Patient report

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Brown-Vialetto-Van Laere syndrome: two siblings with a new mutation and dramatic therapeutic effect of high-dose riboflavin

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Abstract: Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare and severe neurometabolic disease. We present two siblings with BVVLS with a novel homozygous mutation in SLC52A3 (formerly C20orf54) gene. The first sibling was admitted with respiratory insufficiency and required mechanical ventilation. After administration of a high dose of riboflavin, all his clinical symptoms were resolved, which also strongly suggested the diagnosis of BVVLS. The second sibling was also found to have the same genetic mutation as her brother. Although she was symptom-free, riboflavin was initiated empirically. On follow-up, she developed no neurologic or metabolic problems with entirely normal growth and development. BVVLS should be considered in the differential diagnosis of unexplained neurologic symptoms such as polyneuropathy and respiratory insufficiency, as BVVLS and multiple acyl-CoA dehydrogenation defect have broadly overlapping symptoms. Furthermore, our cases once again suggest that with proper diagnosis and early high-dose riboflavin treatment, complete reversal of neurologic deficits in BVVLS is possible.

Keywords: Brown-Vialetto-Van Laere syndrome (BVVLS); diaphragm paralysis; multiple acyl-CoA dehydrogenase defect (MADD); polyneuropathy; riboflavin.

Introduction

Brown-Vialetto-Van Laere syndrome (BVVLS) (OMIM 211530) is characterized by bilateral progressive pontobulbar paralysis with deteriorative involvement of spinal motor nerves, upper and lower motor neurons, and diaphragm in some cases, and with sensorineural deafness. A similar disease phenotype without sensorineural deafness is seen in Fazio-Londe disease (OMIM 211500), which has been recently described as a variant manifestation of the same disease. Both are now considered to be a single disease entity (1).

This syndrome was first described by Charles Brown in 1894 (2) in a Portuguese family; further case reports by Vialetto in 1936 (3) and Van Laere (4) in 1966 followed these index cases. The age of onset of symptoms in BVVLS has ranged from infancy to the third decade of life (5, 6).

Reports have shown that BVVLS affects females more than males with a ratio of 3:1. However, males usually exhibit more severe symptoms; an earlier onset of deafness and an earlier death without treatment (5). The majority of familial cases demonstrate autosomal recessive inheritance, although autosomal dominant (7, 8) and X-linked inheritance (7) have been suggested among few families. Green et al. identified a candidate gene, SLC52A3 (formerly C20orf54-Chromosome 20 open reading frame-54/riboflavin transporter-2), by studying a consanguineous family with multiple affected individuals and subsequently demonstrated that mutations in this gene were the cause of this disease (9).
Multiple acyl-CoA dehydrogenation defect (MADD) is an inherited defect of mitochondrial fatty acid beta-oxidation and branched-chain amino acid catabolism (OMIM 231680). MADD may present at any age, varying from a neonatal lethal form to an infantile form characterized by hazardous hypoketotic hypoglycemia (10) or to a relatively mild adult lipid storage myopathy (11). Riboflavin responsive forms of MADD are usually the consequence of a defective electron transfer flavoprotein oxidoreductase (12). BVVLS is an entity which metabolically mimics MADD and responds to riboflavin treatment (13). Prognosis is poor without treatment and most of the patients die within 10 years.

Here we report a 30-month-old patient and his sister with a novel homozygous mutation in the \textit{SLC52A3} gene.

Case reports

Case 1

A 30-month-old boy was admitted to our pediatric intensive care unit because of respiratory insufficiency, seizure, and ptosis of the right eye.

His past medical history was unremarkable except for two admissions to outside centers because of the similar problems at the ages of 12 and 14 months. At his previous admission to another center, except for the positivity of ethylmalonic aciduria in urinary organic acid analysis, his whole clinical, laboratory, radiologic, cardiologic, and neurologic investigations were found to be normal. Based on these findings, the patient was considered to have ethylmalonic aciduria or MADD and was started on 10 mg/kg/day riboflavin and 100 mg/kg/day of carnitine therapy, with significant clinical improvement. However, 3 months after hospital discharge, the patient’s family stopped giving the medications recommended for the patient, without consulting their physician. His family history was positive for problems suggesting a hereditary disease. His older brother was found to have cord paralysis after the investigation was made for permanent stridor that he experienced following an inguinal hernia surgery. Subsequently, he experienced left-eye ptosis, deterioration in mental status and motor functioning, and he died due to sepsis when he was 2 years old. The index case also had a 6-year-old healthy sister and his mother was 38-weeks’ pregnant on the patient’s last admission.

On his initial physical examination at the pediatric intensive care unit, the patient was pale, looked ill, and had right-eye ptosis. Lung auscultation revealed bilateral crackles at the lower fields. On neurologic examination, he was conscious. He had masked face, excessive salivaition, could not blow or purse his mouth, could not firmly close his eyes, and could not raise his eyebrows. He had diminished muscle tone and strength, and deep tendon reflexes. He had no hearing loss and had signs of wasting or sensory abnormalities in both upper and lower limbs. On his first day at the pediatric intensive care unit, he required mechanical ventilation due to severe respiratory failure. He was always conscious during the mechanical ventilation support period.

Following investigations revealed normal echocardiographic, cerebral, and spinal magnetic resonance imaging findings. Spinal muscular atrophy was excluded using genetic testing. An electromyography revealed the presence of diaphragm paralysis. A moderate level of ethylmalonic aciduria was determined in urine organic acid analysis.

As the patient’s clinical status showed no improvement during the first day of admission, we started him on 25 mg/kg/day of riboflavin treatment after a blood sample was withdrawn for analysis of the \textit{SLC52A3} gene for definitive diagnosis of BVVLS (Figure 1).

\textbf{Figure 1:} The novel mutation detected in our BVVLS cases.
After the initiation of riboflavin treatment, significant improvement was observed in the patient’s clinical status and he required noninvasive mechanical ventilation only during sleep. On the 14th day of riboflavin treatment, he was discharged from the intensive care unit to service (Figure 2A,B). On the 15th day of treatment, ethylmalonic aciduria was not detected in urine organic acid analysis.

Many differential diagnoses should be considered when a child with neurologic symptoms is seen. In our patient, the following patient’s characteristics and data obtained from his past medical history and family history led us to consider the diagnosis of BVVLS: 1) the presence of parental consanguinity; 2) the presence of ptosis, stridor and respiratory insufficiency, diaphragm paralysis, and ethylmalonic aciduria; 3) significant clinical improvement obtained with riboflavin treatment in his previous hospital admission; and 4) the presence of similar symptoms in his dead brother. Although metabolic organic acid investigations in the first case were also consistent with MADD, as he responded dramatically to high-dose riboflavin treatment and weaned off the ventilation swiftly on the 7th day of therapy, a possible diagnosis of BVVLS was favored.

**Case 2**

During the days of hospitalization of the first case, his sister was born. Although she had no respiratory, metabolic or neurologic problems, a 10 mg/kg/day of riboflavin treatment was initiated empirically after blood and urine samples were obtained.

The genetic study revealed a novel mutation of c.44G>T (p.Gly15Val) in the SLC52A3 gene both in the index case and his newborn asymptomatic sister. This mutation was also evaluated by using some mutation prediction programs like MutationTaster (NeuroCure Clinical Research Centre & Klinik für Pädiatrie mit Schwerpunkt Neurologie, Germany), SIFT (J. Craig Venter Institute, USA), Polyphen2 (14), and Mutation Accessor (15) and all predicted this variation as a disease-causing mutation and damaging. Amino acid change from glycine to valine is a change from an aliphatic to a nonaliphatic amino acid. Mutation is in the conserved area in different species like *Macaca mulatta*, *Felis catus*, *Mus musculus*, and several others. This variation most probably causes loss of transmembrane helical domain of the protein. All these data sign that this is a “likely pathogenic variation”.

The mother and the father were heterozygous for this mutation. Details of mutation and in silico evaluation are given in Table 1. The predictions of all tools listed in Table 1 present a high possibility of disease-causing nature of this variation. The parents were heterozygotes and there is no homozygote in healthy family members. However, functional studies are needed to better understand its disease-causing effect.

**Table 1:** Details of mutation of c.44G>T (p.Gly15Val) in SLC52A3 gene and in silico evaluation.

<table>
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<th>DNA changes</th>
<th>c.44G&gt;T</th>
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<tr>
<td>cDNA.286G&gt;T</td>
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<td>g.2757G&gt;T</td>
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<td>model: simple_aae</td>
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</tr>
<tr>
<td>Screening of mutation in 200 healthy persons</td>
<td>No mutation was detected</td>
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<td>1000 genome studies</td>
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On the 31st day of hospitalization the patient was discharged on 25 mg/kg/day of riboflavin treatment and received noninvasive mechanical ventilation only during sleep. Three months later, his neurologic examination was completely normal except for a mild right-eye ptosis, and he no longer required noninvasive mechanical ventilation. At the end of the first year under riboflavin treatment, he still could climb the stairs without help (Figure 3). His sister also had no respiratory, neurologic, or metabolic problems on riboflavin treatment (Figure 4).

Discussion

Brown-Vialetto-Van Laere syndrome is a rare, progressive childhood neurodegenerative disease that is characterized by pontobulbar palsy, sensorineural hearing loss, and respiratory insufficiency. BVVLS is clinically heterogeneous, presenting as early as the neonatal period and as late as the third decade of life (16). After the first case of BVVLS was reported in the late 19th century by Brown, approximately 60 new cases from different countries have been described (5). Bosch et al. (13) first defined an infant with progressive muscle weakness and diaphragm paralysis as BVVLS and then three Brown-Vialetto-Van Laere and Fazio-Londe syndrome patients followed this case. It has been reported that the metabolic results of these patients mimic a variant of MADD and also that they are severely deficient in flavine. This result indicated a relation between Brown-Vialetto-Van Laere and Fazio-Londe syndromes involving likely defects in riboflavin metabolism or transport.

Riboflavin is a precursor of flavin adenine dinucleotide and flavin mononucleotide, which are cofactors involved in oxidative phosphorylation, an essential component of energy metabolism. Deficiency normally presents with inflammation of the mouth and tongue, mouth ulcers, cracked lips, and angular cheilitis (17).

Bosch et al. showed that treatment with riboflavin resulted in resolution of all symptoms and metabolic abnormalities in three patients with presumptive diagnosis of BVVL or Van Laere-Fazio-Londe syndrome. This clinical observation encouraged them to analyze if there are any mutations in the \( SLC52A3 \) gene, which encodes a protein responsible for riboflavin transport. They found \( SLC52A3: \ c.\ 1198-2A>C \) mutation in two patients. The parents and second-degree cousins of these cases were also heterozygous for this mutation. The third patient had a combined heterozygote mutation \( c.49T>C \) (p.W17R)/\( c.639C>G \) (p.Y213X) in the \( SLC52A3 \) gene (13). We were unable to measure riboflavin levels in our patient; nonetheless, dramatic clinical and biochemical improvements achieved by riboflavin treatment – as also seen among the cases treated by Bosch et al. (13) – strongly suggest a very similar or same syndrome even before genetic results.

Green et al. (9) also showed the mutation in the \( SLC52A3 \) gene as a leading cause of BVVLS. The mutation analysis of our index case and his sister revealed a novel homozygous mutation \( c.44G>T \) (p.Gly15Val) in the \( SLC52A3 \) gene. The parents were heterozygous for this mutation. The third patient had a combined heterozygote mutation \( c.49T>C \) (p.W17R)/\( c.639C>G \) (p.Y213X) in the \( SLC52A3 \) gene (13). We were unable to measure riboflavin levels in our patient; nonetheless, dramatic clinical and biochemical improvements achieved by riboflavin treatment – as also seen among the cases treated by Bosch et al. (13) – strongly suggest a very similar or same syndrome even before genetic results.

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of the cases are sporadic and the remaining familial. Most of the familial cases exert autosomal recessive inheritance, although autosomal dominant or X-linked forms were also suggested for very rare cases (12, 18). The mode of inheritance in our patients was autosomal recessive.

Anand et al. were the first to report clinical improvement in a case after prompt employment of high-dose riboflavin therapy following early genetic diagnosis of BVVLS. They treated their patient with 150 mg riboflavin twice a day (25 mg/kg/day). Within 1 week of treatment, the patient improved in motor functioning. From being able to sit only with support, the patient improved to be completely mobile and even walked up the stairs (19). We also treated our patient with a 25 mg/kg/day of riboflavin and similarly observed a dramatic improvement in motor functioning from being dependent on invasive mechanical ventilation to climbing stairs without help. This dramatic response demonstrated that with early diagnosis and appropriate treatment, BVVLS can be fully healed even in patients with diaphragm paralysis. Another important suggestion of our case’s clinical progress is that not only the clinical status of the patient improved with riboflavin, but also metabolic abnormalities such as ethylmalonic aciduria reversed after only 15 days of treatment. In addition, we also observed that with early riboflavin supplementation, a newborn carrying the same mutation as his sibling was symptom-free at least during the first year of follow-up. Thus, as the resolution of symptoms and improvement of the metabolic abnormalities such as ethylmalonic aciduria, riboflavin supplementation seems to prevent the occurrence of disease-specific abnormalities in the subjects with this mutation.

In conclusion, we aimed to emphasize once again the importance of early consideration of BVVLS in children with symptoms described earlier and especially during differential diagnosis of MADD. With timely and accurate diagnosis, initiating high-dose riboflavin treatment exerts very profound therapeutic (and likely also preventive) effects in a deadly disease if untreated.

References