Riboflavin Transporter Deficiency

Riboflavin Transporter Deficiency (RTD) is a progressive inherited neuropathy of childhood onset, characterised by pontobulbar palsy, sensorineural deafness, sensory ataxia, muscle weakness, optic atrophy and respiratory failure. Riboflavin supplementation has been shown to be beneficial in short-term reports but the quantum of benefit in various clinical domains is not well understood.

A PubMed search was conducted which identified 94 genetically confirmed cases of RTD who received riboflavin supplementation and had follow-up assessments. Information on the clinical and functional status before and after riboflavin supplementation was collected and analysed.

Results: Seventy-six of the 94 patients (80.9%) showed an overall improvement after riboflavin supplementation, and the remaining (19.1%) were stable, though some patients had deteriorations in individual domains with no reported deaths. The domains that had the highest rates of response to riboflavin supplementation were gross motor function (93.3% improved), bulbar palsy (91.3%), and ataxia (90.0%). Improvements were also seen in limb muscle weakness, audiology, facial nerve palsy and respiratory function. Despite treatment, many patients required assistance to ambulate and had severe or profound hearing loss and some remained gastrostomy or tracheostomy-dependent.

Interpretation: Riboflavin supplementation is a life-saving intervention for patients with RTD and results in profound improvement in several functional domains, with early diagnosis and treatment further improving outcomes. Despite treatment, patients are left with residual disability. There is a need to accurately measure functional outcomes in children with RTD and develop additional disease modifying therapies [1)].

Brown-Vialetto-van Laere syndrome is characterized by a progressive sensorimotor neuropathy, optic atrophy, hearing loss, bulbar dysfunction, and respiratory insufficiency. Mutations in SLC52A2 and SLC52A3, encoding riboflavin transporters RFVT2 and RFVT3, respectively, are the genetic basis of this disorder, often referred to as riboflavin transporter deficiency types 2 and 3, respectively. We present cases of both types of riboflavin transporter deficiency, highlighting the distinguishing clinical features of a rapidly progressive motor or sensorimotor axonal neuropathy, optic atrophy, sensorineural hearing loss, and bulbar dysfunction. One child presented with isolated central apnea and hypoventilation, not previously described in genetically confirmed Brown-Vialetto-van Laere, later complicated by diaphragmatic paralysis secondary to phrenic nerve palsy. Magnetic resonance imaging showed T2 hyperintensity in the dorsal spinal cord in 2 children, as well as previously unreported cervical nerve root enlargement and cauda equina ventral nerve root enhancement in 1 child. Novel homozygous mutations were identified in each gene-a NM_024531.4(SLC52A2):c.505C > T, NP_078807.1(SLC52A2):p.(Arg169Cys) variant in SLC52A2 and NM_033409.3(SLC52A3):c.1316G > A, NP_212134.3(SLC52A3):p.(Gly439Asp) variant in SLC52A3. Both treated children showed improvement on high-dose riboflavin supplementation, highlighting the importance of early recognition of this treatable clinical entity [2)].

Brown-Vialetto-Van Laere syndrome represents a phenotypic spectrum of motor, sensory, and cranial nerve neuropathy, often with ataxia, optic atrophy and respiratory problems leading to ventilator-dependence. Loss-of-function mutations in two riboflavin transporter genes, SLC52A2 and SLC52A3, have recently been linked to Brown-Vialetto-Van Laere syndrome. However, the genetic frequency,

neuropathology and downstream consequences of riboflavin transporter mutations are unclear. By screening a large cohort of 132 patients with early-onset severe sensory, motor and cranial nerve neuropathy we confirmed the strong genetic link between riboflavin transporter mutations and Brown-Vialetto-Van Laere syndrome, identifying 22 pathogenic mutations in SLC52A2 and SLC52A3, 14 of which were novel. Brain and spinal cord neuropathological examination of two cases with SLC52A3 mutations showed classical symmetrical brainstem lesions resembling pathology seen in mitochondrial disease, including severe neuronal loss in the lower cranial nerve nuclei, anterior horns and corresponding nerves, atrophy of the spinothalamic and spinocerebellar tracts and posterior column-medial lemniscus pathways. Mitochondrial dysfunction has previously been implicated in an array of neurodegenerative disorders. Since riboflavin metabolites are critical components of the mitochondrial electron transport chain, we hypothesized that reduced riboflavin transport would result in impaired mitochondrial activity, and confirmed this using in vitro and in vivo models. Electron transport chain complex I and complex II activity were decreased in SLC52A2 patient fibroblasts, while global knockdown of the single Drosophila melanogaster riboflavin transporter homologue revealed reduced levels of riboflavin, downstream metabolites, and electron transport chain complex I activity. This in turn led to abnormal mitochondrial membrane potential, respiratory chain activity and morphology. Riboflavin transporter knockdown in Drosophila also resulted in severely impaired locomotor activity and reduced lifespan, mirroring patient pathology, and these phenotypes could be partially rescued using a novel esterified derivative of riboflavin. Our findings expand the genetic, clinical and neuropathological features of Brown-Vialetto-Van Laere syndrome, implicate mitochondrial dysfunction as a downstream consequence of riboflavin transporter gene defects, and validate riboflavin esters as a potential therapeutic strategy [3)].

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2)
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3)
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