Brown–Vialetto–Van Laere (BVVL) syndrome is a rare motor neuron disorder of childhood, which forms a continuous spectrum with Fazio–Londe syndrome. It is an autosomal-recessive inherited disease caused by mutations in intestinal riboflavin transporter genes. We describe a child with genetically proven BVVL syndrome where prompt treatment with riboflavin showed good results.

**Keywords:** Brown–Vialetto–Van Laere syndrome, childhood motor neuron disease, Fazio–Londe syndrome, riboflavin, riboflavin transporter defect

**Case Report**

A 2-year-old girl, born of third degree consanguineous marriage, with normal birth and development, presented with insidious-onset progressive bilateral hearing loss noticed since 3 months. She also had gradually decreasing verbal output with eventual loss of speech and use of nonverbal communication to indicate needs. She had developed difficulty in swallowing, occasional choking and drooping of left eyelid a few days before presentation. No alteration of sensorium was observed. History of antecedent infection could not be elicited. The child was active and alert with normal vital signs. Cranial nerve examination showed ptosis of left eye with normal pupils, fundus, and extraocular movements. She had lower motor neuron lesion of left facial nerve with drooling at angle of mouth, palatal palsy on right side with uvular deviation, and normal tongue movements. No appreciable response to loud sounds was reported. Rest of the nervous system and systemic examination was normal.

With this clinical presentation of subacute-onset multiple cranial neuropathies, initially posterior fossa/cerebellopontine angle mass and Guillain–Barre syndrome were considered. Magnetic resonance imaging of the brain, cerebrospinal fluid examination, and EEG were normal.

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was started on oral riboflavin at a dose of 10 mg/kg/24.7–66.6 μmol/L) and normal acylcarnitine profile. She
low levels of free carnitine (7.88 μmol/L; normal range, carnitine profile showed total normal carnitine and very
neuron disease was considered at this point. Her
of phrenic nerve was considered. Possibility of motor
was also seen on ultrasonography. Probable involvement
of chest showed eventration of left diaphragm, which
During this time, the child developed tachypnea. X-ray
of chest showed eversion of left diaphragm, which
was also seen on ultrasonography. Probable involvement
of phrenic nerve was considered. Possibility of motor
deferentation was considered at this point. Her
Carnitine profile showed total normal carnitine and very
low levels of free carnitine (7.88 μmol/L; normal range, 24.7–66.6 μmol/L) and normal acylcarnitine profile. She
was started on oral riboflavin at a dose of 10 mg/kg/ day, which was further increased to 20 mg/kg/day after
a week. Within 15 days of starting treatment, ptosis disappeared and facial weakness and palatal palsy
improved. Targeted gene analysis was carried out to confirm the diagnosis. A homozygous missense variation
was seen in exon 4 of the SLC52A3 gene (chr20:742436; A > G), which resulted in the amino acid substitution of
proline for leucine (p.L369P). No mutations were found in SLC52A1 and SLC52A2 genes (Medgenome Labs Pvt
Ltd, Bengaluru). This mutation has not been previously reported in patients with FLS or BVVL syndrome. This
mutation in a candidate gene, SLC52A3, also encoding for intestinal riboflavin transported protein (hRFT2),
as the candidate gene in BVVL syndrome. Bosch et al.[9] reported the same mutation in patients with FLS, thus establishing the continuity of these genetically homogenous disorders with clinical heterogeneity. SLC52A1 and SLC52A2, also encoding for riboflavin transporters, have been identified as the other causes of BVVL syndrome and are much less common than SLC52A3.[6]

The clinical presentation consists of sensorineural hearing loss, bulbar palsy, respiratory compromise, limb weakness, facial palsy, neck and shoulder weakness, upper motor neuron signs, and ataxia. Ocular abnormalities, autonomic dysfunction, epilepsy, and mental retardation have been reported infrequently.[7] Upper cranial nerve involvement (II–VI) is less common. The age of presentation is variable. Children presenting before 3 years of age present more commonly with respiratory distress, bulbar palsy (both 86%), muscle weakness, and hearing loss (both 67%).[1] It is hypothesized that the children who present very young also succumb early, thus precluding the development of hearing loss.[8] A trigger in the viral form has been thought to precipitate the disease in some cases.[9] Patients with SLC52A2 mutations show a different phenotype consisting of sensorineural hearing loss, early-onset sensory ataxia and nystagmus, optic atrophy, and weakness of neck extension and upper limbs.[7]

The course and prognosis are variable and are also influenced by the initiation of riboflavin treatment. Anand et al.[2] reported improvement in a patient with BVVL syndrome with high-dose riboflavin. A review by Bosch et al.[1] revealed survival in all patients who received riboflavin treatment. In the patients presenting before 3 years of age, mean time to death without riboflavin treatment was around 10 months as compared to around 13 years in children presenting from 3 to 18 years of age. Thus, genetically similar

### DISCUSSION

BVVL syndrome is an inherited motor neuron disease originally described by Brown, Vialetto, and Van Laere. It is a very rare disorder with less than a hundred patients described till date. The inheritance of the disease was debated for a long time,[3] but recent insights into the genetic mechanism have established the autosomal-recessive inheritance. Green et al.[4] identified C20orf54, also known as SLC52A3, encoding for intestinal riboflavin transported protein (hRFT2), as the candidate gene in BVVL syndrome. Bosch et al.[9] reported the same mutation in patients with FLS, thus establishing the continuity of these genetically homogenous disorders with clinical heterogeneity.

SLC52A3 mutations show a
patients may harbor pathophysiological differences resulting in earlier and more severe disease.

Our patient presented with a clinical feature compatible with BVVL syndrome. The diagnostic possibility was considered early in the course and a riboflavin trial was given. She showed improvement with high-dose riboflavin, with resolution of bulbar and oculomotor palsy and respiratory compromise. Her hearing loss has persisted although there is some subjective improvement. She has been started on speech therapy. Persistence and treatment of hearing loss after riboflavin has not been well studied in patients with BVVL, and results of cochlear implants have not been reported to be encouraging.[10] It has been found that patients with earlier onset have poorer outcomes in the absence of treatment. Early suspicion and early institution of treatment probably helped to reverse many manifestations of the disease in this patient, although the recovery is incomplete. Further follow-up will help to determine the effect of riboflavin supplementation.

**Conclusion**

The revelation of genetic basis of BVVL syndrome has simplified the diagnosis and it has been unified with FLS as a single disease entity.[5] A simple and effective treatment in the form of riboflavin supplementation is being used. This makes it critical to consider the diagnosis early in patients presenting with relevant symptoms. Lifelong riboflavin treatment is essential and genetic screening should be performed for families. Research into the pathophysiological mechanisms will help understand the varied clinical spectrum, natural history, and varying response to riboflavin as well as the dose and appropriate trial period.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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