Normal outcome with prenatal intervention for riboflavin transporter defect

Sharika Raga [a, b, c], Natasha Elks [d], Jo M Wilmshurst [b, c] and the ICGNMD Consortium[e]

(a) Paediatric Neurology Department, Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town, South Africa, (b) Neuroscience Institute, University of Cape Town, South Africa, (c) PhD fellow, International Centre for Genomic Medicine in Neuromuscular Diseases Study, University College London, (d) University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Hills Rd, Cambridge, CB2 0SP, United Kingdom, (e) For list of Consortium Members

International Centre for Genomic Medicine in Neuromuscular Diseases

ABSTRACT

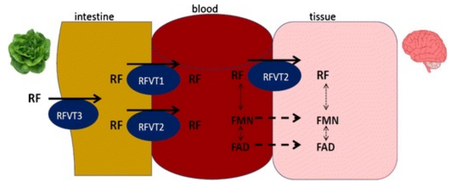
Introduction*:* Riboflavin transporter deficiency is a rare but severe neurometabolic disorder. We report two siblings with pathogenic variants in *SLC52A3* gene, resulting in riboflavin transporter 3 deficiency.

Case Summaries: The first sibling was diagnosed at 11 months of age with severe respiratory compromise and regression of developmental milestones. His symptoms significantly improved with riboflavin supplementation therapy. The younger sibling was diagnosed by antenatal genetic analysis; riboflavin supplementation was initiated in utero and continued from birth. Now 2 years of age, he remains clinically asymptomatic despite genetic confirmation of riboflavin transporter deficiency.

Discussion*:* Antenatal riboflavin supplementation is a safe and effective treatment for the prevention of symptomatic manifestations of riboflavin transporter deficiency. These participants have now been recruited as genetically confirmed cases to the International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) to increase opportunities for participant access to future trials and research.

INTRODUCTION

Vitamin B2, or riboflavin, is a water-soluble vitamin essential for production of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), essential cofactors for cellular respiration. Humans acquire riboflavin via dietary intake – from milk, meat, fatty fish, and green vegetables – with recommended daily intake ranging from 0.3mg in new-borns, to 1.6mg in lactating women [1,2]. Excessive riboflavin, FMN and FAD are excreted in urine, and high doses of supplementation do not cause adverse effects [2,3]



Three riboflavin transporters have been identified: RFVT1, RFVT2 and RFVT3, respectively encoded by genes *SLC52A1, SLC52A2* and *SLC52A3* [4]. Pathogenic variants within *SLC52A2* and *SLC52A3* present with progressive neurological disorders formerly known as Brown-Vialetto-Van Laere (BVVL) or Fazio-Londe syndrome, now considered manifestations of riboflavin transporter deficiency [5].

Presentation is characterised by progressive bulbar palsy, stridor, muscle weakness (axial, proximal and distal) and respiratory compromise, with sensorineural hearing loss specific to the BVVL phenotype [6,7]. Onset is typically in early childhood (mean 4.1 years) although the reported range is 3 months to 27 years [5]. Whilst no mechanism has been identified, treatment with riboflavin supplementation is lifesaving in cases of riboflavin transporter deficiency (RTD) confirmed at the molecular level by genetics [5,7].

PATIENT 1

As detailed by Chaya *et al.* (2018), this boy presented with progressive peripheral and cranial nerve neuropathy. By 11 months of age, he had vocal cord and diaphragm paralysis, with dysphagia, bulbar dysfunction, and regression of motor milestones. Aggressive medical intervention was required, including high dose riboflavin, tracheostomy for ventilation support, and parenteral gastrostomy feeding tube (PEG). Genetic studies identified heterozygous *SLC52A3* gene variants: one known to be pathogenic, and one of unknown significance in a pathogenic region of the gene. Each parent was subsequently found to carry one variant [7].

The proband had bilateral cochlear implants for auditory neuropathy at 2 years of age. By 5 years and 11 months,

- Ventilatory support requirements significantly reduced
- Accessory muscle use during normal quiet breathing
- Polysomnography almost complete resolution of his artificial ventilation needs
- PEG removed at 5 years of age
- Gross motor and fine skills reverted to normal
- Receptive and expressive language progressively improved
- Good school progress (some communication difficulties)
- Language delay remains the main concern

Continues on 80mg/kg/day dose riboflavin supplementation, coenzyme Q10, and carnitine.

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PATIENT 2

Antenatal genetic analysis via amniocentesis confirmed the younger sibling had pathogenic variants of *SLC52A3* at 28/40 weeks gestation. Following consultation with clinicians, the children's mother initiated 200mg/4hrly riboflavin supplementation for the remainder of her pregnancy: the ideal dose was estimated. This boy was born at 38/40 weeks by elective caesarean section, cried at birth and weighed 3.4kg. Prophylaxis riboflavin supplementation continued post-partum, starting neonatally with 10mg/kg every 4 hours, gradually increasing to, and maintained at, 80mg/kg/day. His mother continued 400mg/kg riboflavin supplementation while breastfeeding.

From birth, the younger sibling showed no respiratory or motor compromise: he sat at 5 months, cruised by 9 months, and walked from 11 months. At 16 months of age, he was thriving with normal developmental milestones, and no feeding or sleeping difficulties. There were no fine motor concerns, and he had normal expressive and receptive speech. He played well with other children, with no concerns relating to his behaviour. Systemic and neurological examinations were normal.

Now two years of age, there is no clinical manifestation of his genetically confirmed RTD.

DISCUSSION

We have reported the longitudinal outcome of the first case of genetically confirmed riboflavin transporter deficiency in sub-Saharan Africa, noting marked clinical improvement whilst taking high-dose riboflavin supplementation (200mg/4 hourly). In addition, we report the highly effective outcome of the first case of antenatal riboflavin supplementation for genetically diagnosed RTD, showing this to be a safe and efficacious intervention. Although RTD is rare, this case supports the recommendation by Horoz *et al.* (2015) whereby clinical and genetic diagnosis of BVVL is sufficient to indicate instigation of riboflavin prophylaxis for younger pre-symptomatic siblings, or future children. Horoz *et al.* (2015) reported the initiation of high dose riboflavin in an asymptomatic genetically affected sibling; this sibling remained clinically unaffected at the time of their report. Our report is the first to explore the apparent safety and efficacy of antenatal high dose riboflavin. This treatment is highly effective for treating and potentially preventing symptoms, as well as low cost and minimal risk. Furthermore, in clinically suspected patients there is a strong case to commence treatment with riboflavin supplements whilst awaiting molecular genetic diagnosis of RTD, or in settings where genetic testing is not viable.