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Oral therapy for riboflavin transporter deficiency - What is the regimen of choice?

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Rapid advances in genetic methodology have led to the verification of a steadily increasing number of disorders manifesting with progressing ataxia with or without additional neurological or non-neurological signs and symptoms. Many of these syndromes are rare, but causative treatment options are available for a few of these, why neurologists increasingly use comprehensive genetic testing to identify individuals with these rare but treatable disorders. However, because of the rarity of these disorders, the evidence base for treatment recommendations may be scarce.

Riboflavin transporter deficiency, Brown-Vialetto-Van Laere syndrome-2 (BVVLS2, OMIM 614707) is a rare neuronopathy manifesting with progressing ataxia, optic atrophy, hearing impairment, and muscular weakness, sometimes leading to respiratory failure. It is caused by loss-of-function mutations in *SLC52A2,* encoding the riboflavin transporter 2 (RFVT2). Based on the pathophysiological mechanism, oral riboflavin treatment is commonly implemented. Open-label studies have reported improvement of motor symptoms or of neurophysiological measurements, or hearing level in a third of patients treated with up to 500 mg riboflavin 3 times daily (td); however, no randomized controlled trials have been performed, many of the patients in these studies were children who developed severe symptoms early in life, and started treatment after shorter duration of symptoms than the present patient, and the number of patients studied was small [1–4]. RFVT2 contributes, together with RFVT1, to the transport of riboflavin from the intestine to blood and is solely responsible for the transport from blood to neurons [2]. A pharmacokinetic study has shown that saturation kinetics limit the uptake of an oral dose to a maximum of 27 mg riboflavin in a healthy subject [5]. Riboflavin uptake in patients with *SLC52A2* mutations is likely considerably lower. Riboflavin is very rapidly eliminated; 6 h after administration of an oral riboflavin dose - a situation as in three doses a day - plasma levels are almost back to baseline [5].

We identified a novel patient with BVVLS2, and investigated serum levels of riboflavin under two different treatment regimens. Our patient is a 35 year old Swedish male, with sensory ataxia, severe hearing and visual impairment affecting spatial orientation, proprioception difficulties related to polyneuropathy and weak deep tendon reflexes. He received communication mainly through tactile interpreter. The patient's speech was dysarthric but understandable. He had no muscle weakness, swallowing or respiratory difficulties. After normal development in early childhood, rapid decline of hearing occurred at 3 years, necessitating early hearing aid. Progressive visual loss at 4 years was explained by bilateral optic atrophy. Balance and gait impairment developed in childhood and deteriorated progressively. Neurography showed reduced amplitude in sensory fibers. Whole exome sequencing revealed homozygosity for c.968T > C p.(Leu323Pro) in exon 3 of the *SLC52A2* gene (NM_024531.4). Both parents (non-consanguineous) were heterozygous carriers of this variant. The variant is present in gnomAD, found in 8 of 110,292 exomes from Non-Finnish Europeans, but in no other populations. It alters a highly evolutionary conserved amino acid, and is predicted to be pathogenic in SIFT, MutationTaster, PolyPhen2 and CADD (score 26.2).

The generally recommended treatment with high-dose (500 mg capsules 3td) per-oral riboflavin [1,2] was initiated, and maintained for 6 months. Plasma riboflavin levels were low before the first intake in the morning and rose up to 4 hours after every intake, gradually decreasing thereafter. The doses were then divided into 250 mg 6td. Renewed measurements showed a more constant plasma level, and the baseline level before the first intake in the morning doubled. By trapezoid AUC calculations and extrapolation to a 24 hour period, we found a 27% higher plasma level over a 24 hour period with 250 mg riboflavin 6td (Fig. 1 and Supplementary Table).

Before the initiation of treatment, the patient had a score of 11 points on the SARA ataxia scale, was only able to count the number of examiner's fingers at 0,5 m distance, and unable to complete Goldman perimetry or Farnsworth test for color vision. One year after 6td riboflavin regimen, gait, sitting stability, and alternating hand movements improved slightly to 8 SARA points. There was also a slight improvement in visual acuity to 0.16 (right) and 0.07 (left) eye, almost normal color vision tested by Farnsworth test, and improved peripheral vision

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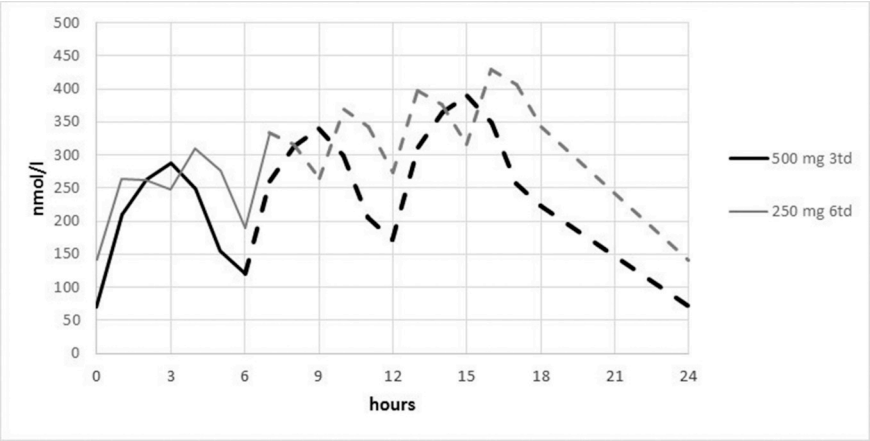

Fig. 1. Concentration of riboflavin in plasma. Black line: measurements on a day when the patient received 500 mg oral riboflavin three times daily at 0 (morning), 6 and 12 hours. Grey line: measurements on a day when the patient received 250 mg oral riboflavin six times daily at 0 (morning), 3, 6, 9, 12 and 15 hours. Solid lines connect measurements and dotted lines represent calculated values, based on steady rate of elimination. See Supplementary Table for values and detailed methodology.

with central scotomas, which eased communication as the patient became able to see sign-interpreting.

Although the exact molecular mechanism causing BVVLS2 is known, optimal treatment doses and intervals remain elusive. Our study does not demonstrate superiority on clinical effect of the 6td regimen, but our plasma measurements may support the more frequent administration of riboflavin dose. Theoretically, parenteral administration of riboflavin may increase uptake and effect.

Ethics statement

The study followed the Declaration of Helsinki. The patient consented to the study and publication of the results. Given the rarity of BLLV2, all treatment regimens are outside of official approvals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.017.

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