

Auditory neuropathy spectrum disorder with Brown–Vialletto–Van Laere syndrome: challenges in hearing rehabilitation

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Abstract

Background: Brown–Vialletto–Van Laere syndrome is a rare neurological disorder characterised by pontobulbar palsy and sensorineural hearing loss. Hearing rehabilitation continues to be a challenge because the exact lesion site is unknown.

Case report: We examined the clinical and audiological profiles of a case series comprising four siblings with Brown–Vialletto–Van Laere syndrome who had decreased hearing and poor speech discrimination. Audiological investigations revealed normal otoacoustic emissions with absent auditory brainstem responses and middle-ear reflexes in sensorineural hearing loss, suggestive of auditory neuropathy spectrum disorder.

Conclusion: The sensorineural hearing loss in Brown–Vialletto–Van Laere syndrome patients is a retrocochlear pathology resembling auditory neuropathy spectrum disorder, with the lesion being most probably of post-synaptic origin. Early cochlear implantation along with high-dose riboflavin represents a possible rehabilitation therapy. However, further research is needed to confirm this. This report emphasises the need for a thorough neurological evaluation of auditory neuropathy spectrum disorder patients.

Key words: Brown–Vialletto–Van Laere Syndrome; Evoked Potential, Auditory, Brainstem; Otoacoustic Emissions, Spontaneous; Cochlear Implantation

Introduction

Brown–Vialletto–Van Laere syndrome is a rare, often familial, condition characterised by bilateral nerve deafness and progressive pontobulbar palsy. The diagnosis is usually based on clinical presentation, with investigations performed to exclude other aetiologies.¹ Bilateral sensorineural hearing loss (SNHL) is a feature of this syndrome. However, a definite lesion site has not been identified.² Recently, Sinnathuray *et al.* suggested that the lesion may be retrocochlear or due to degeneration of the central auditory pathway, based on poor outcomes after cochlear implantation in two siblings affected by Brown–Vialletto–Van Laere syndrome.³

Our case series comprises four siblings born of a consanguineous marriage, with both parents with normal hearing. They were diagnosed with Brown–Vialletto–Van Laere syndrome, and all presented with bilateral hearing loss and difficulty understanding speech. Clinical ENT examination results were normal.

Case report

In the index case, a 14-year-old male (the youngest sibling), presented with complaints of bilateral hearing loss and tinnitus for three years, with difficulty understanding speech. Pure tone average (PTA) audiography showed severe bilateral SNHL with normal tympanograms and absent ipsilateral and contralateral reflexes. Auditory brainstem response

(ABR) audiometry showed absent waves with preserved otoacoustic emissions (OAEs). The patient had poor speech scores, and a speech threshold could not be established. Speech audiometry was performed using a standardised list of native Tamil words delivered via a GSI 61 2-channel audiometer (GrasonStadler, Eden Prairie, Minnesota, USA; SJ Dayalan, unpublished data). Speech reception thresholds and discrimination scores were calculated. Sentence tests were not performed because the speech discrimination score was zero. As summarised in [Table I](#), a similar history was obtained for the other three siblings.

All four siblings had moderate to moderately severe SNHL upon PTA audiography, with poor speech scores (shown in [Table II](#)). They had absent ABRs, with preserved cochlear microphonics, OAEs and middle-ear reflexes. In view of these findings, they were diagnosed with auditory neuropathy spectrum disorder.

Subsequent investigation revealed that all siblings had limb weakness and easy fatigability with temporalis muscle wasting; two had tongue fasciculation at rest ([Table I](#)). Nerve conduction studies showed reduced sensory nerve action potentials, while electromyography showed fibrillation of the mentalis (VIIth cranial nerve), temporalis (Vth cranial nerve) and tongue (XIIth cranial nerve). Contrast-enhanced magnetic resonance imaging of the brain showed no abnormality. In view of the evidence of bulbar muscle denervation, chronic denervation of the C8 (finger flexion)

TABLE I
CLINICAL PROFILES

Characteristic	Sibling 1	Sibling 2	Sibling 3	Sibling 4
Age (yr)	14	17	19	22
Sex	Male	Female	Male	Male
Audiovestibular symptoms				
– Age of onset of hearing loss (yr)	11	14	15	13
– Duration of hearing loss(yr)	3	3	4	9
– Speech discrimination	Poor	Poor	Poor	Poor
– Intolerance to loud sounds	Present	Present	Present	Present
– Tinnitus	Present	Present	Present	Present
– Vertigo	Present	Absent	Present	Absent
Neurological symptoms				
– Limb weakness	Present	Present	Present	Present
– Temporalis wasting	Present	Present	Present	Present
– Tongue fasciculation	Absent	Present	Absent	Present
– Peripheral neuropathy	Present	Present	Present	Present

yr = years

and T1 (finger abduction) myotomes, SNHL, and concurrent sensory neuropathy, the siblings were eventually diagnosed with Brown–Vialletto–Van Laere syndrome.¹

Discussion

Brown–Vialletto–Van Laere syndrome is a rare neurological disorder associated with progressive pontobulbar palsy and SNHL. Since it was first described in 1894, around 80 cases have been reported.¹ The male to female ratio is 3:1, with males generally being affected at a younger age and more severely than females. This was also noted in our series. The age of onset can be from the first year of life up to as late as the third decade. The disease seems to run in families, although 50 per cent of cases are reported to be sporadic.¹ Most familial cases have an autosomal recessive inheritance pattern, with a few cases showing autosomal dominant or X-linked inheritance.^{4–6} Sensorineural hearing loss is a common presenting symptom, although the disease can also present with subtle neurological features such as limb weakness and slurred speech. The disease course is unpredictable, with death occurring in 40 per cent of cases

within 5 years of onset; however, a similar percentage of patients survive for more than 10 years after onset of the first symptom.¹

Although this syndrome is known to be associated with SNHL, to our knowledge there are no reports of normal outer hair cell function in these patients. The presence of OAEs in the absence of any recordable ABR in this family shows that the SNHL associated with Brown–Vialletto–Van Laere syndrome most likely occurs in the pattern of auditory neuropathy spectrum disorder. Auditory neuropathy spectrum disorder is a distinct hearing disorder characterised by disrupted synchronous neural responses of the auditory pathway, with normal outer hair cell function.⁷ The site of involvement can be pre-synaptic (affecting inner hair cells), synaptic or post-synaptic.⁸ In contrast to pre-synaptic lesions, electrical stimulation in dyssynchronies of post-synaptic origin (especially of the auditory neuron) shows variable results after cochlear implantation.⁹

Green *et al.* reported that a *C20orf54* gene mutation causes Brown–Vialletto–Van Laere syndrome.¹⁰ Although there is no definitive evidence for a causative role of this gene in

TABLE II
AUDIOLOGICAL AND ELECTROPHYSIOLOGICAL TESTS

Test	Sibling 1	Sibling 2	Sibling 3	Sibling 4
Right PTA* (dB)	80.0	28.3	66.0	60.0
Left PTA* (dB)	71.6	46.6	68.0	56.6
Speech reception threshold	No words identified	No words identified	No words identified	No words identified
Word recognition score	0	0	0	0
DPOAE	Present	Present	Present	Present
CM	Present	Present	Present	Present
ABR	Waves absent	Waves absent	Waves absent	Waves absent
Middle-ear reflex ipsilateral	Absent	Absent	Absent	Absent
Middle-ear reflex contralateral	Absent	Absent	Absent	Absent
Tympanogram	Type A	Type A	Type A	Type A
ENG	Bilateral hypofunctioning labyrinth	Bilateral hypofunctioning labyrinth	Bilateral hypofunctioning labyrinth	Bilateral hypofunctioning labyrinth

*0.5, 1 and 2 kHz; PTA = pure tone average; DPOAE = distortion product otoacoustic emission; CM = cochlear microphonics; ABR = auditory brainstem response; ENG = electronystagmography

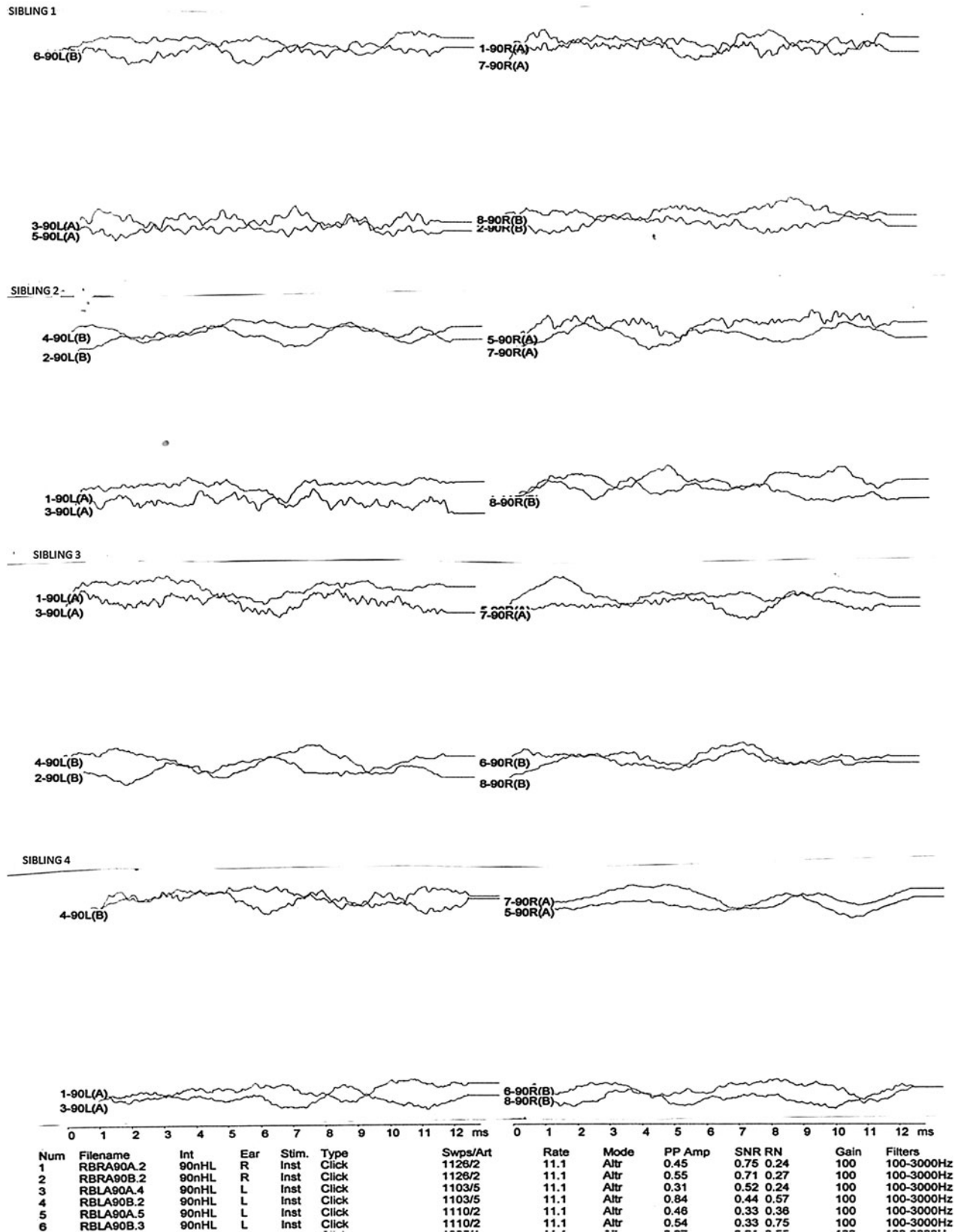


FIG. 1

Auditory brainstem evoked responses of all four siblings with Brown-Vialetto-Van Laere syndrome, showing an absence of recordable waveforms.

the disease, Yamamoto *et al.* have speculated that the rat orthologue encodes a transporter essential for riboflavin transport.¹¹ Bosch *et al.* demonstrated clinical flavin deficiency in Brown–Vialletto–Van Laere syndrome patients despite normal dietary intake, suggesting a transporter deficiency.¹² Riboflavin is a precursor of flavin adenine dinucleotide and flavin mononucleotide, which in turn are electron acceptors important in cell metabolism. Riboflavin is essential for cellular energy generation and DNA repair, and is a plausible candidate for a maintenance role in nervous system function.¹³

Sound transduction and speech perception require a tremendous amount of synchronised activity. Disturbance to auditory nerve synchrony interferes with the temporal coding of sound, which is the most important factor in speech perception.¹⁴ Auditory neurons are constantly firing, and this singularly high rate of firing requires highly active ion pumps and an efficient scavenging system. Giraudet *et al.* speculated that in auditory neuropathy spectrum disorder, the lack of cellular energy means that auditory neuronal ion pumps cannot cope with stimuli. Therefore, the timing of neuronal firing is altered, which affects the temporal coding of sound.⁸ We believe that the flavin deficiencies associated with Brown–Vialletto–Van Laere syndrome may cause dysfunction in auditory neuron firing and thereby auditory dyssynchrony. Recently, Sinnathuray *et al.* demonstrated poor outcomes after cochlear implantation in two siblings with Brown–Vialletto–Van Laere syndrome despite complete electrode insertion.³ This may be because SNHL is an auditory neuropathy spectrum disorder, as we found in our patients, with the lesion most probably post-synaptic at the auditory neuron level. There is evidence that deafness duration is a significant predictor of speech improvement after cochlear implantation.¹⁵ However, the lack of improvement in speech scores in the male patient and the minimal improvement in the female patient in Sinnathuray and colleague's case series suggests that additional factors, such as post-synaptic factors, may be involved. This possibility is supported by post-mortem studies of Brown–Vialletto–Van Laere syndrome patients, which show pathological changes in the auditory pathway (especially the cochlear nucleus), and recent radiological evidence of hyperintensities in the floor of the fourth ventricle and pontomedullary junction.^{16,17} The co-occurrence of other peripheral neuropathies in our patients suggests neuronal damage to the peripheral and cranial nerves, which provides further corroboration of a post-synaptic lesion site.¹⁸

Giraudet *et al.* noted that the ABRs of some patients with auditory neuropathy spectrum disorder showed a rapid fall in wave amplitude at a high stimulation rate, with a partial improvement after recovery.⁸ In our case series, all patients showed a complete absence of any identifiable waveforms, even with click rates as low as 11.1 per second (Figure 1). It is possible that the fatigue phenomenon occurs during the early disease stages when the nerves are still salvageable, but that after a long duration of illness, when total nerve dyssynchrony sets in, no identifiable waveforms are present. Advanced electrophysiological studies are needed to accurately identify the lesion site and stage.

Auditory rehabilitation continues to be a challenge for Brown–Vialletto–Van Laere syndrome patients. Given the improvement, albeit temporary, in the neurological profile of Brown–Vialletto–Van Laere syndrome with high-dose riboflavin, the same treatment regimen may be used to

delay hearing loss.¹⁹ An ABR showing the fatigue phenomenon suggests an imminent threat to already compromised neural function, while a total absence of waveforms suggests complete damage. Early cochlear implantation in patients in the former category, along with high-dose riboflavin, is a potential aural rehabilitation therapy. As high rates of stimulation in auditory neuropathy spectrum disorder are known to produce neural fatigue or a lack of response, cochlear implant reprogramming to a lower stimulation rate is likely to be beneficial for such patients.²⁰

Both the nature of the disease and the prognosis were explained to our patients, and they were given auditory verbal therapy for cued speech. However, after a few sessions, the family preferred to try Siddha, an alternative Indian medicine. Subsequently, the patients were lost to follow up.

The presence of Brown–Vialletto–Van Laere syndrome in all four offspring from a consanguineous marriage of asymptomatic parents is consistent with the common autosomal recessive pattern of inheritance, although no genetic tests were performed.

- **Brown–Vialletto–Van Laere Syndrome is a rare neurological disorder characterised by pontobulbar palsy and bilateral sensorineural hearing loss**
- ***C20orf54* gene mutation and subsequent flavin deficiency is the aetiopathogenetic mechanism**
- **In four siblings with the disease, hearing loss had a retrocochlear pathology resembling auditory neuropathy spectrum disorder, with the lesions probably post-synaptic in origin**
- **Hearing rehabilitation continues to be a challenge**
- **Early cochlear implantation and therapeutic riboflavin therapy in patients with auditory brainstem response fatigue phenomena is a possible rehabilitation strategy**

In this series, siblings with hearing loss and assessed as having auditory neuropathy spectrum disorder were subsequently diagnosed with Brown–Vialletto–Van Laere syndrome. It would be unrealistic to expect a diagnosis of Brown–Vialletto–Van Laere syndrome in patients who initially present with SNHL alone. However, the association between auditory neuropathy spectrum disorder and Brown–Vialletto–Van Laere syndrome emphasises the need to investigate other neurological involvement in auditory neuropathy spectrum disorder patients and maintain regular follow up.

Conclusion

This is the first report of normal outer hair cell function and an absent ABR in Brown–Vialletto–Van Laere syndrome patients. Hearing loss in Brown–Vialletto–Van Laere syndrome has a retrocochlear pathology resembling auditory neuropathy spectrum disorder, with the lesion probably of post-synaptic origin.

Hearing rehabilitation in such Brown–Vialletto–Van Laere syndrome patients poses a significant challenge. In patients with fatigue phenomena in their ABRs, early cochlear implantation along with therapeutic riboflavin is a potential rehabilitation strategy that needs further study. Additional

studies on electrophysiological testing to determine the exact lesion site and stage should be performed to determine the usefulness of cochlear implantation, if any, in such patients.

The association between Brown–Vialletto–Van Laere syndrome and auditory neuropathy spectrum disorder suggests that a thorough neurological evaluation should be performed on all patients with auditory neuropathy spectrum disorder and that regular follow up is necessary to achieve the best outcome.

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Dr A Balraj takes responsibility for the integrity of the content of the paper
Competing interests: None declared
