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# Remarkable motor recovery after riboflavin therapy in adult-onset Brown–Vialeto–Van Laere syndrome

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## ABSTRACT

The clinical diagnosis of Brown–Vialeto–Van Laere syndrome in this woman with rapidly progressive pontobulbar palsy led to empirical high-dose oral riboflavin (1200 mg/day) therapy. This resulted in a dramatic improvement in her motor function from being anarthric, dysphagic, tetraparetic and in ventilatory failure to living independently with mild dysarthria and distal limb weakness. DNA sequencing of the *SLC52A3* gene found compound heterozygous C-terminus mutations, V413A1/D461Y, consistent with recent reports of mutations within the riboflavin transporter genes (*SLC52A2* and *SLC52A3*) in this condition. Early diagnosis and empirical riboflavin therapy can lead to major motor recovery in this condition, that can be sustained with long-term maintenance therapy.

## BACKGROUND

Brown–Vialeto–Van Laere syndrome (BVVL) is characterised by progressive pontobulbar palsy, typically preceded by sensorineural deafness. In its most severe form, death occurs in infancy. Milder phenotypes do occur, but rarely present past the third decade.<sup>1 2</sup> Despite its first description in 1894, only recently has an understanding of the genetic and pathophysiological basis for BVVL opened the opportunity for therapeutic intervention. We report the remarkable motor recovery after riboflavin therapy in a 35-year-old woman with BVVL syndrome.

## CASE PRESENTATION

A 35-year-old British woman presented with a 6-week history of progressive dysphagia, dysphonia, dyspnoea, weight loss, gait disturbance and arm weakness. On admission, she could not speak or swallow and needed the assistance of two people to walk. She had developed moderate deafness over many years, but had no

other neurological symptoms. Eight weeks before admission, she had separated from her husband, and the quality of her diet had significantly deteriorated.

Examination on admission found broken ocular pursuit in all directions, bilateral lower motor neurone facial weakness and absent jaw jerk. Her hearing was poor bilaterally, her cough was very weak and palatal elevation was greatly reduced. Her sternocleidomastoid and trapezius strength were normal but her tongue was severely weak, wasted and fasciculating. Tone was increased at the right elbow. The upper and lower limbs were symmetrically weak, with strength from grade 1–2 distally to grade 3–4 proximally. All limb reflexes were pathologically brisk with crossed adductors but both plantar responses were flexor. Sensation was normal and coordination was difficult to assess with the severe limb weakness.

## INVESTIGATIONS

Arterial blood gases on admission showed a pH of 7.47, PCO<sub>2</sub> of 5.9 kPa (5–6), PO<sub>2</sub> of 14.3 kPa (11–12.5) and a bicarbonate of 30.6 mmol/L (21–28). Her forced vital capacity was 0.7 L/min and her sniff nasal inspiratory pressure was reduced at –22 cmH<sub>2</sub>O (predicted –87). Nasendoscopy found bilateral vocal cord paralyses. Nerve conduction studies and central motor conduction velocities were normal. Electromyography identified acute denervation in both tibialis anterior muscles and chronic denervation findings in her right first dorsal interosseous muscle. Audiometry showed a mixed sensorineural and conductive hearing loss bilaterally. Brainstem auditory evoked potentials were performed but significant artefact precluded accurate interpretation.



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Ophthalmological assessment excluded optic atrophy. A nutritional assessment of the weeks leading up to her neurological decline identified a reduced intake of riboflavin-rich foods, such as cereals and dairy products, as well as weight loss from 57 kg to 45 kg. Her estimated dietary riboflavin intake (0.46–0.72 mg per day) over this period was below the recommended level (1.1 mg per day) for her age and sex.

Serum anti-ganglioside, anti-nicotinic acetylcholine receptor, antinuclear and anti-neutrophil cytoplasmic antibodies were all negative. MR scan of brain was normal. Cerebrospinal fluid (CSF) analysis was normal apart from a mildly elevated protein at 635 mg/L (250–450). CSF viral, Lyme and oligoclonal band tests were negative. Serum lead concentration was normal. Plasma free carnitine, acylcarnitine and riboflavin levels were normal but these assays were performed after she had started treatment. DNA sequencing of the *SLC52A3* gene found compound heterozygous mutations, c.1237T>C/V413A and c.1381T>G/D461Y, in exon 5.

### DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis for her subacute lower brainstem syndrome was broad. This included inflammatory (eg, Guillain-Barré/Miller Fisher syndrome), infective (eg, Listeria or tuberculous meningitis), autoimmune (myasthenia gravis) or toxic (botulism, lead) causes.

### TREATMENT

On admission, she was monitored in the High Dependency Unit and received oxygen, intravenous immunoglobulin, high-dose corticosteroids and nutritional supplements via a nasogastric tube. Nineteen days after admission, we made the clinical diagnosis of BVVL and started high-dose oral riboflavin at 1200 mg/day, initially via nasogastric tube and subsequently via radiologically inserted gastrostomy.

### OUTCOME AND FOLLOW-UP

Her motor functions steadily improved over 5 weeks such that at discharge she could walk short distances unaided with ankle-foot orthoses for bilateral foot drop and mild weakness of her intrinsic hand muscles. She was no longer breathless on mild exertion and her lung function had improved (forced vital capacity 2.44 L, 83% of predicted). Mild dysphonia and dysarthria persisted due to moderate vocal cord and facial muscle paresis. She has remained stable 3 years after the diagnosis, owing to the continued riboflavin therapy (initially 400 mg three times daily, slowly weaned to 200 mg daily) and improved nutrition.

### DISCUSSION

#### Clinical characteristics

The age of onset of BVVL is typically between infancy and the third decade.<sup>2–3</sup> Our patient presented in her

fourth decade, much older than the reported mean age of presentation (4.1–8.2 years).<sup>3–4</sup> The clinical presentation is highly variable and, as well as the characteristic features of lower cranial nerve involvement (nerves VIII–XII), can include lower and upper motor neurone limb signs, respiratory compromise, facial weakness, sensory ataxia and optic atrophy.<sup>2–4</sup> Half of the cases are familial, arising with an autosomal recessive pattern of inheritance with homozygous or compound heterozygous mutations.

#### The riboflavin transporter genes

The underlying genetic cause of BVVL was identified in 2010. The first report described seven patients with homozygous mutations and one compound heterozygote affecting exons 2, 3 and 5 of the riboflavin transporter gene *SLC52A3* (aka *C20orf54* or *RFVT3*).<sup>1</sup> A novel homozygous pathogenic mutation in a related riboflavin transporter gene *SLC52A2* (aka *RFVT2*) was found in a Lebanese kindred.<sup>5</sup> Further mutations in this gene have subsequently been described in 18 child-onset cases.<sup>6</sup> Bosch *et al*<sup>4</sup> have summarised the published mutations in *SLC52A2* and *SLC52A3* up until 2012.

*SLC52A2* and *SLC52A3* genes code for the human riboflavin transporters (*RFVT*) 2 and 3, respectively. A third member of the family, *SLC52A1* (coding for *RFVT1*), has not yet been shown to harbour pathogenic mutations in BVVL itself, but was abnormal in a case of maternal riboflavin deficiency.<sup>7</sup>

Our patient was compound heterozygous for the *SLC52A3* gene (V413A/D461Y). This evolutionarily conserved gene contains five exons and eleven predicted transmembrane helices.<sup>1</sup> The V413A mutation has previously been reported in a compound heterozygous pattern. This patient had a milder phenotype, manifested by disease onset in the second decade, an initial presentation of peripheral neuropathy and untreated survival into the sixth decade.

The D461Y mutation has been reported in 36 European ExAC samples in a heterozygous manner, but has not been previously reported to cause BVVL. Its pathogenicity is endorsed by its absence in 900 of our screened controls and predicted ‘damaging’ effect using FATHMM prediction software (see table 1). Thus, the D461Y mutation, similar to other pathological *SLC52A3* mutations (eg, F457L, N21S), occurs at low frequencies in the general European population in the heterozygous state. We suggest that it causes BVVL when either homozygous or, as in this case, compound heterozygous with another known pathogenic variant.

#### Genotype–phenotype relationship

The clinical phenotypes related to *SLC52A2* and *SLC52A3* mutations are distinguishable. The *SLC52A2* mutation phenotype is associated with an ataxic gait as the presenting symptom, with a higher likelihood of sensorimotor neuropathy, optic atrophy, weakness of the upper limbs and neck and late-

**Table 1** Characteristics of compound heterozygous mutations found in our patient in the *SLC52A3* gene

Exon	Nucleotide	Amino acid change	Reference	Present in 900 controls	Present in 150 sALS	FATHMM prediction
5	c.1237 T>C	p.V413A	rs267606687 <sup>1</sup>	No	No	Damaging
5	c.1381T>G	p.D461Y	rs140360713	No	No	Damaging

FATHMM, functional analysis through hidden Markov models (prediction software for the functional consequences of coding and non-coding variants); sALS, sporadic amyotrophic lateral sclerosis.

onset deafness.<sup>6</sup> In contrast, people with *SLC52A3* mutations typically present with sensorineural deafness, followed by pontobulbar palsy, respiratory compromise and generalised limb weakness.<sup>4</sup> It has been suggested that the umbrella term of BVVL syndrome be renamed ‘riboflavin transporter deficiency, types 2 and 3’, to reflect better the underlying patho-aetiology and distinct clinical phenotypes in this condition.<sup>4 6</sup>

#### Nutritional trigger

The metabolic hallmark of BVVL is abnormal mitochondrial fatty acid oxidation and branched-chain amino acid catabolism. This stems from an acquired functional riboflavin deficiency, owing to defective riboflavin transporter activity in the gut and/or the brain. It is possible to detect the biochemical defect by a reduction in plasma riboflavin, flavin mononucleotide or flavin adenine dinucleotide concentration, with an abnormal plasma acylcarnitine profile (selective increase in short- and medium-chain fatty acid plasma concentrations).<sup>8</sup> However, a recent report suggests only 58% of genetically confirmed patients with BVVL had abnormal acylcarnitine profiles.<sup>3</sup> Additionally, urinary organic acid profiles can resemble those seen in the multiple acyl-CoA dehydrogenation defect.

Our patient developed symptoms after an abrupt change in the quality of her diet 8 weeks before admission. This very likely triggered motor neuronal dysfunction and degeneration, as her genetic defect left her vulnerable to a low dietary intake of riboflavin.

#### Riboflavin therapy in BVVL

The general management of patients with BVVL includes supportive measures, such as nasogastric tube or gastrostomy insertion to ensure adequate nutrition, and non-invasive ventilation to overcome any neurogenic respiratory compromise. Corticosteroids and immunoglobulins do not help.<sup>2</sup>

Riboflavin treatment (reported dose range 7–60 mg/kg/day) can normalise the metabolic abnormalities detected in BVVL and lead to clinical stabilisation and improvement in most people.<sup>3 4 9 10</sup> Currently there is no recommended metabolic biomarker to assess response to treatment. Early treatment is encouraged as soon as the diagnosis is considered, as some neurological deficits, in particular diaphragmatic paralysis, may be irreversible. Once our patient started oral riboflavin, she made a remarkable recovery in motor

function (see online supplementary file/video). Her clinical improvement has been sustained for 3 years with regular dietician input and a weaning dose of maintenance riboflavin supplementation (minimum 200 mg daily).

#### Key points

- ▶ Brown–Vialeto–Van Laere syndrome syndrome is a rare genetic neurological condition, often presenting with subacute pontobulbar palsy on a background of sensorineural deafness.
- ▶ Intervention with riboflavin and improved nutrition can reverse potentially lethal motor weakness leading to a sustained clinical recovery, highlighting the importance of early diagnosis.
- ▶ Compound heterozygous mutations at the C-terminus of the *SLC52A3* gene may preserve partial riboflavin transporter function and explain the late presentation following dietary deficiency.

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