Clinical report

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

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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.

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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.

Fig. 1. Sandhoff disease: progression of the facial phenotype. Mild facial coarseness early in the disease process can obscure the diagnosis. The facial features become progressively more coarse. Patients become more macrocephalic over time as well. mo = months old, yo = years old.

4. Discussion

We describe a patient who showed drastic improvement of his neurological and cardiac disorder resulting from Sandoff disease. Specifically, we note a decreased frequency of seizures and reduction of his autistic behavioral features with improved ADOS-G scores. Small case series of patients with Sandhoff disease treated with miglustat have shown minor effects in the neurological progression in the late-onset forms of the disease, but larger trials are needed to confirm these findings. [Masciullo et al., 2010] In contrast, other reports suggested no effect in the central nervous system deterioration in patients with Tay-Sachs disease. [Bembi et al., 2006] In this last study CSF miglustat concentration was achieved with oral therapy and patients did not develop macrocephaly. This suggests a reduction of the substrate storage after treatment with miglustat and consequently slowing the rate of inflammation in the CNS. Ketogenic diet also has antiepileptic and neuroprotective effects by diminishing inflammation and oxidative stress. [Lee et al., 2000; Morgan et al., 1999] The patient described in this manuscript has improvement of neurological symptoms, seizure control, and better quality of life suggesting an additive effect of miglustat and the ketogenic diet.

Treatment with miglustat and a ketogenic diet in this patient significantly improved the cardiac manifestations of the disease (Table 2). It is unclear if the cardiomyopathy was due to glycosphyngolipids storage given that glycosphingolipids are not the main constituents of heart tissues. However, cardiomyopathy has been reported as a complication of Sandhoff disease. [Guertl et al., 2000] A cardiac biopsy was not clinically indicated in this patient and, thus, was not performed. Miglustat has secondary effects that have been documented in other lysosomal storage diseases, such as increasing bone density in patients with Gaucher disease. These findings suggest that cardiac involvement in Sandhoff disease is susceptible to therapy with miglustat but the mechanism of action is still undetermined. Given the rarity of such disorders, randomized trials are difficult to perform. Therefore, the results of isolated cases can aid in determining the efficacy of miglustat and a ketogenetic diet in Sandhoff disease.

Cardiac disease is rarely observed in patients with Sandhoff disease. This could be attributed to the lowest glycosphingolipid concentration of all vertebrate tissues in the skeletal and heart muscles [Muthing and Cacic, 1997]. Interestingly, after reviewing the published literature, we identified 4 additional patients with Sandhoff disease and cardiac involvement (Table 3) [Blieden and

Table 1
Clinical findings by age in a patient with Sandhoff disease.

Age (years)	Miglustat dose (mg/day)	Seizures	Status epilepticus (# episodes)	Hospital admissions	Weight/height centile	Total fat diet (grams)	EFA	Hepatomegaly	Walk	Stereotypies	Communication
4	100	weekly	4	5	10th/25th	30%	+	Moderate	Assisted and ataxic	+++	Not eye contact
4.5	200	monthly	1	1	10th/25th	80%	+	−	Assisted and stable	+++	Establish eye contact
5	300	None	None	None	25th/50th	80%	+	Mild	Assisted and stable	++	Follow simple commands
5.5	300	None	None	None	50th/50th	80%	+	−	Unassisted	+	Signing
6	300	None	None	None	50th/50th	80%	+	Normal	Unassisted	+	Interacts with sibling and parents

EFA, essential fatty acids.

Table 2
Cardiac imaging characteristics of a patient with Sandhoff disease.

Cardiac imaging findings						
Echocardiogram measurements	Echocardiogram 1 (4-years-old) pre-Miglustat	Mean (Normal range)	z-score	Echocardiogram 2 (5-years-old) post-miglustat	Mean (normal range)	z-score
RVSD	2.76 cm	3.11 (2.64−3.67)	2.36	2.16 cm	1.92 (1.56−2.37)	0.92
LVPWs	1.25 cm	0.80 (0.63−1.03)	2.91	0.80 cm	0.80 (0.63−1.03)	0.03
LVDD	3.94 cm	1.92 (1.56−2.37)	2.86	3.63 cm	3.11 (2.64−3.67)	1.54
LVPWd	0.98 cm	0.42 (0.30−0.57)	4.42	0.45 cm	0.42 (0.30−0.57)	0.38
LVSd	0.92	0.48 (0.34−0.68)	3.03	0.60 cm	0.48 (0.34−0.68)	1.04
Myocardial mass index (grams/m2)	262	57.72 ± 14.84		126.2	57.75 ± 12.47	
Ejection fraction	50%			72%		

RVSD: right ventricular systolic diameter, LVPWs: left ventricular posterior wall in systole, LVDD: left ventricular diastolic diameter, LVPWd: left ventricular posterior wall in diastole, LVSd: left ventricular septum in diastole.
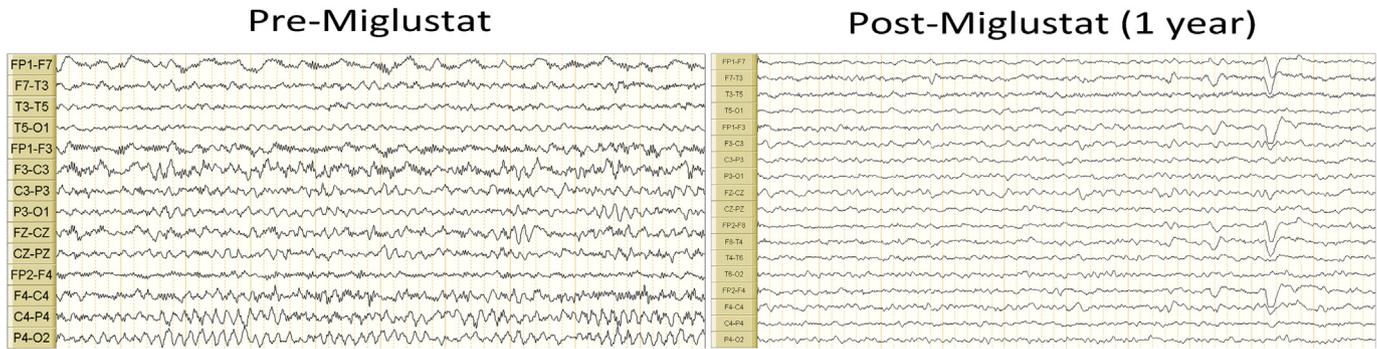
Fig. 2. EEG at baseline showed continuous paroxistic interictal activity with sharp waves that are most pronounced in the right parietal and occipital lobes. EEG after treatment for 1 year showed normal activity during daytime and sleep.

Table 3
Clinical and cardiac features in patients with Sandhoff disease.

Patient characteristics	Krivit et al.	Blieden et al.	Sakpichaisakul K et al.	Venugopalan et al.	Present patient
Sandhoff disease onset	3-months-old	3-months-old	9-months-old	6-months-old	6-months-old
Cardiac murmur	Yes	Yes	Yes	Yes	No
Valvulopathy	Yes (Mitral, tricuspid, and pulmonary valves)	Yes (Mitral, tricuspid, and pulmonary valves)	Yes (Mitral valve prolapse)	Yes (Mitral and aortic valves)	No
Cardiomegaly	Yes	Yes	Yes	Yes	Yes
Hypertrophic cardiomyopathy	Yes	Yes	No	Yes	Yes
Mortality	Yes (2-years-old)	No data	Yes (2-years-old)	No data	No

Moller, 1974; Krivit et al., 1972; Sakpichaisakul et al., 2010; Venugopalan and Joshi, 2002]. Cardiac disease in these patients was typically unsuspected, with exception of one patient who presented with congestive heart failure and required therapy with digitalis after failure to standard therapy with diuretics and an angiotensin converting enzyme inhibitor. The most common cardiac abnormalities reported in these patients were cardiomyopathy (3 hypertrophic, 1 dilated), followed by cardiac valvar disease with frequent involvement of the mitral valve (3 out of 4 patients). Two patients passed away related to progression of their disease and no long-term follow up of cardiac findings were performed. Autopsy of patients with Sandhoff disease showed thick endocardium of left atrium and ventricle, endocardial fibroelastosis, and coronary luminal narrowing due to intimal proliferation. [Blieden et al., 1974].

The lack of emphasis in cardiac assessments in patients with Sandhoff disease could be secondary to the rapid and severe progression of their neurological symptoms. However, cardiac involvement in our reported patient led to the diagnosis of storage disease. Individuals with Sandhoff disease should receive a baseline screening echocardiogram and cardiology referral during their initial evaluation. This will become essential as more effective treatments are identified so as to better monitor all target tissues and track improvement of the disease manifestations.

In conclusion, treatment with miglustat and ketogenic diet has an unclear mechanism for the CNS and cardiac effects in patients with Sandhoff disease. These therapies remain experimental, however the improvement in the quality of life for this patient is an important consideration and the need for additional studies to confirm the combinatory effects of miglustat and ketogenic diet in patients with Sandhoff disease.

Conflicts of interest

The authors have indicated they have no financial relationships or conflicts of interest relevant to this article to disclose.

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