Child Neurology: Brown-Vialetto-Van Laere syndrome

Dramatic visual recovery after delayed riboflavin therapy

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Brown-Vialetto-Van Laere syndrome (BVVL) is a rare, progressive neurodegenerative disease with fewer than 100 cases reported in the literature. It is characterized by pontobulbar palsy and sensorineural hearing loss.1 The age at onset varies from infancy to early adulthood, commonly presenting with cranial nerve VII–XII palsies and deafness. Other findings include gait ataxia, limb weakness, optic atrophy, epilepsy, and respiratory compromise.1 The genetic etiology of BVVL has recently been linked to mutations affecting the riboflavin transporter genes SLC52A2 and SLC52A3, which code for human riboflavin transporters RFVT2 and RFVT3, respectively.2 Consequently, several studies have reported improved clinical outcomes with riboflavin supplementation in patients confirmed to have mutations in the SLC52A2 and SLC52A3 genes.3–7 In this report, we describe a case of BVVL in a 6-year-old girl with dramatic visual recovery and neurologic improvement after delayed initiation of riboflavin supplementation. Consent was obtained from the child’s parents.

Case report

A 6-year-old girl was seen in the pediatric ophthalmology clinic after failing a vision screening test. Her family reported increasing clumsiness over the past year, resulting in frequent falls. On examination, her best-corrected visual acuity was 20/150 in each eye monocularly and 20/100 binocularly. She also was noted to have a small-angle exophoria with decreased stereopsis. The remainder of her ophthalmologic examination was unremarkable.

Visual evoked potential (VEP) testing demonstrated reduced amplitudes (~60% of normal) and prolonged latencies (~40 ms increased) on flash VEP and reduced acuity on spatial-sweep VEP testing. MRI of the patient’s brain and orbits revealed no intracranial abnormalities, but the optic nerves and tracts appeared mildly decreased in size. Based on these findings, the presumed diagnosis was bilateral optic nerve hypoplasia.

Approximately 13 months after initial presentation, the patient presented to the emergency department with progressive worsening in fine and gross motor skills. Physical examination demonstrated decreased visual acuity of 20/400 bilaterally and horizontal nystagmus in primary gaze that dampened with directional gaze. Sensory testing was normal and strength testing (table 1) was decreased for age with +1 tendon reflexes. She had bilateral dysmetria and prominent ataxia. She was born to healthy, nonconsanguineous parents without relevant family history, and had one healthy 4-year-old brother.

Laboratory testing included normal thyroid function testing, serum lactate and pyruvate ratio, and serum ammonia levels. Total plasma carnitine was slightly low for age at 34 μmol/L. Quantitative serum acylcarnitine profile was normal. Serum amino acid profile exhibited nonspecific abnormalities including mildly low glutamine and arginine levels and slightly
The ophthalmologist with vision loss. 1 When the patient heterozygous variants in SLC52A2. The by whole-exome sequencing, which identi-

Foot dorsiflexion 18/18a 27/31
Knee flexion 19/22a 25/26
23/21a 34/32
Arm flexion 3/3a 7/7a
Hip flexion 0/0.5a 1/2a
13/12a 15/15a
Arm extension 23/23a 32/34
Knee extension 23/21a 34/32
Knee flexion 19/22a 25/26
Foot dorsiflexion 18/18a 27/31

a Values that are low for age based on clinical experience (P.T.G.).

The second is a maternally inherited variant designated as c.1140delG:p.Leu381CysfsX9, which creates a frameshift starting with codon leucine 481 to cysteine, and results in a premature stop codon at position 9 of the new reading frame.

Ocular examination 18 months after initiation of riboflavin showed improvement in visual acuity to 20/20 bilaterally and complete resolution of nystagmus. Flash VEP testing demonstrated improved amplitudes (~82%, right eye; ~74%, left eye) and latencies in both eyes. Neurologic examination demonstrated improved coordination, gait, and muscle strength. Muscle strength measurements performed pre-
treatment and after 12 months of riboflavin treatment are shown in table 1. A formal hearing study showed no impairment.

Of note, subsequent targeted genetic testing also confirmed the same compound heterozygous variants in the patient’s 4-year-old brother who exhibited mild symptoms including tremor when holding heavy objects and occasional choking episodes. At 2 years of age, he was found to have a significant hyperopic refractive error (~+7.0 diopters) causing a 30-

Discussion

BVVL syndrome is a treatable genetic condition caused by mutations affecting the genes that code for riboflavin transporters. Riboflavin is absorbed in the small intestine by human riboflavin transporters RFVT1 and RFVT3, and is exchanged in the brain via a third transporter, RFVT2. Riboflavin is the precursor for essential flavo-coenzymes (flavin mononucleotide [FMN] and flavin adenine dinucleotide [FAD]). FMN and FAD are important coenzymes that catalyze the various electron transfer reactions involved in fatty acid

Table 1 Quantitative muscle strength test results demonstrating muscle strength in pounds before and after treatment with riboflavin

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Before treatment (right side/left sides) in pounds</th>
<th>After treatment (12 mo) (right side/ left sides) in pounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder abduction</td>
<td>6/8a</td>
<td>10/11</td>
</tr>
<tr>
<td>Arm flexion</td>
<td>3/3a</td>
<td>7/7a</td>
</tr>
<tr>
<td>Arm extension</td>
<td>13/12a</td>
<td>15/15a</td>
</tr>
<tr>
<td>Wrist extension</td>
<td>0/0.5a</td>
<td>1/2a</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>23/23a</td>
<td>32/34</td>
</tr>
<tr>
<td>Knee extension</td>
<td>23/21a</td>
<td>34/32</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>19/22a</td>
<td>25/26</td>
</tr>
<tr>
<td>Foot dorsiflex</td>
<td>18/18a</td>
<td>27/31</td>
</tr>
</tbody>
</table>

BVL = Brown-Vialletto-Van Laere syndrome; CMAP = compound muscle action potential; FAD = flavin adenine dinucleotide; FMN = flavin mononucleotide; VEP = visual evoked potential.

Glossary

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oxidation. Interestingly, recent work has identified mutations in the genes SLC52A2 (coding for RFVT2) and SLC52A3 (coding for RFVT3) as the cause of many cases of BVVL syndrome.2,3 As a result of this discovery, treatment with high-dose riboflavin supplementation has significantly improved morbidity and mortality rates in a condition that was previously often fatal due to respiratory failure. Furthermore, Foley et al. demonstrated an increase in riboflavin levels in 9 out of the 10 patients assessed before and after initiation of riboflavin therapy.4

A review of the literature revealed 47 cases where riboflavin treatment was initiated; however, only 38 reports documented the clinical treatment response (24 RFVT2 cases; 14 RFVT3 cases).3–9 Clinical improvement was reported in 28 patients (74%) and stabilization without progression was documented in the remaining 10 patients (26%).

In regards to the effect of riboflavin treatment on optic atrophy, only 3 of the 17 cases with optic atrophy provided documentation on specific visual function change after treatment.6–9 A previously reported case of a 2-year-old girl with the SLC52A2 mutation showed visual acuity improvement to 20/300 after 6 months of riboflavin treatment.9 Mild visual improvement after initiating treatment was also seen in 2 patients with SLC52A2 mutations (11-year-old girl; 2-year-old boy).4 In this report, we describe a 6-year-old girl who exhibited remarkable visual recovery from 20/400 to 20/20, as well as improvement on VEP studies. To our knowledge, this could be one of the most dramatic recoveries in visual function reported after treatment with riboflavin.

The magnitude of visual recovery raises many questions regarding the downstream cellular effect of the SLC52A2 and SLC52A3 mutations. Variable neurohistopathologic findings of neuronal loss, myelinated fiber loss, and gliosis in the brainstem cranial nerve nuclei and anterior horns of the spinal cord with accompanying nerve root atrophy were reported in 2 patients with genetically confirmed SLC52A3 gene mutations who were not treated with supplemental riboflavin.10 Given the magnitude of visual improvement exhibited in the present case, the mutation in BVVL syndrome likely does not

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### Table 2 Nerve conduction and EMG study results showing evidence of non-length-dependent axonal neuropathy

<table>
<thead>
<tr>
<th>Nerve/sites</th>
<th>Latency, ms</th>
<th>Amplitude, mV</th>
<th>Segments</th>
<th>Distance, mm</th>
<th>Latency diff</th>
<th>Velocity, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>R median—APB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>4.69</td>
<td>0.8</td>
<td>Wrist—APB</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>7.97</td>
<td>0.7</td>
<td>Elbow—wrist</td>
<td>148</td>
<td>3.28</td>
<td>45.1</td>
</tr>
<tr>
<td>R peroneal—EDB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>4.58</td>
<td>4.4</td>
<td>Ankle—EDB</td>
<td>100</td>
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<td></td>
</tr>
<tr>
<td>Fib head</td>
<td>9.22</td>
<td>6.3</td>
<td>Fib head—ankle</td>
<td>223</td>
<td>4.64</td>
<td>48.1</td>
</tr>
</tbody>
</table>

Pops fossa—ankle

<table>
<thead>
<tr>
<th>Nerve/sites</th>
<th>Onset lat, ms</th>
<th>Peak lat, ms</th>
<th>Amplitude, μV</th>
<th>Onset diff, ms</th>
<th>Distance, ms</th>
<th>Cond vel, m/s</th>
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</thead>
<tbody>
<tr>
<td>SNC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>L median, ulnar—digits 2, 4, 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median digit 2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>140</td>
<td>NR</td>
</tr>
<tr>
<td>R sural—ankle (calf)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>140</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th>Insertional activity</th>
<th>Spontaneous Activity</th>
<th>MUAP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L deltoid (middle)</td>
<td>Normal</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>L fist dorsal interosseous</td>
<td>Normal</td>
<td>2+</td>
<td>2+</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: Amp = amplitude; APB = abductor pollicis brevis; Cond vel = conduction velocity; EDB = extensor digitorum brevis; Fasc = fasciculation; Fib = fibrillation; lat = latency; MNC = motor nerve conduction; MUAP = motor unit action potential; NR = no response; PSW = positive sharp wave; Sl Incr = slight increase; SNC = sensory nerve conduction.
result in an isolated axonal loss. We hypothesize a combined axonal neuropathy with coinciding reactive demyelination as a result of microglia and macrophage infiltration. However, initiation of riboflavin supplementation may halt further axonal death and reduce additional microglia- and macrophage-induced inflammation. Consequently, areas with myelin loss may undergo remyelination, producing a recovery in neuronal function as exhibited in our patient.

It is critical to consider BVVL syndrome in the differential diagnosis in patients presenting with cranial neuropathies, balance difficulties, and sensorineural hearing loss. Treatment with riboflavin supplementation should be initiated immediately while awaiting genetic confirmation. In addition, extensive genetic counseling should be provided to affected families, and genetic screening for at-risk family members should be recommended to identify any asymptomatic siblings with positive molecular results who may benefit from prophylactic riboflavin treatment.

**Author contributions**

A.K. Bamaga: data collection, literature review, writing the manuscript. R.N. Maamari: data collection, literature review, writing the manuscript. S.M. Culican: data interpretation, critical revision of the manuscript. M. Shinawi: data interpretation, critical revision of the manuscript. P.T. Golumbek, data interpretation, critical revision of the manuscript.

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**Disclosure**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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