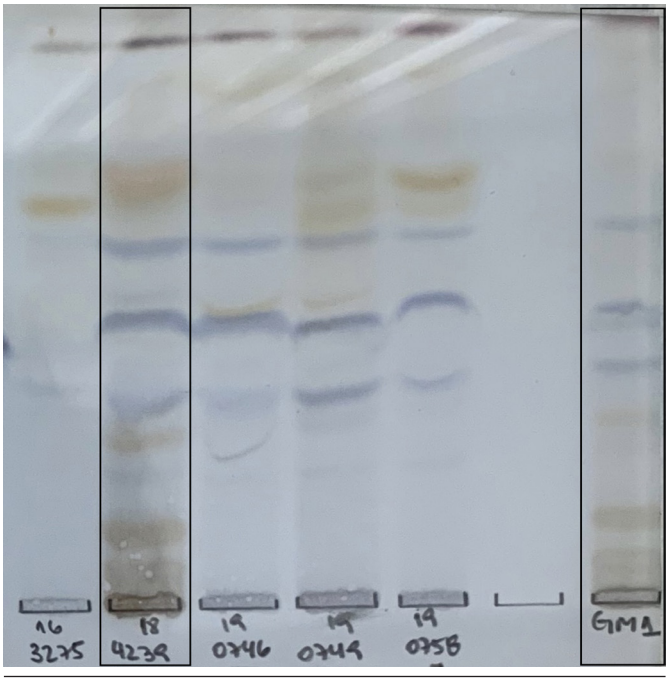

FIGURE 4 – *Analysis of urinary oligosaccharide by chromatography showing GM1-gangliosidosis pattern*

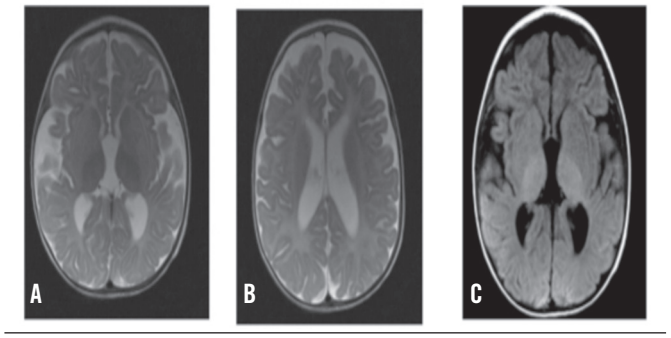

FIGURE 2 – *A e B (axial T2) showing diffuse hypomyelination and signal alteration throughout the basal ganglia, T2 hyperintensity signal; C (axial T1) showing increased signal intensity in the thalamus*

DISCUSSION

The presence of vacuolated lymphocytes in a peripheral blood sample or bone marrow, when positive, is suggestive of lysosomal disease[3]. The lack of beta-galactosidase enzyme leads to the accumulation of glycosphingolipids in lymphocytes, which leads to the presence of cytoplasmic inclusions similar to large vacuoles. Vacuumization is early and may be present in up to 80% of all lymphocytes; neutrophils and lymphocytes may contain basophilic cytoplasmic granulations. In the bone marrow, there are foam cells and vacuolated lymphocytes[1].

Some authors use the search for this finding in peripheral blood as screening for type I GM1 gangliosidosis[4].

In a study carried out in Lisbon, Portugal, the search for vacuolated lymphocytes, carried out in six patients diagnosed with GM1, was positive in four of them: three in the peripheral blood (55%, 45%, 35%) and one in the bone marrow (13%); in this case, vacuolization was negative in lymphocytes in a peripheral blood sample[5]. In another study carried out in Malta, from 1970 to 1993, with 40 patients with confirmed GM1 gangliosidosis, the presence of vacuolated lymphocytes was evidenced in all patients[4].

In GM1 gangliosidosis, only half of the patients have a cherry-red spot at the macula. This macula appears in the foveola – the central region of the fovea, where there are no ganglion cells – and contrasts with the paleness of the rest of the macula, in which, in these cases, there is an accumulation of gangliosides[6-8]. However, during disease progression, lesion regression may occur. Therefore, when the diagnosis is late, this finding may often not be found due to the death of retinal cells associated with lipid accumulation in the retina. In our case, the presence of this finding had a great contribution to defining the diagnosis in the patient described, since this abnormality is characteristic of few diseases, which, for the most part, can be confirmed through biochemical tests.

The patient's cranial CT did not suggest alterations compatible with GM1 gangliosidosis. The cases that present specific findings of the disease in this exam are rare, and the main characteristic reported are the diffuse and symmetric thalamic hyperintensity. The patient's NMR showed changes compatible with those described in the literature. Some reviews of GM1 and other lysosomal diseases report findings such as thalamic hyperintensity and white matter hypointensity on T1, as well as reduced thalamic signal intensity on T2[9, 10].

So far, there is no effective treatment for GM1 gangliosidosis, that is, patients with the disease receive symptomatic and palliative measures. Some new therapeutic strategies have been explored, mainly in animals, such as bone marrow transplantation, gene therapies, and substrate reduction therapies. However, these approaches are still far from reaching a viable clinical application. Thus, the early diagnosis of the disease is extremely important, as its only form of prevention, at the moment, is through genetic counseling[1].

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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