Brown-Vialetto-Van Laere Syndrome: Case Report of Dramatic Response to Riboflavin

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ABSTRACT

Brown-Vialetto-Van Laere syndrome (BVVL) is a rare neurodegenerative disorder caused by riboflavin transporter genes SLC52A2 and SLC52A3 variants. It manifests as a combination of cranial nerve palsies and sensorineural hearing loss. This study presents the case of a 5.5-year-old boy with progressive swallowing difficulties, ptosis, severe hearing loss, and a progressive speech disorder. Remarkably, he showed a significant response to high-dose riboflavin supplementation. Subsequent genetic testing confirmed the diagnosis. Whole exome sequencing identified a homozygous missense variant, [c.239G>A; (p.Gly80Asp)], in the SLC52A3, consistent with BVVL 1. It is essential to remember that BVVL is a set of sensorineural hearing loss and a variety of cranial nerve palsies. Riboflavin should be started as soon as possible because it has a crucial role in neuronal preservation and even reverses the disease.

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Introduction

Brown-Vialetto-Van Laere syndrome (BVVL) is an uncommon progressive neurodegenerative condition characterized by sensorineural hearing loss and various cranial nerve palsies, predominantly affecting the motor component of the lower cranial nerves. This syndrome manifests as a combination of pontobulbar palsy and sensorineural deafness (1). The age of onset can range from infancy to the third decade of life, and if left untreated, the disease progresses over time (2). Recent studies have focused on mutations in riboflavin transporters in BVVL patients, with some showing improvement following riboflavin treatment in cases with confirmed riboflavin mutations (3). Here, the researchers describe the case of a 5.5-year-old boy with severe hearing loss and swallowing difficulties who exhibited remarkable improvement after initiating riboflavin therapy.

Case presentation

A 5.5-year-old boy was admitted with symptoms of progressive swallowing difficulties, ptosis, severe hearing loss, and a progressive speech disorder about two weeks prior to admission. Based on the medical history, the patient exhibited a masked face due to bilateral facial nerve involvement, although this feature was not consistently present as facial nerve involvement was sometimes unilateral. During admission and electrophysiological studies, facial nerve conduction appeared normal, as the symptoms

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were not constant. The patient experienced dysphonia and articulation issues, was unable to inflate a balloon, and exhibited tongue fasciculation without any limb movement difficulties. Parents noted respiratory issues, particularly during sleep, and fine hand tremors during periods of illness starting one month before the hospital visit. A video laryngoscopy revealed bilateral partial vocal cord paralysis in the midline position.

Upon physical examination, the patient showed no sensory or motor deficits in the upper and lower extremities nor any bowel or bladder dysfunction.

The patient responded appropriately to questions and received routine vaccinations. His prenatal and perinatal history was unremarkable, without any delivery complications, and his neurodevelopment was normal. The parents are closely related.

The patient's male sibling passed away due to respiratory insufficiency and pneumonia. This sibling also experienced swallowing difficulties after turning one year old. Due to the unclear etiology of the symptoms and the progressive nature of the disease, the patient underwent multiple hospitalizations. Unfortunately, he passed away at 1.5 years old without a conclusive diagnosis. However, the patient now has two healthy siblings.

A lumbar puncture was performed on the patient, and cerebrospinal fluid (CSF) was analyzed for viral and autoimmune causes. The CSF protein level was 50 mg/dl, with no significant cell count or culture findings. PCR testing for viral infections and autoimmune antibodies in the CSF returned negative results. Acylcarnitines and amino acids were normal in the metabolic study.

Brainstem auditory evoked potentials (BAEP) indicated bilateral severe sensorineural hearing loss at high frequencies. Magnetic resonance imaging (MRI), blood chemistry, electrocardiogram, and echocardiography revealed no significant abnormalities.

Electrophysiological study

During the needle electromyography (EMG) and nerve conduction study (NCS), three limbs and bilateral cranial nerves (VII, XII) were examined. Standard temperature (T=37.0) was ensured in the tested limbs before conducting the tests. Compound muscle action potentials (CMAP) were recorded for the Median, Ulnar, Tibial, and Peroneal nerves, sensory nerve action potentials (SNAP) for the Median and Sural nerves, and F-waves from the Tibial, Median, and Ulnar nerves. All NCS responses were within normal limits.

The needle EMG of both distal and proximal muscles in the limbs and cranial muscles revealed a neurogenic pattern, specifically in the cranial muscles (tongue muscles). The condition featured high-amplitude and prolonged duration motor unit action potentials (MUAPs), reduced recruitment, as well as the presence of spontaneous potentials such as fibrillation (Fib) and positive sharp waves (PSW). These findings indicated a chronic denervation process with ongoing regeneration, consistent with anterior horn cell diseases.

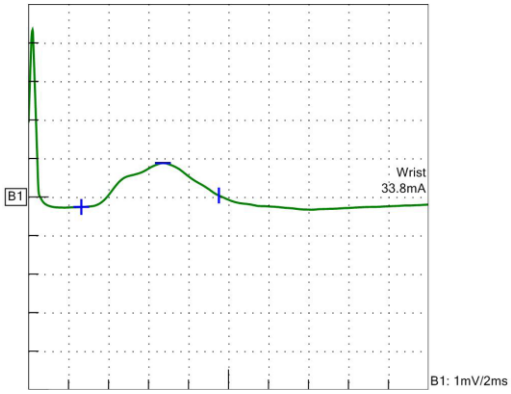

Figure 1: Compound muscle action potential of nasalis muscle (Left)

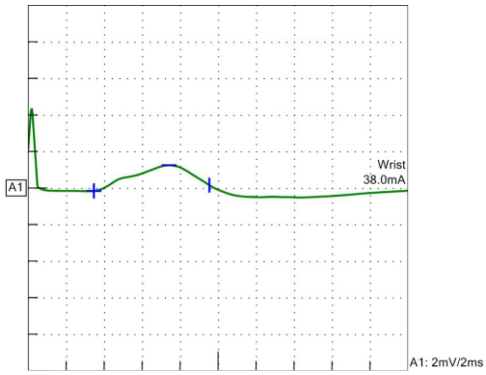

Figure 2: Compound muscle action potential of nasalis muscle (Right)

During his hospital stay, he was administered a riboflavin supplement based on the history and physical examination, with the primary diagnosis of BVVL. A significant improvement was observed in signs and symptoms, leading to an adjustment and increased dosage in response to the clinical progress.

His hearing improved, breathing became easier, and bilateral facial movements were restored. Upon discharge, he was prescribed a high dose of riboflavin at 1400mg per day, equivalent to 48mg/kg/day.

Three months after being discharged, he returned for a follow-up visit in a stable condition without any progressive auditory, respiratory, or bulbar impairment. The results from whole exome sequencing were available and confirmed the primary diagnosis. The patient was found to be homozygous for SLC52A3.

Whole-exome sequencing and bioinformatics analysis

Initially, genomic DNA was extracted from the blood samples of the proband and her family based on the salting-out standard protocol. Subsequently, Whole-exome Sequencing (WES) was performed using the Agilent SureSelect Human All Exon V7 Kit from Illumina to enrich the whole human exome, containing exons, along with flanking +/-20 intronic bases. The data was generated and sequenced on the NovaSeq 6000 platform, resulting in approximately eight GB of data with an average sequencing depth of around 100x. An in-house bioinformatics pipeline of Pardis Gene Exomine Technology was performed. Prioritization and filtering of the most relevant variants were manually assessed based on similar studies (1-3) to identify the variants that matched clinical outcomes and were observed in the family. Primers were designed using the PrimerQuest tool and UCSC genome browser blat tools. Then, this study examined the quality and features of primers using the OligoAnalyzer Tool.

WES results

Based on the clinical information, the genes related to the following HPO (The Human Phenotype Ontology) terms were considered in the molecular analysis: Developmental regression (HP: 0002376), Dysphagia (HP: 0002015), Abnormality of speech or vocalization (HP: 0002167), Dysphonia (HP: 0001618), Tremor (HP: 0001337), Tongue fasciculation (HP: 0001308), Hearing loss (HP: 0000365), and Ptosis (HP: 0000508). The final list of variants was then classified based on the American College of Medical Genetics and Genomics (ACMG) guideline. Finally, the depth of reads of the final variants was checked using the IGV (Integrative Genomics Viewer) software. A homozygous missense variant in the SLC52A3 [NM_033409.4:c.239G>A; (p.Gly80Asp)] was identified and classified as a variant of uncertain significance (VUS) based on the ACMG guideline. Pathogenic variants in the SLC52A3 are consistent with autosomal recessive BVVL 1 (OMIM: 211530). As a result, the c.239G>A variant in the SLC52A3 segregated with the disease in this family and was considered the disease-causing variant in the proband.

Discussion

BVVL syndrome is a rare neurometabolic disorder. The first description with undetermined etiology was in 1894 (4). Recent studies have identified that a problem with the genes responsible for producing proteins involved in transporting vitamin B2 (riboflavin) from the small bowel into the bloodstream causes BVVL. Riboflavin is absorbed via riboflavin transporters RFVT1 and RFVT3 from the small intestine, and it enters the brain through the third transporter, RFVT2. Surprisingly, mutations in the genes SLC52A2 (coding for riboflavin transporter 2, RFVT2) and SLC52A3 (coding for riboflavin transporter 3, RFVT3) are demonstrated in many cases of BVVL syndrome. Riboflavin is a precursor of active coenzymes with a crucial role in carbohydrate, amino acid, and lipid metabolism. BVVL is now defined as a treatable inherited motor neuron disease (5).

The clinical presentation is characterized mainly by pontobulbar palsy and sensorineural hearing loss, but it also consists of a spectrum of findings. Upper motor neuron involvement, ataxia, limb weakness, ptosis, and neck and shoulder weakness are also reported. Cranial nerve involvement II-VI is not common (6). Viral triggers have been noted in several studies (7). In the present case, respiratory compromise and hand tremors were prominent, specifically during illness.

Considering differential diagnoses in comparable conditions is essential. Progressive bulbar paralysis of Fazio-Londe is very similar without hearing loss. The Nathalie syndrome is another one with deafness and some associations such as cardiomyopathy, cataracts, spinal muscular atrophy, and hypogonadism. The Boltshauser syndrome is a combination of deafness, vocal cord paralysis, and muscular atrophy in the distal area, but the absence of bulbar palsy and autosomal dominant inheritance help to differentiate. The Madras motor neuron disease (MMND) is a very similar condition with deafness, cranial nerve involvement, and limb weakness. Cranial nerve dysfunction III and VI have not been found in MMND (8).

Precise history and physical examination are important for diagnosis because early treatment with riboflavin should be considered while waiting for the genetic answer (9). Riboflavin supplementation has been shown to stop or even improve hearing loss and cranial nerve degeneration. No consensus is available on how riboflavin supplementation should be started, but a range of 10-60 mg/kg/day is mentioned. Some studies suggest gradually increasing the dose, but the maximum dose is unclear. Side effects of high-dose supplementation are excessive urination, urine discoloration, and diarrhea. Allergic reactions are rare (10). We increased riboflavin dosage gradually from 10mg/kg/day to 48mg/kg/day (1400mg daily) in about three months. No side effects were reported, and a significant clinical improvement happened. The patient's gag was normal without a swallowing problem. The facial nerve was intact in the examination, and hearing loss and ptosis were reversed.

A genetic study confirmed a homozygote mutation of SCL52A3 in follow-up after three months of discharge.

In Conclusion

Notably, BVVL is associated with sensorineural hearing loss and a range of cranial nerve palsies. A detailed history and physical examination are key in narrowing down potential diagnoses. Prompt initiation of riboflavin treatment is crucial, as it plays a vital role in preserving neurons and can even reverse the disease's progression. Confirmation of the diagnosis through genetic studies is important. Assessing asymptomatic family members who are affected and providing riboflavin prophylaxis may aid in neuronal protection and prevent the onset of symptoms.

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Authors' Contribution

Badv and Heidari diagnosed the disease and stated that the report of this patient could help identify and treat these patients because appropriate and timely treatment of the disease can aid in neuronal protection and prevent the onset of symptoms. Ghahvechi Akbari did the electrodiagnostic (EMG, NCV) study. ShahbodaghKhan helped in collecting data. Masoud Garshasbi did Whole-exome Sequencing and bioinformatics analysis. Yousefimanesh helped in summarizing and collecting data, recording the information, and writing and editing the article.

Conflict of Interest

The authors declare that they have no conflict of interest.

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