Neurology Asia 2025; 30(3) : 925 – 928

Tracing the roots of paralysis: A Brown-Vialetto-Van Laere syndrome case report

Bhawna Sharma, Swati Garg, Shubham Agrawal, Aditi Jain

Department of Neurology, University S.M.S Medical College and Hospital, Jaipur, India

Abstract

Brown-Vialetto-Van Laere Syndrome (BVVLS) is a rare, inherited neurological disorder characterized by cranial nerve dysfunction, progressive neuropathy, and sensorineural hearing loss. Mutations in riboflavin transporter genes, such as *SLC52A2* result in impaired riboflavin metabolism, leading to neurodegeneration. We present a case of a 16-year-old male with progressive sensorineural hearing loss, visual impairment, tongue atrophy, and distal muscle weakness of the hands and feet. This case highlights that if a patient presents with multiple cranial nerve involvement accompanied by small muscle atrophy, we should consider the possibility of this rare metabolic disease. Early recognition of BVVLS is crucial, as high-dose riboflavin supplementation (10– 40 mg/kg/day) can halt or even reverse disease progression. Differentiation from conditions like Madras motor neuron disease is essential for accurate diagnosis and management. This case emphasizes the potential for favourable outcomes with timely intervention.

INTRODUCTION

Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare neurological disorder that primarily affects the cranial nerves and motor neurons, leading to progressive neuropathy, cranial nerve palsies, and respiratory difficulties. The sensorineural hearing loss is the most consistent finding associated with BVVLS.[1] It is an autosomal recessive inherited disease.[2] It is linked to mutations in riboflavin transporter genes (*SLC52A2* or *SLC52A3*), which cause impaired riboflavin metabolism.[3] This impaired riboflavin transport leads to dysfunction of flavoproteins essential for cellular energy production and nerve health.[4] The resulting oxidative stress and energy deficits contribute to neurodegeneration, particularly in cranial nerve nuclei and peripheral nerves. Early riboflavin supplementation has shown promise in halting disease progression and even reversing some symptoms.[5]

CASE REPORT

A 16-year-old male, born to non-consanguineous parents with normal developmental milestones, presented with a history of progressive hearing loss over the past 4–5 years. Initially, he could respond only to loud sounds, but he now perceives sounds only at close distances. He underwent multiple consultations in the ENT department and was diagnosed with bilateral severe sensorineural hearing loss, which was not associated with dizziness, tinnitus, or vertigo.

Two years ago, the patient began experiencing progressive visual difficulties, and his vision loss has gradually worsened. Over the past 1.5 years, he reported progressive difficulty in gripping objects, such as holding a pen or breaking chapatis. This eventually progressed to abnormal, involuntary clawing of the fingers in both hands and feet. His parents also noted thinning of the small muscles in his hands.

Over the past year, the patient developed slurred speech with a nasal twang and unclear articulation of words. There were no associated sensory symptoms. On examination, his visual acuity was 6/60 in the left eye and perception of light in the right eye. The right optic disc appeared pale (Figure 1). Bilateral gag reflexes were absent. He had atrophy and fasciculations of the tongue.

There was atrophy of the small muscles in both hands and feet, involving the palmar and dorsal interossei, as well as the thenar and hypothenar muscles (Figure2), while the power in all joints was otherwise preserved at 5/5. All reflexes were intact, and sensory and cerebellar examinations

Address correspondence to: Dr. Swati Garg, Department of Neurology, University S.M.S Medical College, Jaipur, Rajasthan, India. Tel: 9530675707, Email: SWATIGARG820@gmail.com

Date of Submission: 11 January 2025; Date of Acceptance: 2 April 2025

https://doi.org/10.54029/2025rua

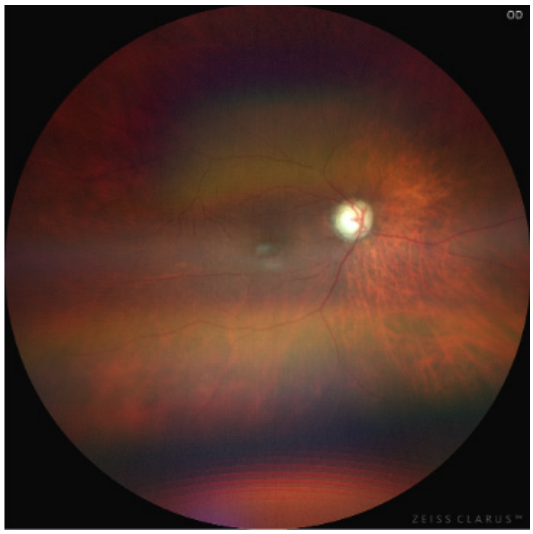

Figure 1. This is a wide field fundus photograph of the right eye showing chalky white disc with well-defined disc margins.

were normal.

Laboratory investigations showed normal routine blood parameters, except for elevated creatine phosphokinase-MB (330 U/L) and lactate dehydrogenase (985 U/L).The renal functions, thyroid function tests were normal. His visual evoked potentials (VEP) for both eyes showed prolonged latency; while brainstem evoked response audiometry was non-recordable in both ears.

Nerve conduction studies revealed bilateral motor axonal involvement affecting the median, peroneal, and tibial nerves (Table 1). Electromyography showed neurogenic involvement in the abductor pollicis brevis and the first dorsal interossei muscles. MRI of the brain with orbital cuts and cervical spine screening showed no abnormalities.

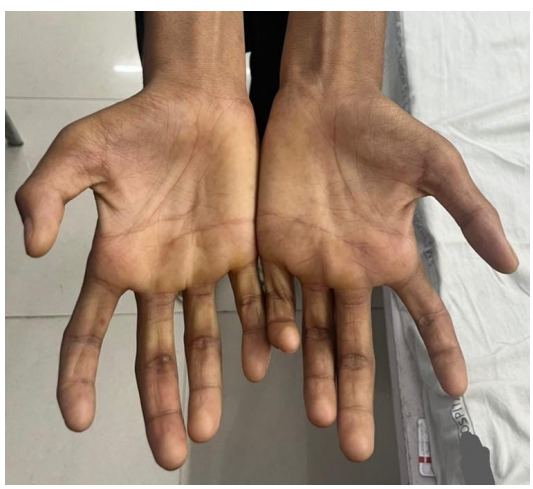

Figure 2. Atrophy of the small muscles in both hands, involving the palmar and dorsal interossei, as well as the thenar and hypothenar muscles.

Given the patient's presentation of progressive hearing and vision loss, tongue atrophy, and bilateral weakness in the hands and feet, a suspicion of BVVLS was considered. Whole-exome genetic testing identified a heterozygous variant in *SLC52A2* on exon 5, confirming the diagnosis of BVVLS (Figure 3). Genetic testing revealed a heterozygous variant, despite BVVLS being an autosomal recessive disorder. This raises the possibility of compound heterozygosity, as a whole exome study may not always detect small genetic defects such as deletions. Given the patient's clinical presentation and positive response to riboflavin therapy, the diagnosis of BVVLS remains strongly supported, warranting further genetic analysis to explore potential undetected mutations.

DISCUSSION

BVVLS is a rare, progressive neurodegenerative disorder that primarily affects the cranial and peripheral nerves. It was first identified by Brown in 1894 as a form of familial amyotrophic lateral sclerosis. Subsequent reports by Vialetto in 1936 and Van Laere in 1966 led to the condition being named BVVLS.[1]

This syndrome is characterized by progressive pontobulbar palsy with sensorineural hearing loss.[2] It is part of the riboflavin transporter deficiency spectrum, caused by mutations in the *SLC52A2* or *SLC52A3* genes, which impair riboflavin transport. This impairment leads to dysfunction of flavoproteins critical for cellular energy production and nerve function. Green *et al*. conducted a study in a consanguineous family with multiple affected members and identified a mutation in the *C20orf54* gene, suggesting a possible association with this syndrome.[7]

The hallmark features of BVVLS include progressive hearing loss, optic neuropathy, bulbar palsy, and motor neuropathy.[4] In this case, the patient presented with progressive sensorineural hearing loss over 4–5 years, followed by visual loss due to optic neuropathy. Neurological examination revealed tongue atrophy with fasciculations, absent gag reflexes, and weakness with atrophy of the small muscles in the hands and feet. Nerve conduction studies confirmed motor axonal neuropathy, and visual evoked potentials demonstrated optic nerve dysfunction. These

Table 1: Nerve conduction studies revealed bilateral motor axonal involvement affecting the right median, peroneal, and tibial nerves

Nerve	Latency (ms)	Amplitude (mV)	Duration (ms)	Velocity (m/s)
Motor nerve conduction				
Right median - Abductor pollicis brevis				
Wrist	3.54	1.3	6.67	
Elbow	8.44	1.2	6.56	46.94
Right peroneal				
Ankle	3.54	2.0	9.9	
Knee	11.25	1.9	9.38	46.69
Right tibial				
Ankle	4.6	1.9	10	
Knee	13.7	1.1	12.4	44.15

findings are consistent with BVVLS.

The possibilities of other disorder were - folio Londe disease, Bolhauser syndrome, Nathalie syndrome, Madras variant of motor neuron disease. The presence of sensory neural hearing deafness with optic atrophy is against the folio Londe syndrome. In folio Londe there is only presence of progressive bulbar palsy and respiratory difficulty. On the other hand, Boltshauser syndrome shares similarities with BVVLS due to the presence of sensorineural hearing loss, vocal cord paralysis, and distal muscle wasting. However, unlike BVVLS, where brainstem involvement is more widespread, Boltshauser syndrome primarily affects the vocal cords without additional brainstem signs. Nathalie syndrome is an uncommon disorder marked by spinal muscular atrophy, hearing loss, cataracts, cardiac conduction abnormalities, and hypogonadism these all features are absent in our case.

The Madras variant of motor neuron disease, a regional variant of motor neuron disease first described in southern India, is an important differential diagnosis for BVVLS.[5] Both conditions share overlapping features wasting and weakness predominantly of distal muscles of the limbs, involvement of facial and bulbar muscles, and associated sensorineural hearing impairment. However, there are also some key distinctions between the two but final diagnosis can be made by genetic testing only. In Madras motor neuron disease, hearing loss is less common, and when present, it typically manifests later in the disease course. Additionally, pyramidal signs are often observed in affected individuals.

Other conditions, such as Charcot-Marie-Tooth disease, mitochondrial disorders, and other hereditary neuropathies, should also be considered. However, the combination of sensorineural hearing loss, optic neuropathy, and bulbar palsy strongly suggests BVVLS.[6] The cornerstone of BVVLS management is early diagnosis and riboflavin supplementation, which can halt or even reverse disease progression in some cases. High-dose riboflavin (10–40 mg/kg/day) has shown promising results in improving neurological function, although responses vary depending on the stage of the disease and specific genetic mutations.[8]

Gene[1] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[5]
SLCS2A2(+) (ENST00000643 9944.2)	Exon 5	c.1226G>A (p.Gly409Asp)	Heterozygos**	Brown-Vialetto-Van Laere syndrome-2 (OMIM#614707)	Autosomal recessive	Uncertain significance (PM2,PP3)

Figure 3. Whole-exome genetic testing suggestive of heterozygous variant in *SLC52A2* on exon 5, confirming the diagnosis of BVVL syndrome

Following the administration of high-dose riboflavin, there was notable improvement in distal upper limb atrophy and weakness. However, hearing loss and visual impairment showed no significant improvement, which aligns with the known response patterns in BVVLS.

This case underscores the clinical variability of BVVLS and the need for heightened awareness of this treatable disorder in patients with progressive cranial and peripheral nerve involvement.

In conclusion, BVVL is a rare metabolic disorder. This case report highlights the importance of early diagnosis and treatment in patients suspected of having this condition. BVVLS can often masquerade as other disorders, such as the Madras variant of motor neuron disease. However, unlike motor neuron disease, BVVLS has a specific treatment. Administering high-dose riboflavin therapy can significantly improve the patient's condition.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Sathasivam S. Brown-Vialetto-Van Laere syndrome. *Orphanet J Rare Dis* 2008;3:9. doi: 10.1186/1750-1172-3-9.
2. Malheiros JA, Camargos ST, Oliveira JT, Cardoso FE. A Brazilian family with Brown–Vialetto–Van Laere syndrome with autosomal recessive inheritance. *Arq Neuropsiquiatr* 2007;65:32-5. doi: 10.1590/s0004-282x2007000100008.
3. Foley AR, Menezes MP, Pandraud A, *et al.* Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2. *Brain* 2014;137(Pt 1):44-56. doi:10.1093/brain/awt315
4. Nalini A, Pandraud A, Mok K, Houlden H. Madras motor neuron disease (MMND) is distinct from the riboflavin transporter genetic defects that cause Brown-Vialetto-Van Laere syndrome. *J Neurol Sci* 2013;334(1-2):119-22. doi:10.1016/j.jns.2013.08.003.
5. Bosch, A.M., Stroek, K., Abeling, N.G. *et al*. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. *Orphanet J Rare Dis* 2012; **7:** 83. https://doi.org/10.1186/1750-1172-7-83
6. Anand G, Hasan N, Jayapal S, *et al*. Early use of high-dose riboflavin in a case of Brown-Vialetto-Van Laere syndrome. *Dev Med Child Neurol* 2012;54(2):187-9. doi:10.1111/j.1469-8749.2011.04142.x
7. Green P, Wiseman M, Crow YJ, *et al*. Brown-Vialetto-Van Laere syndrome, a ponto-bulbar palsy with deafness, is caused by mutations in c20orf54. *Am J Hum Genet* 2010;86(3):485-9. doi:10.1016/j.ajhg.2010.02.006
8. Hawkins SA, Nevin NC, Harding AE. Pontobulbar palsy and neurosensory deafness (Brown-Vialetto-Van Laere syndrome) with possible autosomal dominant inheritance. *J Med Genet* 1990;27(3):176-9. doi: 10.1136/jmg.27.3.176.