Many genes in which mutations cause motor neuron disorders have been identified, helping to provide early diagnosis or prognosis to patients; but there is still no cure for any of these pathologies. Only symptomatic and supportive therapies can provide better quality of life and may extend survival in the most severe cases, such as amyotrophic lateral sclerosis. In this issue of Brain, Foley and colleagues present a multicentre study on a promising and potentially life-saving treatment for Brown-Vialetto-Van Laere syndrome documented with genetic and clinical studies (Foley et al., 2013). This severe neurodegenerative disorder was first described as familial amyotrophic lateral sclerosis with onset in infancy (Brown, 1894). After Vialetto (1936) and Van Laere (1966) reported on this rare disorder, the disease became generally known as Brown–Vialetto–Van Laere syndrome (BVVL). With an increasing number of patients with BVVL being reported in the literature (Bosch et al., 2012), it became clear that the main clinical feature of this syndrome is progressive bulbar palsy often preceded by sensorineural deafness, with facial weakness and respiratory failure. The condition is genetically heterogeneous with mainly autosomal recessive inheritance, but dominant forms also occur. The female to male prevalence is 3:1, with boys being more severely affected than girls. Patients have variable age at onset (first to third decade), and those with early-onset tend to have rapid disease progression but survival can be prolonged with active management of respiration and weakness.

The first genetic studies were performed in a consanguineous family in which patients were excluded for mutations in the survival of motor neuron (SMN1) and neuronal apoptosis inhibitory protein (NAIP) genes associated with spinal muscular atrophy (Mégarbané et al., 2000). More recently, 44 patients were screened and excluded for SMN1 deletions, superoxide dismutase 1 (SOD1) gene mutations, and for common mitochondrial mutations and deletions (Johnson et al., 2012). Mégarbané and colleagues (2000) indicated that ‘the identification of the BVVL gene by a whole genome screening is likely to provide more information about the pathogenesis, and that pooling such families worldwide is the only chance to achieve it’. Indeed, homozygosity mapping assigned a first locus on chromosome 20p13 and a second one on 8q24.3 (Green et al., 2010; Johnson et al., 2012). Subsequent Sanger sequencing of positional candidate genes or exome sequencing identified homozygous or compound heterozygous mutations in SLC52A3 (C20orf54, RFT2) and SLC52A2 (RFT3), respectively, genes coding for riboflavin transporters (Green et al., 2010; Johnson et al., 2012). In these genetic studies no mutations were reported in another riboflavin transporter gene, SLC52A1 (RFT1); however, a deletion was previously reported in a single patient presenting with clinical and biochemical features of multiple acyl-CoA dehydrogenase deficiency (Ho et al., 2011). The patient’s clinical condition dramatically improved within 24h of commencement of therapy including oral riboflavin (Ho et al., 2011).

Foley et al. (2013) summarize the molecular findings of 78 familial and isolated patients with BVVL from 18 countries worldwide. In 18 patients, recessive mutations were found in the SLC52A2 riboflavin transporter, suggesting that SLC52A2 mutations are a frequent cause for this childhood neuronopathy. These patients share the core BVVL phenotype with a rapidly progressive axonal sensory and motor neuropathy, hearing loss, optic atrophy and respiratory insufficiency (Foley et al., 2013). In this study no mutations were found in SLC52A1 and SLC52A3.

The SLC52A1, -A2 and -A3 genes are members of the solute carrier family 52, encoding human riboflavin transporters (RTF1, RTF3 and RTF2, respectively), and are localized within the cytoplasm and endosomal vesicles. The SLC52A1 and SLC52A3 proteins are highly expressed in the small intestine, testis and placenta. The SLC52A2 protein is also present in the small intestine, however, its expression is more pronounced in foetal brain and spinal cord (Yao et al., 2010). Biochemical and cellular studies in BVVL patient skin fibroblasts with mutant SLC52A2 revealed concomitant reduction of SLC52A1 and SLC52A3 protein levels. This reduction was also detected in leucocytes and fibroblasts obtained from the patient’s parents who were heterozygous for a mutant SLC52A2 allele. This finding suggests functional cooperation between the riboflavin transporters (Ciccolella et al., 2013).
Riboflavin (vitamin B2) is essential for the biosynthesis of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), important cofactors for several metabolic processes. More specifically, these flavins contribute to oxidative stress by forming parts of redox enzymes, which are flavoproteins involved in signal transduction, apoptosis and DNA repair. It is therefore possible that SLC52A2, coding for the riboflavin transporter in the nervous system, plays an important function in neuronal maintenance and homeostasis. Homozygous or compound heterozygous mutations in the SLC52A2 riboflavin transporter may thus affect energy pathways in motor neurons thereby causing BVVL syndrome. Motor neurons are highly specialized cells demanding optimal energy metabolism, and mis- or disregulation of essential proteins as the riboflavin transporters may thus also be involved in several other motor neuron diseases including amyotrophic lateral sclerosis, spinal muscular atrophy, and distal hereditary motor neuropathies. As humans cannot synthesize vitamin B2, its supply depends on food intake which is secured by the riboflavin transporters. Riboflavin transport itself can be assessed by a radiochemical method. The uptake of \(^{3}H\)-riboflavin in primary fibroblasts derived from patients with BVVL and control subjects was recently studied by Ciccolella et al. (2013), and experimental cell lines transiently expressing mutant and wild-type SLC52A2 gene constructs were also tested by Foley et al. (2013) in this issue of Brain. The uptake of radiolabelled riboflavin increased in a time-dependent manner in all samples; however, the riboflavin transporter activity was clearly reduced but not absent in patient or mutant cells with respect to control samples (Ciccolella et al., 2013; Foley et al., 2013).

These genetic and biochemical findings suggest riboflavin supplementation as a possible therapeutic strategy. Bosch et al. (2011) initiated this by treating three patients with BVVL with a high dose of riboflavin and observed rapid improvement in muscle weakness and correction of biochemical abnormalities. A promising result was also observed in a single patient with BVVL studied by Johnson et al. (2012). These studies report preliminary findings on short-term treatment with riboflavin supplementation thus suggesting a positive response. Therefore, the need for a long-term follow-up of a larger cohort of early-treated children was warranted. Foley et al. (2013) report on high-dose oral riboflavin therapy continued for 1–20 months in 16 patients with known or novel mutations in SLC52A2. They describe in detail the results of repeated clinical, neurophysiological and pulmonary examinations in two patients with significant and sustained response to treatment. Both patients significantly improved by gaining motor function and muscle strength, alleviating the need for respiratory support. The remaining patients were reported to have stable or improved function after the initiation of riboflavin treatment, without further details. Taken together, they suggest that riboflavin supplementation can ameliorate disease progression and can be life-saving, particularly when initiated soon after onset of the first symptoms (Foley et al., 2013). It should be stressed that BVVL represents one specific, genetically defined disorder among other childhood-onset motor neuron diseases (spinal muscular atrophy, juvenile amyotrophic lateral sclerosis or distal hereditary motor neuropathies), and that an effect of riboflavin supplementation has only been tested in this particular pathology. However, it can be hoped that this promising treatment of BVVL might also have consequences for the therapy of other devastating motor neuron diseases if riboflavin metabolism should turn out to be involved in similar conditions.

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doi:10.1093/brain/awt342

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