CASE REPORT

Brown-Vialetto-Van Laere syndrome: a novel diagnosis to a common presentation

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SUMMARY

Brown-Vialetto-Van Laere syndrome (BVVLS) or riboflavin transporter deficiency (OMIM 211530) is a rare treatable autosomal recessive neurodegenerative disorder. This condition is associated with progressive pontobulbar palsy. We describe the clinical course of a 16-month-old boy with BVVLS and a novel homozygous mutation from Pakistan. Our patient presented with stridor and respiratory insufficiency. Hearing loss which is the most common sign of this condition was absent, making it an unusual presentation of BVVLS. His examination revealed ptosis and tongue fasciculation. His riboflavin receptor mutational analysis showed the homozygous mutation in the *SLC52A3* gene. Per oral riboflavin was administered, and subsequently, he was able to be weaned off the ventilator. Now the child is improving and attaining developmental milestones.

BACKGROUND

Brown-Vialetto-Van Laere syndrome (BVVLS) or riboflavin transporter deficiency type 2 (OMIM 211530) is a rare autosomal recessive neurodegenerative disorder, first reported in 1894 by Charles Brown. He described it as an 'infantile' form of amyotrophic lateral sclerosis with associated hearing loss, and subsequently, Vialetto in 1936 and Van Laere in 1966 reported similar findings.^{1 2} In 2010, mutations in riboflavin transporter (RFVT) genes, *SLC52A2* (RFVT2) and *SLC52A3* (also known as *C20orf54* coding for RFVT3) genes, were identified as a cause of BVVLS.³ Of these, RFVT2 is mostly expressed in the brain, whereas RFVT3 is mostly expressed in the small intestine.⁴

To date, 34 patients with molecular diagnosis of BVVLS caused by mutations in the *SLC52A3* gene have been reported.⁴ The age of onset extends from infancy to adolescence with an average age in the second decade. BVVLS is associated with sensorimotor and cranial neuropathy which results in progressive pontobulbar palsy, respiratory compromise and involvement of the cranial nerves VII to XII being the usual presentation with or without hearing loss.⁵

High-dose riboflavin supplementation has shown to significantly improve clinical outcomes.^{4 6} We present a case of BVVLS from Pakistan with a novel homozygous *SLC52A3* mutation.

CASE PRESENTATION

A 16-month-old male child presented with fever, cough and breathing difficulty. He developed

stridor at the age of 9 months for which work-up including examination under anaesthesia (EUA) had been done, which was inconclusive. Later, he presented to the emergency department again with stridor and severe respiratory distress resulting in emergent tracheostomy tube placement. His distress improved, and he was discharged home. His prenatal, perinatal and postnatal periods were uneventful, and his development was normal. His parents were consanguineous, and there was a history of early neonatal death in the eldest two siblings, followed by two siblings who were healthy (figure 1).

On general examination, he was irritable, with tachypnoea and tachycardia, and his oxygen saturation was 90% at 5 L oxygen. There were bilateral crepitations in the chest, while his cardiovascular examination was normal. Motor examination showed normal bulk, tone, power and reflexes in all four limbs. On cranial nerve examination, there were bilateral ptosis (right>left) and tongue fasciculation. His palatal movements were poor, while the uvula was centrally placed. Initial impression of pneumonia was made and managed.

INVESTIGATIONS

Investigations including electrolytes, calcium, magnesium, creatine phosphokinase, plasma ammonia, lactate and cholinesterase levels and echocardiography were all within normal ranges. Chest X-ray was suggestive of pneumonia. An electrodiagnostic study including repetitive nerve stimulation (RNS) was performed at frequencies of 3, 5 and 15 and post 15 Hz that showed an electrodecremental response in the right accessory and right axillary nerves. This supported the diagnosis of a postsynaptic neuromuscular junction disorder, and myasthenia gravis was considered as the provisional diagnosis. Pyridostigmine was, therefore, started, but his clinical condition deteriorated after few days, warranting mechanical ventilation. The RNS was again repeated, and additional after discharges were recorded on stimulation of the left median and posterior tibial nerve, leading us to consider slow-channel congenital myasthenic syndrome. Thus, pyridostigmine was substituted by fluoxetine, but he was unable to be weaned off from the ventilatory support. MRI brain was done to identify a brainstem structural defect, this was also normal. He underwent an EUA to check for his vocal cords movements which were normal, but a small nodule was identified and excised, the histopathology report was normal. The cerebrospinal

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Figure 1 Pedigree of the described child: affected individual (proband) is indicated by black shading and symbol p. Asterisk (*) used to denote individuals undergoing genetic work-up. DOL: day of life.

fluid analysis was also done to rule out infection which was also normal. Madras motor neuron disease (MMND) and BVVLS were considered after more common diagnoses were excluded, and relevant molecular work-up was sent. His molecular diagnostics carried out abroad identified homozygous missense mutation in the *SLC52A3* gene: a c.106G>A substitution in exon 2 resulted in the missense mutation p.Glu36Lys, while both of his parents were heterozygous carriers. His acylcarnitine profile was normal.

DIFFERENTIAL DIAGNOSES

Underlying differential diagnoses of myasthenia, cranial nerve palsy, brainstem encephalitis, MMND and Fazio-Londe syndrome were considered due to ptosis, tongue fasciculation, poor palatal movements and stridor with no involvement of the limbs.

TREATMENT

Riboflavin 25 mg per kg per day was started empirically. He showed improvement in his ventilator requirements and ptosis within a week of riboflavin therapy. He was discharged on the home ventilator and supportive care. He did not undergo brainstem auditory evoked response (BAER) as there was no apparent hearing loss, and it was difficult to move him to the neurophysiology department. Within few months, he was weaned off the home ventilator.

OUTCOME AND FOLLOW-UP

On the last follow-up which was at 3 years (2 months back), he had started walking with support and taking orally. We plan to perform BAER in the future to assess the involvement of the eighth cranial nerve as there are case reports to suggest that hearing loss may occur later in life.⁷

DISCUSSION

BVVLS is characterised by pontobulbar palsy with respiratory distress to be the most common non-neurological finding occurring due to diaphragmatic and bulbar weakness. Although *SLC52A3* is one of the several genes implicated, the exact molecular basis of pathogenesis is unknown.⁸ Previous work has revealed strong links between mutations in two genes (*SLC52A2* and *SLC52A3*) and BVVL syndrome, both of which encode RFTs.^{1 7 8} Similar mutation was reported by Malafronte *et al* in one of his cases, who reported neuropathological and immunohistochemistry findings of three individuals with BVVLS. This was a 12-year-old boy diagnosed with BVVLS who had presented with sensorineural hearing loss at the age of 5 years.⁵ Green *et al* also published the characteristics of seven families with BVVLS. One of the patients had the same mutation as in our patient but with heterozygosity. This boy presented in the second decade of life with progressive muscle weakness with truncal ataxia and had multiple peripheral neuropathies, he was reported alive at 57 years.¹

The differentials include MMND and other complex motor neuron diseases such as Nathalie syndrome, Fazio-Londe syndrome and Boltshauser syndrome. It has been argued that as BVVL, Fazio-Londe syndrome, MMND and other early-onset motor neuron disease have remarkable similarities, it is plausible that these share a common pathogenesis pathway.⁹ MMND differs from BVVL by being more sporadic, with the lack of cranial nerve involvement as well as the genetic mutation.⁵

Dipti *et al* reported four siblings showing features of pontobulbar palsy with a mixed spinal and upper motor neuropathy and variable deafness. Two of them were of the same age as our patient who is 16 months with no hearing loss.¹⁰ Although hearing loss has often been observed to precede other neurological manifestations, there are case reports that suggest of the existing variation in the age of presentation as well as in the severity and duration of hearing loss and the neurological

disease.^{7 11 12} Chaya *et al* have also described a similar presentation in an 11-month-old infant with respiratory failure without hearing loss.¹³ There is evidence to show that life expectancy improves after active management.¹

This case illustrates that BVVL can present in the absence of any obvious auditory impairment and emphasises the importance of considering BVVL in the differential diagnosis of patients with a progressive onset of paralysis as it is a treatable condition.

Learning points

- BVVLs can be attributed as the treatable type of motor neuron disease.
- There is variability in the phenotypical presentation of BVVL, and sensorineural hearing loss might not always be the earlier symptom as the case with our patient.
- We emphasise the importance of correctly diagnosing the disease, as its treatment is relatively benign and will stop progression of the disease and may even reverse it.

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