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Clinical report

Neurological and cardiac responses after treatment with miglustat and a ketogenic diet in a patient with Sandhoff disease

Ives T. Villamizar-Schiller [a,1], Laudy A. Pabón [a,1], Sophia B. Hufnagel [d], Norma C. Serrano [a], Gabriela Karl [b], John L. Jefferies [c,d], Robert J. Hopkin [d], Carlos E. Prada [a,d,*]

[a] Centro de Medicina Genómica y Metabolismo, Fundación Cardiovascular de Colombia, Floridablanca, Colombia
[b] Department of Cardiology, Fundación Cardiovascular de Colombia (FCV), Floridablanca, Colombia
[c] The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[d] Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

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ABSTRACT

Sandhoff disease is a progressive neurodegenerative disorder characterized by accumulation of GM2 gangliosides. We describe a 6-year-old male with coarse facial features, developmental delay, refractory seizures, hypertrophic cardiomyopathy, who was later found to have Sandhoff disease. Previous studies have revealed that caloric restriction in combination with miglustat increased survival and motor behavior in mouse model of Sandhoff disease. These findings suggest that combination therapy may result in improved outcomes for patients with Sandhoff. Initiation of treatment with miglustat and a ketogenic diet was followed by improvement of the patient's seizure control and cardiac function. Further clinical investigation is required to better determine the benefit of management in late-onset forms of Sandhoff disease.

1. Introduction

Sandhoff disease (OMIM 268800) is an autosomal recessive disorder caused by mutations in *HEXB* resulting in enzymatic deficiency of hexosaminidases A and B. With the lack of hexosaminidases A and B, fewer GM2 gangliosides are catabolized, leading to its accumulation in organ tissues throughout the body, particularly in the brain, liver, spleen, bone, and rarely the heart. [Bley et al., 2011] GM2 storage leads to cell degeneration, autophagy, and cell death. [Krivit et al., 1972].

Substrate Reduction Therapy (SRT) by miglustat might be useful to delay the neurological progression in GM2 gangliosidosis, especially in those patients affected by more chronic forms of the disease. [Masciullo et al., 2010] In the juvenile and adult forms of Sandhoff disease, miglustat therapy has known neurological stabilizing effects. [Shapiro et al., 2009].

A ketogenic diet, which is characterized by high fat and low carbohydrates concentrations, has shown improvement of motor behavior and longevity in Sandhoff disease mouse models. [Denny et al., 2010] A study by Denny et al. [2010] showed that adult Hexb−/− mice treated with miglustat had less forebrain ganglioside and GM2 content than control mice. [Denny et al., 2010] Combination therapy was also more successful than either treatment with a ketogenic diet or miglustat alone. Hexb−/− mice that received a ketogenic diet and miglustat had a 3.5 fold higher level of miglustat in the brain tissue than mice on a standard diet with miglustat. These data suggest a potential additive effect resulting in increased delivery of miglustat to the central nervous system. [Denny et al., 2010].

We present clinical and laboratory data from a patient with Sandhoff disease with neurological and cardiac disease, who responded to treatment with miglustat and a ketogenic diet.

2. Methods

2.1. Participants

The mother and father of the patient described in this manuscript provided written informed consent for publication. The study was approved by the IRB of Cardiovascular Foundation of Colombia.

* Corresponding author. Centro de Medicina Genómica y Metabolismo, Fundación Cardiovascular de Colombia (FCV), Calle 155A No. 23 – 58, Urbanización El Bosque, Floridablanca, Colombia. Tel.: +57 7 6399292; fax: +57 7 6380182.
E-mail addresses: carlosprada@fcv.org, carlos.prada@cchmc.org (C.E. Prada).
[1] I.T.V. and L.A.P contributed equally to this work.

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2.2. Clinical presentation

We describe a 6-year-old Colombian male with coarse facial features, a history of developmental delay, and epilepsy presented at 4 years of age with fatigue and weight loss. The patient was the product of a 34-week pregnancy to a 29-year-old primigravida mother. This pregnancy was complicated with HELLP syndrome. The patient's mother denies consanguinity and exposure to alcohol, tobacco, or drugs during the pregnancy. The APGAR scores were 6 at 5 min and 8 at 10 min. The immediate neonatal course was uncomplicated. The patient's birth weight was 1.8 kg (50th centile), crown-heel length was 49 cm (50th centile), and head circumference was 35 cm (90th centile). He was subsequently noted to have an exaggerated startle response during infancy. He developed a seizure disorder at 12 months of age. Atypical absences seizures were noted in the mornings and hypomotor seizures throughout the rest of the day, often up to 10 to 20 episodes per day. Seizures did not improve with the initiation of phenobarbital and valproic acid. He continued to deteriorate neurologically, and at 17 months of age, he developed focal motor seizures and myoclonic jerks despite the aforementioned antiepileptic therapies.

Physical examination at initial evaluation (4-years-old) was remarkable for macrocephaly (HC = 53.5 cm, >3 SD), coarse facial features, hypertelorism, short neck, and kyphoscoliosis (Fig. 1). Ophthalmologic examination was negative for corneal opacities and a cherry red spot of the macula. A recent paper reported that patients with GM2 gangliosidosis (Sandhoff and Tay Sachs disease) have cherry-red spot of the macula in about 88% of cases. [Karimzadeh et al., 2014] A grade II/VI systolic ejection murmur was auscultated, and best heard at the left lower sternal border. Abdominal examination revealed hepatomegaly, in which the liver margin was 6 cm below rib cage, without splenomegaly. Umbilical and bilateral inguinal hernias were also noted. He had generalized hypotonia and symmetric muscle wasting. His gait was ataxic and broad based in nature. He had poor expressive and receptive language skills with frequent stereotypies. The Autism Diagnostic Observation Schedule-Generic (ADOS-G) evaluation showed a social impairment score of 9.0 and a stereotypy score of 4.0, and he was formally diagnosed with an Autism Spectrum Disorder.

Previous diagnostic evaluation included a brain magnetic resonance imaging (MRI) that showed megalencephaly, cerebellar atrophy, and decreased myelination of the occipital region with dilated Virchow robin spaces. Video electroencephalogram (EEG) detected diffuse slow waves, focal spikes in the frontal lobes, severe interictal disorganization of background activity, and 20 absence seizures. He received treatment with levetiracetam and oxcarbazepine; however, such intervention resulted in minimal improvement of his seizure control. His seizures remained refractory and the patient continued to become progressively encephalopathic.

Cardiac imaging was obtained due to the history of fatigue that started at 4-years-old, weight loss, and hepatomegaly. An echocardiogram revealed increased myocardial mass index (262 g/m^2), elevated left ventricular posterior wall in diastole (0.98 cm, *z*-score 4.42) and left ventricular diastolic diameter (3.94 cm, *z*-score 2.86), as well as borderline ventricular function with an ejection fraction of 50%. Abdominal ultrasound confirmed moderate hepatomegaly. These cardiac and liver findings, in combination with his neurological disease and coarse facial features, suggested the potential etiology of a lysosomal storage disease.

A comprehensive diagnostic evaluation included urine glycosaminoglycans, oligosaccharides, urine organic acids, and amino acids, the results of which returned within normal limits. Enzyme assays for α-l-iduronidase and β-glucosidase were also normal. Total hexosaminidase activity in peripheral blood, however, was found to be low, measuring at 0.090 μmol/ml/hr (Referenced normal control: 0.328 μmol/ml/hr) suggesting the possibility of a GM2 gangliosidosis. Hexosaminidase B was measured at 0.005 μmol/ml/hr (Referenced normal control: 0.121 μmol/ml/hr), and hexosaminidases A was found to be 92% (Reference normal control range: 63%–75%). These findings were later confirmed by low hexosaminidase B activity in cultured skin fibroblasts. Analysis of these results lead to the diagnosis of Sandhoff disease in our described patient.

2.3. Treatment administration

Upon informed consent from his parents, treatment with miglustat at a dose of 100 mg per day was started and gradually increased to a final dose of 300 mg per day.

2.4. Ketogenic diet

A ketogenic diet was also initiated given difficulty with seizure control. His dietary fat was transitioned at 4 years of age from 30% percent to 80% of his total caloric intake, he was supplemented with essential fatty acids to prevent nutritional deficiencies. With the guidance of a nutritionist, the patient's parents made their own ketogenic diet.

2.5. Evaluations

Standard clinical evaluations were performed at a 6 month intervals by the same examiners to evaluate for progression of symptoms. Laboratory and electrophysiology studies were also done at 6 months intervals, while cardiac and liver imaging were performed yearly.

3. Results

The patient tolerated treatment with miglustat well. His mother noted that his energy level was improved and he had stabilized weight gain, with his weight now at the 50th percentile (Table 1). Diarrhea, a side effect of a miglustat, was not reported as a problem and his mother denied any history of gastrointestinal distress. We monitored serum vitamin B12 levels as well as his neurologic exam for tremors, due to its association with miglustat, both of which were normal. Repeat echocardiogram at 5 years of age, 12 months after the initiation of the ketogenic diet and miglustat, revealed a reduction in ventricular enlargement with a myocardial mass index (126.2 g/m^2), left ventricular posterior wall in diastole (0.45 cm, *z*-score 0.38) and left ventricular diastolic diameter (3.63 cm, *z*-score 1.54), as well as a marked improvement in ventricular function, with an ejection fraction of 72%. His liver was no longer palpable below the costal margin on abdominal examination and a liver ultrasound showed normal measurements. See Table 1 and Table 2 for details of clinical and cardiac imaging evaluation. Six months after the initiation of miglustat and a ketogenic diet, his seizures were better controlled. The patient has been seizure free for over 1 year and has had a decreased number of hospital admissions. At 2 years post therapy initiation, a repeat video EEG showed a normal background activity without spikes or absence seizures (Fig. 2). Furthermore, clinically, his gross and fine motor skills as well as his behavior have improved. The ADOS-G evaluation showed improvement of the social impairment score (5.0) and the stereotypy score (3.0). At 6-years-old, he is able to ambulate independently and he has gained the ability to perform activities of daily living.