

## Case Report

# Brown Vialetto Van Laere syndrome, a fatal disease with a simple solution: a case series

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### ABSTRACT

Brown Vialetto Van Laere (BVVL) syndrome is an extremely rare neuro metabolic disorder postulated to be caused by a defect in riboflavin transporter. The disease is characterized by progressive hearing loss with ataxia and difficulty in swallowing and breathing. The diagnosis of the disease requires great deal of suspicion on the part of treating physician. Here authors present 2 cases of BVVL who presented to us with dysphagia and hearing loss and responded to therapy. Brown Vialetto Van Laere (BVVL) syndrome is an extremely rare neuro metabolic disorder postulated to be caused by a defect in Riboflavin transporter. The disease is characterised by progressive hearing loss with ataxia and difficulty in swallowing and breathing. It is a subset in multiple acyl CoA dehydrogenase deficiency (MADD disorder). Age of onset is generally first to third decade of life. Lower cranial nerve involvement with LMN and UMN signs concomitantly is the striking feature. There is no specific treatment for BVVL except supportive care. Response to high dose riboflavin (20mg/kg/day) has produced promising results but the results may take anywhere from 1 week to 12 months to appear.

**Keywords:** Brown Vialetto Van Laere (BVVL) syndrome, MADD disorder, Neurometabolic, Riboflavin

### INTRODUCTION

Brown-Vialleto-Van Laere Syndrome (BVVL) also called progressive ponto bulbar palsy with deafness or bulbar hereditary neuropathy type I is a rare disorder characterized by rapid onset progressive sensorineural hearing loss (SNHL) with lower motor cranial nerve disorders and respiratory difficulties.<sup>1,2</sup> It was first described by Brown in 1894 and later by Vialetto in 19364 and Van Laere in 1966.<sup>3-6</sup> Less than 60 cases have been described in literature till date and majority of them have been reported to be sporadic.<sup>7</sup>

The majority of familial cases demonstrate autosomal recessive inheritance, although autosomal dominant,<sup>1,8</sup> and X-linked inheritance have also been described. The

female to male ratio is approximately 3:1 in reported cases.<sup>9</sup> It has been postulated to be caused by defect in human riboflavin transporter hRFVT genes (SLC52A2 and SLC52A3).

Here authors analyse a series of 3 cases of BVVL, one of the largest case series in the subcontinent.

### CASE REPORT

#### Case report 1

A 10-year-old child born out of 2<sup>nd</sup> degree consanguineous marriage presented to CDC pediatric neurology OPD with complaints of dysphagia for 6 months, hearing loss for 4 months, recent change in voice

for 1 month and respiratory difficulty for 15 days. He was grossly emaciated and had gross muscle wasting. At presentation, he had head bobbing with labored breathing but there was no clinical respiratory distress. Detailed neurological examination revealed exaggerated lower limb reflexes with bilateral moderate sensorineural hearing loss. Gag reflex was sluggish and fasciculations were noted on the tongue. Routine hematological and radiological imaging parameters were normal. Presence of both LMN and UMN prompted us to think of some motor neuron disease (Figure 1).



**Figure 1: Clinical photograph of case 1, before treatment showing wasting of the tongue with undulations.**

Association with progressive hearing loss has been previously reported in Brown Vialetto Van Laere syndrome. DNA was sent for genetic analysis and in the meanwhile, the child was put empirically on high dose riboflavin (20mg/kg/day). Within 2 to 3 weeks, the jerky pattern of breathing and swallowing improved and subsequently the child started walking independently without ataxia. The child was discharged on high dose oral riboflavin. On follow up, his hearing ability had also improved, and disuse atrophy of appendicular muscles also decreased (Figure 2).



**Figure 2: Clinical photograph of case 1 after 3 months of riboflavin treatment showing normal tongue with reversal of atrophy.**

### Case report 2

A 11-year-old child born of 2nd degree consanguineous marriage presented to CDC pediatric neurology OPD with complaints of progressive hearing loss, ataxia, weakness and decreased scholastic performance. He had recently started developing labored breathing too. Detailed neurological examination in this child also showed a combination of both LMN and UMN signs.

He had multiple verrucous lesions on the extremities. imaging studies showed a benign arachnoid cyst. BERA showed bilateral auditory desynchrony. DNA was sent for genetic analysis and high dose riboflavin was initiated on clinical suspicion. The child had a better gait within 7 days of initiation of therapy and on follow up had better auditory performance.

### Case report 3

An 8-year-old child born of a non-consanguineous marriage presented to CDC pediatric neurology OPD with complaints of decreased hearing for 4 months, tremors and tinnitus for 2 months and off and on episodes of vomiting for 1 month. He also had a history of fall during play in school. On examination, he had fine tremors of both hands. He had fasciculations of the tongue. His uvula was deviated to one side with absent gag reflex. He also had an ataxic gait. His neuroimaging was non-conclusive. DNA could not be sent for confirmation due to financial constraints, but child was initiated on therapy for BVVL on clinical suspicion. His gait also improved within 10 days of initiation of therapy. He hasn't turned up for follow up.

### DISCUSSION

Brown Vialetto Van Laere syndrome or hereditary bulbar neuropathy type 1 is a rare neurological disorder.<sup>6</sup> The etiology was unknown since its first description in 1894. In 2010, Green et al, demonstrated a SLC52A3 mutation in a few of these mutations.<sup>7</sup> In 2011, Bosch et al, demonstrated that this gene coded for riboflavin transporter in human intestines and postulated that riboflavin deficiency could be a possible cause of the disease.<sup>8</sup> Sensorineural hearing loss, mostly progressive, is the most consistent symptom of the disease although one case without any hearing loss in the lifetime has also been reported.<sup>9,10</sup> In present study, this was seen in all the three patients. It is generally the cause of presentation to the OPD although cases with ataxia as the presenting symptom have been reported Sumners et al.<sup>11,12</sup> In present study, two patients presented with hearing loss and one presented with labored breathing due to vocal cord weakness although he also had significant hearing loss.

Although cases from infancy to mid-forties have been described, the typical age group of presentation is 7 to 15 years.<sup>13</sup> In present case, they were aged 8 years, 10 years and 11 years. Respiratory involvement requiring

tracheostomy has also been described and 5-year survival rate in the reported cases has been less than 40%. Involvement of lower cranial nerves (7<sup>th</sup>-12<sup>th</sup>) has also been commonly reported in these cases. Patients present with both LMN and UMN signs.<sup>7,8,11</sup> Supplementation of riboflavin proved a lifesaving treatment for a number of young patients. Both oral and intravenous preparations have been reported but IV preparations aren't available in our country. Doses of 10mg/kg/day to 20mg/kg/day have been documented.<sup>7,8,14-16</sup> In our patients, authors used a dose of 10mg/kg/day but due to absence of intravenous preparations and due to costly availability of pure riboflavin, the children were put on a combination drug containing low amounts of riboflavin. So, they had to consume almost 20 tabs a day. However, the improvement was remarkable.

## CONCLUSION

Brown Vialletto Van Laere (BVVL) syndrome is an extremely rare neuro metabolic disorder postulated to be caused by a defect in Riboflavin transporter. The disease is characterised by progressive hearing loss with ataxia and difficulty in swallowing and breathing. It is a subset in multiple acyl CoA dehydrogenase deficiency (MADD disorder). Age of onset is generally first to third decade of life. Lower cranial nerve involvement with LMN and UMN signs concomitantly is the striking feature. There is no specific treatment for BVVL except supportive care. Response to high dose riboflavin (20mg/kg/day) has produced promising results but the results may take anywhere from 1 week to 12 months to appear.

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## REFERENCES

- Hawkins SA, Nevin NC, Harding AE. Pontobulbar palsy and neurosensory deafness (Brown-Vialletto-Van Laere syndrome) with possible autosomal dominant inheritance. *J Med Genet.* 1990;27:176.
- Prabhu HV, Brown MJS. Brown-Vialletto-Van Laere syndrome: a rare syndrome in otology. *J Laryngol Otol.* 2005;119(6):470-2.
- Brown CH. Infantile amyotrophic lateral sclerosis of the family type. *J Nerv Ment Dis.* 1894;21:707-16.
- Vialletto E. Contributo to the hereditary form of progressive bulbar paralysis. *Riv Sper Freniat* 1936;40:1-24.
- Van Laere J. Paralysis Progressive chronic familial bulbo-pontine with deafness. A case of Klippel syndrome. *Rev Neurol.* 1966;115:289-5.
- Sathasivam S. Brown-Vialletto-Van Laere syndrome review. *Orphanet J Rare Dis* 2008;3:9.
- Green P, Wiseman M, Crow YJ, Houlden H, Riphagen S, Lin JP, et al. Brown-Vialletto-Van Laere syndrome, a ponto-bulbar palsy with deafness, is caused by mutations in c20orf54. *Am J Human Genetics.* 2010;86(3):485-9.
- Bosch AM, Abeling NG, Ijlst L, Knoester H, van der Pol WL, Stroomer AE et al. Brown-Vialletto-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;34:159-64.
- Megarbané A, Desguerres I, Rizkallah E, Delague V, Nabbout R, Barois A, et al. Brown-Vialletto-Van Laere syndrome in a large inbred Lebanese family: confirmation of autosomal recessive inheritance?. *Am J Med Genet.* 2000;92:117-21.
- Gallai V, Hockaday JM, Hughes JT. Ponto-bulbar palsy with deafness (Brown-Vialletto-van Laere syndrome): a report of three cases. *J Neurol Sci.* 1981;50:259-75.
- Summers BA, Swash M, Swartz MS, Ingram DA. Juvenile onset bulbospinal muscular atrophy with deafness: Vialletto-van Laere syndrome or Madras type motor neuron disease? *J Neurol.* 1987;234:440-2.
- Voudris KA, Skardoutsou A, Vagiakou A. Infantile progressive bulbar palsy with deafness. *Brain Dev.* 2002;24:732-5.
- Descatha A, Goddet S, Aboab J, Allary J, Gergereau A, Baer M et al. Cardiac arrest in a patient with Brown Vialletto- Van Laere syndrome. *Amyotroph Lat- eral Scler.* 2006;7:187-8.
- Anand G, Hasan N, Jayapal S, Huma Z, Ali T, Hull J et al. Early use of high-dose riboflavin in a case of Brown-Vialletto-Van Laere syndrome. *Dev Med Child Neurol.* 2012;54:187-9.
- Ciccolella M, Catteruccia M, Benedetti S, Moroni I, Uziel G, Pantaleoni C, et al. Brown-Vialletto-van Laere and Fazio-Londe overlap syndromes: A clinical, biochemical and genetic study. *Neuromuscular Disorders.* 2012;22(12):1075-82.
- Koy A, Pillekamp F, Hoehn T, Waterham H, Klee D, Mayatepek E et al. Brown-Vialletto-Van Laere syndrome: a riboflavin-unresponsive patient with a novel mutation in the C20orf54 gene. *Pediatr Neurol.* 2012, 46:407-9.

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