A Case with Brown-Vialetto-Van Laere Syndrome: A Sudden Onset Auditory Neuropathy Spectrum Disorder

Case Report

Başak Mutlu[1], Merve Torun Topçu[1], Ayça Çiprut[2]
[1]Department of Audiology, İstanbul Medeniyet University School of Health Sciences, İstanbul, Turkey
[2]Department of Audiology, Marmara University School of Medicine, İstanbul, Turkey

Abstract

The Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare neurological disorder that may present at all ages with sensorineural hearing loss, bulbar palsy and respiratory compromise. We describe a 6-year-old male patient who suffered bilateral sudden onset severe hearing loss for two years. Audiological investigations revealed sudden onset auditory neuropathy spectrum disorder bilaterally. He also had neurological complaints. During riboflavin therapy an improvement in hearing loss and the benefit of hearing aids were observed. In BVVLS, it is difficult to plan and apply auditory rehabilitation interventions and the results vary from patient to patient. In audiological evaluation, it should be borne in mind that subjective and objective tests are complemental. Early medical intervention and regular audiological follow-up are very important for effective hearing rehabilitation in the patients with BVVLS.

Keywords: Brown-Vialetto-Van Laere syndrome, riboflavin, hearing aid, auditory neuropathy spectrum disorder

Introduction

Brown-Vialetto-Van Laere Syndrome (BVVLS) is a rare disorder characterized by progressive ponto-bulbar palsy and bilateral hearing loss (1-3). The age of onset of initial symptoms varies from infancy to the third decade and the course is irregularly progressive. Its diagnosis is usually based on clinical presentation. Recently, mutations in SLC52A2 and SLC52A3 encoding the riboflavin (RF) transporters RFVT2 and RFVT3, respectively, have been identified in a number of individuals with BVVLS (4). The aim of this case report is to emphasize the importance of audiological evaluation in the diagnosis and follow-up of patients with BVVLS.

Case Presentation

We report a 6-year-old boy, with sudden severe bilateral hearing loss and cranial nerve palsy that developed suddenly two years ago. At the age of four, two weeks prior to his first audiological examination, he was examined by a pediatric neurologist for difficulties in swallowing, breathing and hearing. He was slightly hypotonic throughout. Then he was examined in our ENT department. He had bilateral facial paralysis, motion limitations in his tongue and vocal cords.

Magnetic resonance imaging of the brain was unremarkable. A diagnosis of BVVLS was suggested. He was hospitalized for further evaluation and started on high-dose riboflavin (RF, Swanson Health Products, USA) supplementation therapy (03.02.2017 - 750 mg/day) prior to genetic confirmation. Presently his RF therapy and audiological follow-up are ongoing.

There were compound homozygous pathogenic mutations of SLC52A3. His mother and father, on the other hand, were found to be carriers, and his sister showed heterozygote variant. He does not need nutrition or respiratory support. His parents are not in a consanguineous relationship. An informed consent form was taken from the patient's family.

ORCID IDs of the authors:
B.M. 0000-0002-9803-9258;
M.T.T. 0000-0002-0673-7818;
A.Ç. 0000-0002-0295-8760.

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Corresponding Author:
Başak Mutlu, basakogun@yahoo.com

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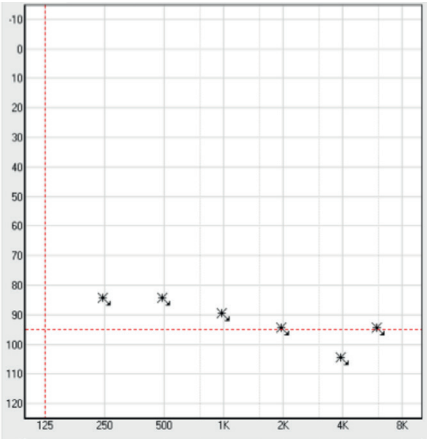
Play audiometry with supra-aural headphone was tried in the first visit of the patient to our audiology department but he was unable to cooperate. Therefore, a free-field (FF) conditioned play audiometry (CPA) test was performed using the Madsen Astera 2 (GN Otometrics, Denmark) and results indicated bilaterally profound hearing loss (Figure 1). Brainstem Auditory Evoked Potentials were recorded using Eclipse EP 25 (Interacoustics, Denmark) and gave absent response at high level (100 dBnHL) to click and CE-Chirp tone stimuli in both ears, but with cochlear microphonics (CM were present) to rarefaction and condensation polarities (R+C) indicated auditory neuropathy spectrum disorder (Figure 1). Otoacoustic emissions were within normal limits bilaterally (Echoport ILO 292 USB 2 V6 -Otodynamics, UK) (Figure 1). Tympanograms and acoustic reflexes were recorded using AT 235h (Interacoustics, Denmark). Tympanograms were within normal limits bilaterally; ipsi- and contra-lateral acoustic reflexes were absent.

In the first four months, he was hospitalized intermittently because of his breathing and feeding problems. In the fifth month of RF therapy, his general medical condition was more stable and his behavior to high intensities of free-field warble tones in CPA were reliable (Figure 2). In the sixth month of RF, BTE hearing aid was fitted unilaterally in the clinic to support his listening quality. But he was irritated and could not use the hearing aid.

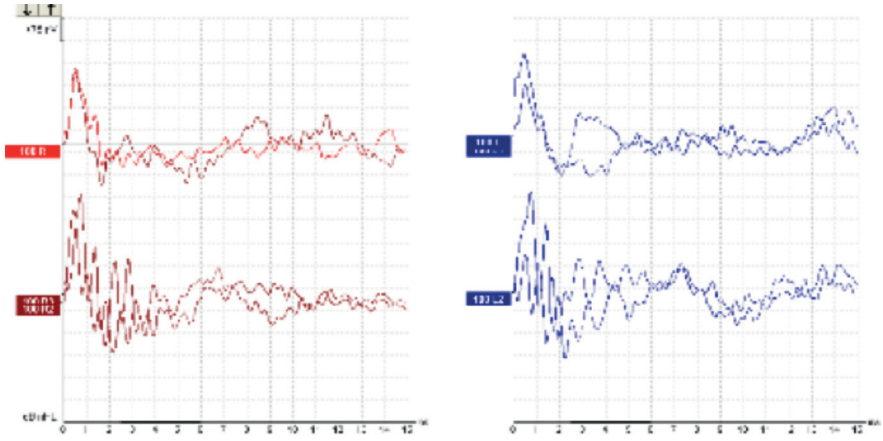
In the 18th month of the RF therapy, auditory evoked late potentials were recorded using Smart EP (Intelligent Hearing Systems Co., Miami, USA) by giving stimuli from the free field of cortical evoked potentials. The cortical potentials were recorded

a



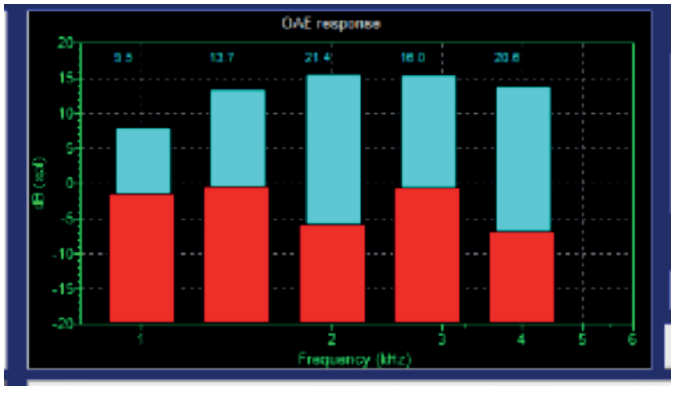
First Free-field conditioned play audiometry with Warble tone: No Response

b



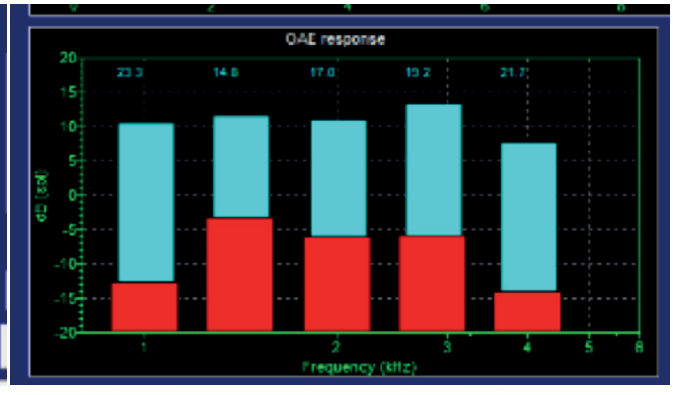
Brainstem Auditory Evoked Potentials with Click, Rarefaction+Condensation polarity: Bilaterally Cochlear Microphonics

c



Right Ear Transient Evoked Otoacoustic Emissions: Normal response

d



Left Ear Transient Evoked Otoacoustic Emissions: Normal response

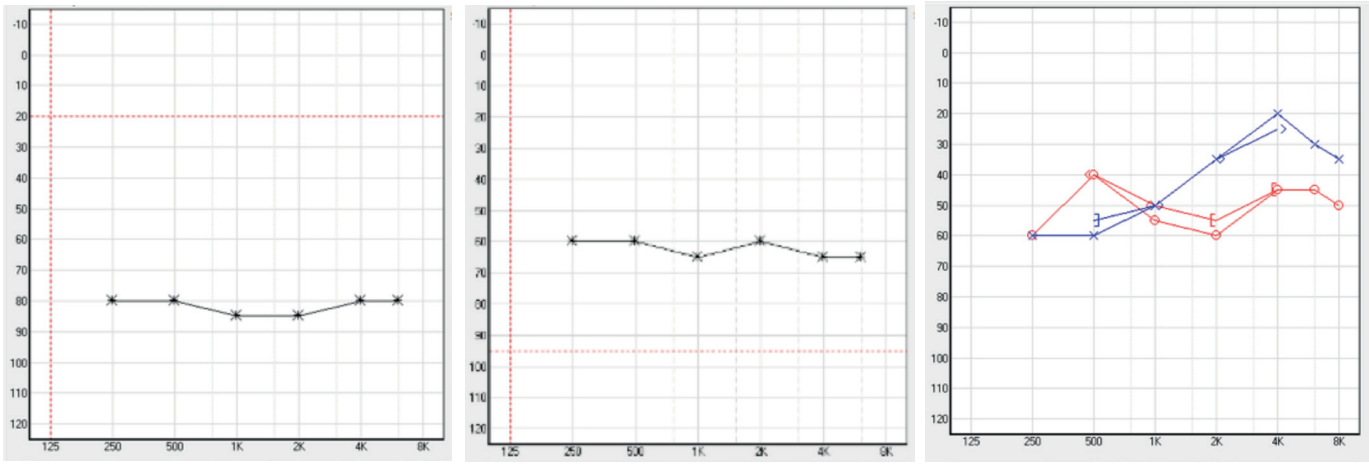
Figure 1. First audiological findings of the BVVLS case

with speech stimuli ("da") presented through a speaker at a repetition rate of 1.1/sec at 70- and 80-dB SPL. Stimulus level used to elicit cortical waveforms were supra-threshold. There was no P1 response.

Auditory steady state response (ASSR) measurements were performed in the 18th month of RF therapy using Eclipse EP 25 (Interacoustics, Denmark). ASSRs to carrier frequencies of 0.5, 1, 2, and 4 kHz were measured. Differences and correlations between the ASSRs and the behavioral thresholds were determined. In general, ASSR thresholds overestimated the behavioral audiogram. Results of these tests were compatible with bilateral severe hearing loss.

In the 19th month of the RF therapy, partial motor improvement was observed. There was meaningful change on hearing. He could understand and execute directives. His articulation was better than 19 months ago. ABR test was repeated but results were once more compatible with bilateral ANSD.

In the 20th month of the RF therapy, hearing aids were fitted bilaterally. This time the patient was not irritated. He tried on the hearing aids for several days at home and at school before they were prescribed. Eventually, he was bilaterally fitted with digital hearing aids. Hearing aids were programmed according to the last audiometric results. Free field measurements were performed after the patient wore the hearing aids for a month

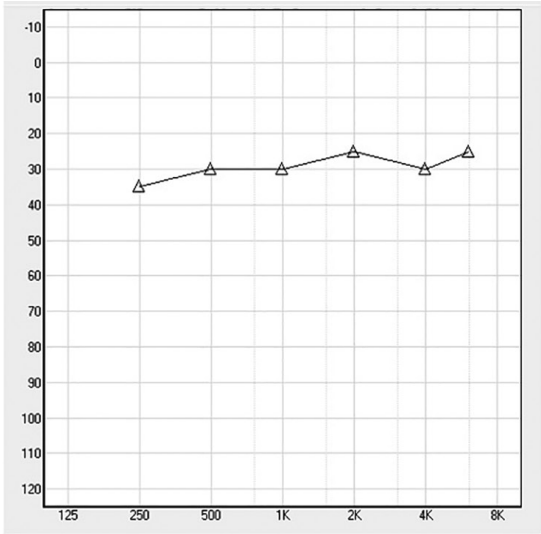


Before riboflavin (900 mg/day) therapy:
Conditioned Play Audiometry (free field-warble tone), reliable responses at the high intensities

6th months of riboflavin therapy:
Conditioned Play Audiometry (free field-warble tone), reliable better response

18th months of riboflavin therapy:
Play audiometry with pure tone speech recognition thresholds; 25 dB HL left ear, 30 dB HL right ear
Speech Discrimination Scores; 60% right ear, 56% left ear

Figure 2. Audiograms showing the progress during the riboflavin teatment



20th months of riboflavin therapy and hearing aids were fitted.

Speech Recognition Threshold: 30 dB SPL
Speech Dscirimination Score: 84%

Figure 3. Warble tone hearing thresholds with bilateral hearing aids in the free field

(Figure 3). In quiet, his speech recognition threshold (SRT) was 30 dB SPL and speech discrimination score (SDS) was 84% with hearing aids.

Currently, the patient is followed-up with objective and subjective audiologic tests. Both the nature and the prognosis of the disease were explained to the parents. Presently the patient is attending an aural rehabilitation program and going to kindergarten. Cochlear implantation is always kept in mind as an alternative hearing rehabilitation method in case the patient does not benefit from the hearing aids.

Discussion

In BVVLS the male to female ratio is 3:1, with males generally being affected at a younger age and more severely than females (5, 6). In the literature there are several case reports on this pathology (5, 7-10).

Our patient's audiological data were consistent with auditory neuropathy spectrum disorder. To date, hearing aids and cochlear implantation have been reported for auditory rehabilitation in BVVLS patients. Benefits of hearing aids were reported to be limited especially in noisy environments (10). When we tried the hearing aid for the first time, our patient was irritated and we did not proceed further. This was in the sixth week of the RF therapy. We made a second attempt in the 20th week of the RF therapy, and surprisingly, the patient was happy with the device and very enthusiastic about using it. He initially used his hearing aids during the rehabilitation sessions and at the kindergarten, but now he is wearing them at all times. His aided free field evaluation revealed warble tone thresholds between 25 to 35 dBHL.

Hearing loss due to ANSD may not always be measured by behavioral methods; thus, early electrophysiological evaluation should be performed. Of the initial symptoms of BVVLS in young children, vital symptoms such as respiratory or nutritional difficulties may prevent early recognition of hearing impairments by the family. The patient should be evaluated electrophysiologically as early as possible.

Looking at the literature, we found that patients with BVVLS who applied to the clinic with acute symptoms were given immunoglobulin or steroid treatment until genetic verification was performed (11). Confusing the diagnosis prevents early administration of RF supplement. After RF therapy, audiological follow-up findings can be identified only in limited cases. In our case, RF therapy was started in the early period without waiting for genetic confirmation. This may be a major advantage in terms of reducing hearing loss and of benefiting from the hearing aid. The benefit of RF therapy may also be due to mutation. It has been reported in the literature that cases with SLC52A3 mutation benefit more from RF therapy (4).

Chandran et al. (5) reported four BVVLS siblings aged 14-22 years. In all four of the patients, moderate to moderate-severe sensorineural hearing loss and low speech scores were obtained. Their OAEs were normal, but BAEPs were absent. BVVLS associated auditory neuropathy was first reported in the referred report (5). Auditory neuropathy was defined in all four patients, and audiologic evaluation was made before and after the 12th and the 24th months of RF treatment. Only one of the patients was referred to cochlear implantation in the 18th month of RF treatment. The other three siblings did not benefit from hearing aids.

Menezes et al. (9) reported seven BVVLS cases from four families. In five of the seven children the baseline symptom of BVVLS was hearing loss. Hearing aids and frequency modulation amplification were used in six of the seven patients with poor speech discrimination but were found to be of limited or no benefit. RF therapy resulted in an improvement in hearing thresholds on pure tone audiograms in two cases that were treated within the 12 months of the onset of the hearing loss. In one of these two cases, hearing loss improved completely after six months of RF therapy. The other case had better hearing thresholds but speech recognition did not improve. Cochlear implantation was applied in this case and better results were achieved. Four cases didn't respond to the 24-month RF therapy.

In our case, transtympanic electrocochleography for the differentiation of site of lesion was not preferred because of the need for general anesthesia. There are no studies in the literature that document inner ear pathology in individuals with genetically confirmed RFVT2 deficiency, but post-mortem examination of genetically unclassified BVVL has shown loss of neurons and gliosis in the cochlear nerve and the cochlear nuclei (12, 13). A detailed study of the auditory and vestibular pathway demonstrated that the cochlear nuclei were almost devoid of neurons and severely gliotic in BVVLS. The possibility of post-synaptic involvement in BVVLS is prominent (14).

Woodcock et al. (15) reported a study with three cases. Case 1 was a 5-year-old male who had auditory neuropathy that emerged in the first three months of BVVLS. After a 3-month RF therapy he showed hearing, speech and vision improvement; however, no post-treatment audiological findings were reported. Case 2 was the older brother of Case 1. He died at the age of four and had similar symptoms. He received no medical treatment. Case 3 was an 8-month old infant who had auditory neuropathy. The authors reported that he showed hearing improvement after RF therapy but did not give any post-treatment audiological results in their report.

Conclusion

In BVVLS, it is difficult to plan and obtain auditory rehabilitation and the results vary from patient to patient. In audiological evaluation, it should be borne in mind that subjective and objective tests are complemental. In such complex cases, auditory evoked brainstem responses, behavioral tests, and otoacoustic emissions results are necessary. Cochlear implantation should always be considered as an option, but that some patients may also benefit from hearing aids should not be overlooked. Hear-

ing aid, as an option for aural rehabilitation in these cases shows variable results. We associated the improvement in hearing loss and the benefits of hearing aids with the RF therapy, which was started at the appropriate dose in the early period. It is also very important to regularly carry out audiological follow-ups, especially in the first 24 months of RF therapy, and to ensure the cooperation of the family.

Informed Consent: Written informed consent was obtained from the parents' of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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