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Case Report

Brown–Vialetto–Van Laere Syndrome Type 2 in a Child: A Case Report with Review Of Literature

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Abstract

Brown–Vialetto–Van Laere syndrome (BVVLS) is a rare autosomal recessive neurodegenerative disorder caused by pathogenic variants in riboflavin transporter genes. We report an 11-year boy who presented with progressive myopathy. In view of the progressive neuromuscular phenotype, whole-exome sequencing was performed,which identified a homozygous missense variant in the SLC52A2 gene, c.401C>T (p.Pro134Leu), associated with Brown–Vialetto–Van Laere syndrome type 2. Although classified as a likely pathogenic, the patient's clinical features demonstrated a strong phenotypic correlation with SLC52A2-related riboflavin transporter deficiency. This case expands the clinical and genetic spectrum of SLC52A2-associated disease and highlights the importance of genetic testing in children with unexplained progressive neuromuscular weakness.

Keywords: BVVL (Brown–Vialetto–Van Laere Syndrome); Riboflavin Transporter Genes, Myopathy

Introduction

Brown–Vialetto–Van Laere syndrome (BVVLS) is an uncommon neurodegenerative disorder characterized by progressive sensorineural hearing loss, bulbar dysfunction, respiratory insufficiency, and muscle weakness due to involvement of multiple cranial nerves, particularly VII, IX, and XII [1]. It is most commonly inherited in an autosomal recessive pattern, although rare autosomal dominant and X-linked cases have been described [2]. BVVLS is now recognized as a riboflavin transporter deficiency syndrome, resulting primarily from pathogenic variants in the genes SLC52A2 and SLC52A3, which encode the riboflavin transporters RFVT-2 and RFVT-3, respectively.Several loss-of-function variants in SLC52A2 and SLC52A3 have been associated with motor neuron disorders and neuronopathies, including BVVLS, whereas pathogenic variants in SLC52A1 have been linked to glutaric aciduria [3].

Case Report

An eleven years male presented to us with the complaint of inability to stand from sitting position since3 years of age. On examination, the child was conscious, hemodynamically stable, with bilateral horizontal and vertical nystagmus with generalized reduction in muscle bulk and tone with marked weakness in all group of muscles in all four limbs (Medical Research Council grade 2/5 in both upper limbs and 3/5 in both lower limbs),

diminished reflexes, and tongue fasciculations,other systemic examinationswerewithin normal limit.

Laboratory investigations showed hemoglobin of 13.3 g/dL, total leukocyte count of 6570/mm^3, platelet count of 1.62 lakh/mm^3, with normal liver and renal function tests, mildly elevated CPK (315.8 U/L) and LDH (270 U/L). He had normal calcium and phosphorus levels, but had vitamin D insufficiency [25(OH) Vit D level 17.3 ng/mL]. Based on the clinical presentation and investigation findings, a hereditary neuromuscular disorder was suspected.

Considering the patient's history, examination findings, and initial investigative workup, Spinal Muscular Atrophy Type III, juvenile GM2 gangliosidosis, and mitochondrial myopathy were kept as possible differential diagnosis.

Magnetic resonance imaging (MRI) of the brain was normal and did not reveal any structural abnormalities, signal changes, or evidence of brainstem or cerebellar involvement (Figure 1).

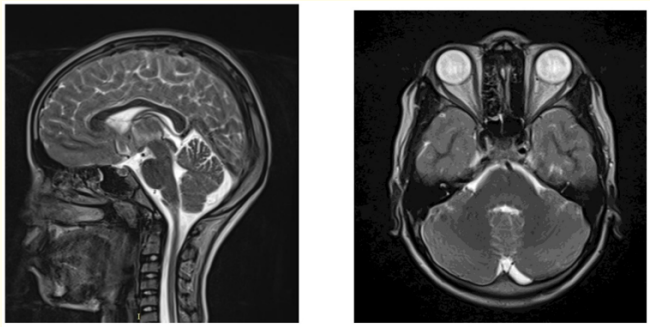

Figure 1: Magnetic resonance imaging of brain. (A) T2W Imaging of mid sagittal section of brain shows normal brain stem with no signal abnormalities. (B) T2W axial image of cerebellum at the level of superior cerebellar peduncle shows normal volume and signal intensity.

Whole-exome sequence (Table 1) identified a homozygous missense variant in the SLC52A2 gene, c.401C>T (p.Pro134Leu), inherited in an autosomal recessive pattern. This variant is currently classified as a likely pathogenic and has been associated with Brown–Vialetto–Van Laere syndrome type 2 (riboflavin transporter deficiency). The patient's clinical phenotype of early-onset progressive weakness, hypotonia, areflexia, tongue fasciculation, and nystagmus showed significant overlap with the reported spectrum of SLC52A2-related disease.

Gene and Transcript	Exon/ Intron Number	Variant Nomenclature	Variant Type	Zygosity	Classification	OMIM Phenotype	Inheritance	Computational evidences
SLC52A2 (NM_00136318.2)	Exon 3/ Exon 5	p.P134L c.401C>T p.Pro134Leu [147x/147x]	missense_ variant	Homozygous	Likely pathogenic	Brown–Vialetto–Van Laere syndrome 2	Autosomal recessive	Revel: 0.8

Table 1: Findings of whole exome sequence.

The patient responded well to oral high dose Riboflavin(1200 mg/day) supplementation and on followup, child started to show an improvement in motor function and muscle strength after 5th month.

Discussion

Brown–Vialetto–Van Laere syndrome type 2 (BVVLS2) is a rare autosomal recessive riboflavin transporter deficiency caused by biallelic pathogenic variants in *SLC52A2* [3]. Classically, BVVLS2 is characterized by sensorineural hearing loss, cranial neuropathies, progressive limb weakness, bulbar dysfunction, and respiratory compromise [4,5].

Our patient exhibited several features that differ from the classical phenotype. Childhood-onset generalized myopathy was the predominant manifestation. Although weakness is reported in approximately 73% of patients, it is typically accompanied by hearing loss, cranial nerve deficits, or respiratory involvement [5]. In contrast, our patient lacked hearing impairment, bulbar and respiratory compromise despite significant motor disability.

Another notable feature was the presence of bilateral horizontal and vertical nystagmus. Ocular manifestations are less frequently emphasized in major cohorts and may contribute to diagnostic delay when classical manifestations are absent.

Neuroimaging was unremarkable despite severe neuromuscular involvement. Previous studies have shown that radiological findings may be variable and do not necessarily correlate with disease severity [6]. Therefore, a normal MRI should not preclude consideration of BVVLS2 in an appropriate clinical setting.

This case expands the phenotypic spectrum of *SLC52A2*-related disease and highlights that severe early-onset myopathy and nystagmusmay occur in the absence of more typical hearing loss and respiratory dysfunction. Early recognition is crucial because riboflavin supplementation can significantly improve outcomes and alter disease progression [4,6].

The Review of literature (Table 2) also demonstrates a clear relationship between treatment timing and outcome in riboflavin transporter deficiency. When supplementation is started early, results are excellent i.e. clinical improvement within days alongwith biochemical normalization [7], and Foley., *et al*. 2024 noted that high-dose riboflavin partially ameliorates progression, with the greatest benefit when initiated soon after symptom onset [4]. The 2026 Arabian Peninsula cohort, in which one- third of patients were treated pre-symptomatically, similarly links early diagnosis to better outcomes [8]. These findings justify immediate empirical riboflavin without awaiting genetic confirmation.

Study (Author, Year)	Study Type	N	Gene	Key Findings
Green., *et al*. 2010 (Am J Hum Genet)	Genetic discovery	Several families	SLC52A3	First study to identify SLC52A3 (C20orf54) mutations as the molecular basis of BVVL syndrome.
Bosch., *et al*. 2011 (J Inherit Metab Dis)	Mechanistic case study	2 siblings	SLC52A3	BVVL/Fazio–Londe overlap due to an SLC52A3 mutation, highlighting riboflavin transporter deficiency as a treatable inborn error of metabolism
Bosch., *et al*. 2012 (Orphanet J Rare Dis — 'BVVL revisited')	Comprehensive systematic review	74 patients (<18 yrs), 35 publications	SLC52A2 & SLC52A3	Largest clinical synthesis at the time; most prevalent features: bulbar palsy, hearing loss, facial weakness, respiratory compromise; 28/61 untreated patients died; all 13 riboflavin-treated survived (8 markedly improved); proposed renaming as RTD Types 1/2/3.
Jaeger and Bosch, 2016 (J Inherit Metab Dis — mini-review)	Pooled review	70 (37 SLC52A2 + 33 SLC52A3)	SLC52A2 & SLC52A3	Pooled clinical frequency data: hearing loss 73%, weakness 73%, cranial nerve deficit 74%, respiratory compromise 66%; cognition reported normal in all patients.
Kentab., *et al*. 2024 (Front Pediatr — Saudi Arabia)	Case report	1	SLC52A3	BVVL masqueraded as chronic inflammatory demyelinating polyneuropathy (CIDP); resolved with riboflavin.
Al Shamsi., *et al*. 2026 (Eur J Hum Genet)	Large retrospective cohort — Arabian Peninsula	23 (16F, 7M)	SLC52A3	Largest SLC52A3 cohort; dominant variant p.Arg212Cys (20/23 homozygous); facial diplegia commonest (12/13), hearing loss & dysarthria 10/13; riboflavin 15–100 mg/kg/day (median 26); pre-symptomatic treatment linked to best outcomes.

Table 2: Review of literature of published studies.

Conflict of Interest

None.

Source of Support

Nil.

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