# Case Report: A Rare Association Between Brown-Vialetto-Van Laere Syndrome type 2 (BVVLS2) and Cyclic Vomiting Syndrome (CVS) in a Pediatric Patient

Rita Alfattal[1,2]*, Adeeb Algaith[3], Hussain Sadeq[1], Rasha Alsafi[4] and Eman Buhamrah[5]

[1]Department of Pediatrics, Al-Amiri Hospital, General Paediatrics Unit, Ministry of Health, Kuwait City, Kuwait.

[2]Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait

[3]University of Szeged, Faculty of Medicine, Hungary.

[4]Department of Pediatrics, Adan Hospital, Metabolic disease Unit, Ministry of Health, Hadiya, Kuwait

[5]Department of Pediatrics, Al-Amiri hospital, Gastroenterology Unit, Ministry of Health, Kuwait City, Kuwait

*Received: 29 April 2024*

*Accepted: 2 October 2024*

*Corresponding author: ritaalfattal@gmail.com

**DOI 10.5001/omj.2027.25**

## *Abstract*

This case report details the clinical journey of an 11-year-old boy who initially presented with concerns about delayed walking at 21 months. Despite normal early development, the patient later developed progressive neurological symptoms, along with repeated severe vomiting episodes occurring at 21 to 30 day intervals. Genetic investigations revealed the presence of a homozygous mutation in the SLC52A2 gene, associated with Brown-Vialetto-Van Laere Syndrome type 2 (BVVLS2). The patient demonstrated signs of autonomic dysfunction during vomiting episodes, potentially indicating cyclic vomiting syndrome (CVS). Riboflavin therapy, which is effective for both BVVLS2 and CVS, was initiated with positive outcomes. This case highlights a potential rare gastrointestinal manifestation of BVVLS2, expanding our current understanding of the impacts of this genetic disorder.

**Keywords:** Brown-Vialetto-Van Laere Syndrome; Riboflavin transporter deficiency; Cyclic Vomiting Syndrome; *SLC52A2* Gene; Riboflavin, Vitamin b2.

## Introduction

Brown-Vialetto-Van Laere Syndrome (BVVLS) is a rare disease with less than 400 diagnosed cases all-over the world.[1-5] It is due to Riboflavin Transporter deficiency (RTD), which was first described by Brown in 1894 and later by Vialetto and Van Laere in 1936 and 1966, respectively.[4]

This condition is mainly defined by progressive neurological deficits, such as cranial nerve palsies, sensorineural hearing loss, and muscle weakness.[2,5] The only gastrointestinal symptom previously reported in association with this syndrome has been dysphagia, sometimes necessitating gastrostomy tube feeding.[5] The link with cyclic vomiting syndrome is a novel finding in this case.

## Case Report

Initially, the patient had been brought into the healthcare facility at 21 months of age, due to concerns about delayed walking. There were no concerns about his general health or any other developmental domains, as he was able to sit, stand without support, scribble with a pen, feed himself with a spoon and speak a few words. The patient was born through normal vaginal delivery at full term with a birth weight of 2.9 kg. His parents were first cousins, and he had two older, healthy siblings (a brother and a sister) with no family history of chronic or inherited neurological disorders. Clinical examination showed normal growth with no dysmorphic features. His heart, chest, abdomen, genitalia and skin examinations were all normal. His neurological examination, however, exhibited decreased muscle bulk in the lower limbs along with hypotonia, hyporeflexia and decreased muscle power, with a MRC scale score of 4/5. There were no abnormalities observed in his cranial nerves, sensory or cerebellar examinations. The results of laboratory investigations were all normal, including a complete blood count (CBC), renal and liver function, vitamin D level, thyroid function, iron, ammonia, lactate, blood amino acid and acyl carnitine profiles. Magnetic resonance imaging (MRI) of the brain showed bilateral flare sub-cortical white matter hyper-intensities, with prominent Virchow-Robin periventricular space and a dilated central spinal canal from D4 to D10. Electromyography (EMG) was also performed, the results of which were normal. The patient was referred for inclusion in the whole exome sequence (WES) study, although follow up contact was lost due to a change in the patient's country of residence. The patient restarted his follow up at the age of 10 years, by which point he was unable to sit without support and had lost his ability to walk or stand. Furthermore, his hearing had become affected, and his speech was slurred.

WES analysis was performed at that time, resulting in the detection of a homozygous c.917G>A (p.Gly306Glu) mutation in the *SLC52A2* gene, linked to an autosomal recessive genetic disorder called Brown-Vialetto-Van Laere Syndrome type 2 (BVVLS2) [OMIM: 614707]. Clinically, at 10 years of age the patient was conscious, alert, non-dysmorphic, but was relatively small for his age with weight and height both being below the 5$^{th}$ percentile according to his age and sex, unable to walk or stand, but able to obey orders. Central nervous system (CNS) examination showed that the patient had generalized reduced muscle bulk, with generalized hypotonia and scoliosis, muscle power was 3/5 in the upper and lower limbs, although his cognitive function, cranial nerve, sensory and cerebellar examinations were all normal. At around the age of 10, the patient progressively started to have episodes of repeated severe bilious (and sometimes non-bilious) vomiting, occurring up to 25 times per day and 6 times per hour. These episodes generally occurred 21 to 30 days apart, with each episode persisting for around 7 to 10 days. The vomiting was associated with generalized mild to moderate abdominal pain, severe dehydration and a decreased level of consciousness, for which hospitalization was required on 9 separate occasions, including 3 intensive care unit admissions where he was intubated, ventilated and managed with intravenous fluids, ondansetron and esomeprazole. The vomiting episodes were associated with transient autonomic dysfunction in the form of hypertension requiring treatment with intravenous hydralazine, along with urinary retention and decreased urine output in the absence of a local urological cause.

**Figure 1:** An 11-year-old boy with BVVLS and CVS along with generalized hypotonia and failure to thrive.

Laboratory investigations during these episodes exhibited that the patient had high blood glucose levels of up to 11.1 mmol/L, low plasma sodium levels of 124 mmol/L, low plasma chloride levels of 90 mmol/L, low plasma osmolarity of ~251 and low blood urea nitrogen (BUN) and creatinine levels. Despite the patients dehydrated state and decreased urine output (<1 mL/kg/hour), increased urine osmolarity was detected (>100 mosm), as observed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). All laboratory result abnormalities returned to normal levels once the vomiting episodes subsided, with blood pressure readings and urine output also returning to normal levels outside of vomiting episodes. Ultrasound scans of the patient's abdomen and pelvis were performed with Doppler echocardiography, to exclude cardiac, renal, or adrenal causes for his hypertensive episodes, the results of which were all normal. A pH probe study and a computed tomography (CT) abdominal scan follow through study (with barium contrast) were performed, in order to rule out surgical or any other gastrointestinal (GI) causes for the vomiting episodes, the results of which were unremarkable. Furthermore, there was no evidence of any infectious etiology being involved in the vomiting episodes. Repeated MRI scans of his brain and spine were performed to rule

out neurological causes, showing non-specific bilateral cerebral white matter high signal foci with no paraspinal abnormalities. Accordingly, a diagnosis of cyclical vomiting syndrome (CVS) was suspected based on the latest ROME IV diagnostic criteria (Table 1). The patient was started on riboflavin (vitamin B2) at an initial dose of 200 mg daily, gradually building up to 600 mg daily (40 mg/kg/day). the patient suffered only one vomiting episode, occurring 2 weeks after the riboflavin treatment had been initiated, after which no vomiting episodes were reported throughout the 5 month follow up period.

**Table 1:** Criteria for cyclic vomiting syndrome* [adapted from ROME IV Diagnostic Criteria for Disorders of Gut-Brain Interaction (DGBI)].

1. Two or more periods of unremitting paroxysmal vomiting with or without retching, lasting hours to days within a 6-month period.
2. Episodes are stereotypical in each patient.
3. Episodes are separated by weeks to months with return to baseline health between episodes of vomiting.

**All of the criteria must be met to adhere to the consensus definition of CVS.*

## Discussion

Three types of riboflavin transporter deficiency (RTD) disorders are known,[1] which are mainly caused by mutations in the *SLC52A1* [OMIM: 615026], *SLC52A2* [OMIM: 614707] and *SLC52A3* [OMIM: 211530] genes.[1] Type 1 RTD disorders caused by the *SLC52A1* mutation, are extremely rare, with only one reported case to date, in a 4-month-old girl with homozygous *SLC52A1* deletion,[1] while two other cases reported in the literature were of maternal-related *SLC52A1* microdeletion.[2,3] Brown-Vialetto-Van Laere Syndrome type 1 (BVVLS1) corresponds to the *SLC52A3* gene mutation (type 3 RTD disorder), while BVVLS2 is a *SLC52A2*-related disease (type 2 RTD disorder) in which the problem would be at the level of transporting the Riboflavin from the blood into the tissues.[4] Distinguishing between BVVLS1 and BVVLS2 can be challenging as both types share similar features of clinical presentation.[4,5] Riboflavin is considered a suitable treatment for all RTD disorders, with evidence showing that early treatment with high doses of riboflavin can help limit the progression of the disease and reduce symptoms.[4,6,7]

Individuals diagnosed with type 2 and type 3 RTD disorders typically experience neurological symptoms characterized by progressive peripheral and cranial manifestations, such as muscle weakness, vision loss, deafness and sensory ataxia.[4,8] GI-related manifestations are usually attributed to progressive muscle weakness, as patients often experience dysphagia and aspiration episodes.[4,9] To the best of our knowledge and after extensive review of the available literature, this is the first case report of a BVVLS patient having cyclic episodes of vomiting. In this specific case, CVS could be a rare GI manifestation of BVVLS, or it could simply be an unfortunate associated condition. One important differential diagnosis of BVVLS is the multiple acyl-COA dehydrogenation defect (MADD).[6,10-12] BVVLS shares biochemical similarities with MADD, with both potentially causing intermittent vomiting episodes. However, patients with MADD usually presents with hypoglycemia, deranged liver enzymes, rhabdomyolysis, hepatomegaly and renal dysplasia, all of which were absent in the present case.[6,10-12] Furthermore, genetic investigations did not identify *ETFDH*, *ETFA* or *ETFB* gene mutations, which are usually associated with MADD.[10-12]

CVS was suspected in this patient as he met all ROME IV diagnostic criteria required for the diagnosis of this syndrome in children (Table 1)[13] and there was no evidence indicating that these episodes arose from infectious, neurological, or surgical causes. Furthermore, during vomiting episodes the patient exhibited signs of autonomic dysfunction in the form of hypertension and urine retention, which is commonly seen in CVS patients.[14,15] Conversely, outside of these episodes, there was no occurrence of vomiting, high blood pressure, or reduced urine output, with laboratory investigations yielding normal results. Additionally, it was observed that all of the patient's vomiting episodes were associated with hyponatremia, decreased blood osmolarity, with decreased urine output and increased urine osmolality. These findings may indicate Sato type CVS, a rare variant that has been described in only 6% of CVS cases.

Several studies have demonstrated the efficacy of riboflavin as a prophylactic medication for CVS,[16-18] which proved to be particularly beneficial in this case, as riboflavin is also effective for the treatment of BVVLS1.[4,6,7]

## Conclusions

Cyclical Vomiting Syndrome (CVS) could potentially be a rare gastrointestinal (GI) manifestation of Brown-Vialetto-Van Laere Syndrome type 2 (BVVLS2). Riboflavin treatment had beneficial results, serving the dual purpose of providing a vital therapy for BVVLS2, particularly when initiated early in order to minimize neurological damage, while also being effective for the treatment of CVS.

## References


1. Kang U, Yang DH, Nam SO, Lee Y-J, Yeon GM. Riboflavin Transporter 1 Deficiency Caused by a Homozygous Single Exonal Deletion of SLC52A1. Ann Child Neurol 2020;28(4):160-163 .

2. Mosegaard S, Bruun GH, Flyvbjerg KF, Bliksrud YT, Gregersen N, Dembic M, et al. An intronic variation in SLC52A1 causes exon skipping and transient riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. Mol Genet Metab 2017 Dec;122(4):182-188.

3. Ho G, Yonezawa A, Masuda S, Inui K, Sim KG, Carpenter K, et al. Maternal riboflavin deficiency, resulting in transient neonatal-onset glutaric aciduria Type 2, is caused by a microdeletion in the riboflavin transporter gene GPR172B. Hum Mutat 2011 Jan;32(1):E1976-E1984.

4. Cali E, Dominik N, Manole A, et al. Riboflavin Transporter Deficiency. Seattle (WA): University of Washington, Seattle; 2015. https://www.ncbi.nlm.nih.gov/books/NBK299312/

5. Foley AR, Menezes MP, Pandraud A, Gonzalez MA, Al-Odaib A, Abrams AJ, et al. Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2. Brain 2014 Jan;137(Pt 1):44-56.

6. Bosch AM, Stroek K, Abeling NG, Waterham HR, Ijlst L, Wanders RJ. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. Orphanet J Rare Dis 2012 Oct;7:83.

7. Fennessy JR, Cornett KM, Burns J, Menezes MP. Benefit of high-dose oral riboflavin therapy in riboflavin transporter deficiency. J Peripher Nerv Syst 2023 Sep;28(3):308-316.

8. Gorcenco S, Vaz FM, Tracewska-Siemiatkowska A, Tranebjærg L, Cremers FP, Ygland E, et al. Oral therapy for riboflavin transporter deficiency - What is the regimen of choice? Parkinsonism Relat Disord 2019 Apr;61:245-247.

9. Amir F, Atzinger C, Massey K, Greinwald J, Hunter LL, Ulm E, et al. The Clinical Journey of Patients with Riboflavin Transporter Deficiency Type 2. J Child Neurol 2020 Mar;35(4):283-290.

10. Bosch AM, Abeling NG, Ijlst L, Knoester H, van der Pol WL, Stroomer AE, et al. Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. J Inherit Metab Dis 2011 Feb;34(1):159-164.

11. Bennett MJ. Brown-Vialetto-Van Laere and Fazio Londe syndromes: defects of riboflavin transport with biochemical similarities to multiple acyl-CoA dehydrogenation defects (MADD). J Inherit Metab Dis 2012 Nov;35(6):941-942.

12. Yılmaz BŞ, Ceylaner S, Mungan NÖ. Brown Vialetto Van Laere syndrome: presenting with left ventricular non-compaction and mimicking mitochondrial disorders. Turk J Pediatr 2021;63(2):314-318.

13. Rome Foundation. (2019). *ROME IV Diagnostic Criteria for Disorders of Gut-Brain Interaction.* RomeFoundation. https://theromefoundation.org/wp-content/uploads/Rome-Foundation-Diagnostic-Criteria-Booklet-2019.pdf

14. Chelimsky TC, Chelimsky GG. Autonomic abnormalities in cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2007 Mar;44(3):326-330.

15. Chelimsky G, Madan S, Alshekhlee A, Heller E, McNeeley K, Chelimsky T. A comparison of dysautonomias comorbid with cyclic vomiting syndrome and with migraine. Gastroenterol Res Pract 2009;2009:701019.

16. Martinez-Esteve Melnikova A, Schäppi MG, Korff C. Riboflavin in cyclic vomiting syndrome: efficacy in three children. Eur J Pediatr 2016 Jan;175(1):131-135.

17. Li BU. Managing cyclic vomiting syndrome in children: beyond the guidelines. Eur J Pediatr 2018 Oct;177(10):1435-1442.

18. Venkatesan T, Levinthal DJ, Tarbell SE, Jaradeh SS, Hasler WL, Issenman RM, et al. Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association. Neurogastroenterol Motil 2019 Jun;31(Suppl 2)(Suppl 2):e13604.