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Audiologic results of a child with BVVL syndrome

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Abstract

Brown-Vialetto-Van Laere (BVVL) syndrome is an autosomal-recessive inherited disease, which has mutations in specific genes responsible for the transportation of riboflavin in the intestines. Fifty-eight cases of BVVL have been reported in just over a century. This rare syndrome is generally characterized by motor, sensory, and cranial nerve neuropathy. Although this syndrome manifests with bulbar palsy, sensorineural hearing loss is the second most common consistent manifestation of BVVL syndrome. While auditory neuropathy spectrum disorder (ANSD) often awaits due to the nature of the disease here, we present the results of cochlear hearing loss patient with BVVL syndrome. Timely recognition and proper management of BVVLS are crucial to offer necessary support and interventions for affected individuals because of the progressive nature of hearing loss.

Introduction

Brown-Vialetto-Van Laere (BVVL) syndrome, also known as riboflavin transporter deficiency, is a neurodegenerative condition initially described in 1894 by Charles Brown as a type of amyotrophic lateral sclerosis affecting infants and accompanied by hearing impairment [1]. In recent times, mutations in the genes SLC52A2 and SLC52A3, which encode the riboflavin (RF) transporters RFVT2 and RFVT3, respectively, have been discovered in a number of individuals diagnosed with BVVLS.

BVVL syndrome is characterized by neurological manifestations such as lower cranial nerve impairment and the presence of upper and lower motor neuron limb signs. Additional potential features include optic atrophy, retinitis pigmentosa, macular hyperpigmentation, autonomic dysfunction, and epilepsy [2]. Diagnosis primarily relies on the clinical presentation of symptoms.

The age of onset for this syndrome is variable, with cases reported to present from infancy up to the third decade of life. On average, the age of presentation is around 8.2 years [3]. According to Sathasivam (2008), females are reported to be three times more likely to be affected by the syndrome compared to males. However, the available data also indicate that males tend to be affected at an earlier age and exhibit more severe symptoms [4]. Although the patients have variable symptoms, the main symptom of BVVL syndrome is progressive hearing loss. While the timing of other symptoms may differ, sensorineural hearing loss typically manifests in early childhood, setting it apart from the onset of other potential symptoms [5].

We present a case report of a patient with symptoms starting at 4 months due to a mutation in the SLC52A3 gene, resulting in sensorineural hearing loss (SNHL). This report highlights the significance of audiological evaluation in diagnosing patients with BVVLS.

Case Report

Informed consent was obtained from the patient's parent to share the test results and information.

We present a case of a 4-month-old male patient born to consanguineous parents. The pediatric neurology examination revealed the patient's consciousness, but he lacked the ability to track objects or visually engage with faces. The ophthalmology examination showed a positive fixa-

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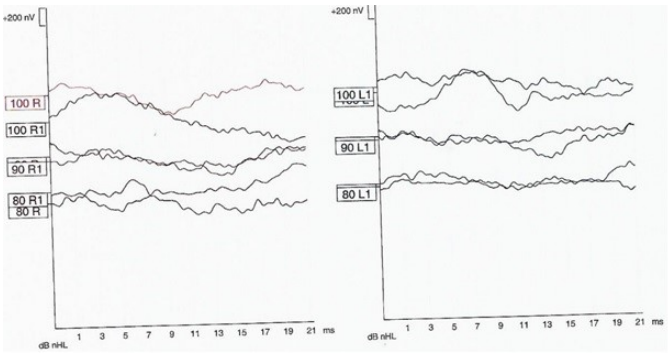

Figure 1. Click ABR results.

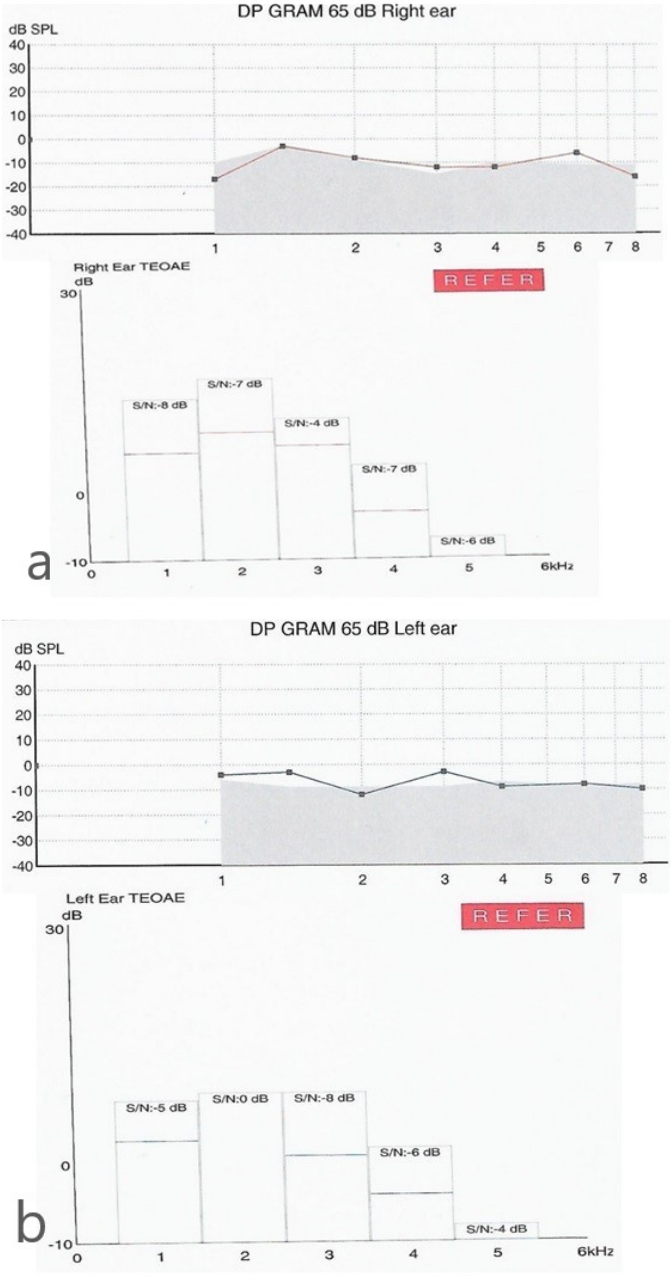

Figure 2. DPOAE and TEOAE results; a) Right ear results, b) Left ear results.

tion response but limited object tracking. Furthermore, the optic nerve appeared pale, and the presence of nystagmus was observed.

A genetic test at the Medical Genetics Lab using next-generation sequencing revealed a "probably pathogenic" homozygous missense mutation (p.S128L) in the SLC52A2 gene, based on a blood sample (EDTA) from the patient. The patient presented various symptoms, including growth retardation, hypotonicity, rod cone dystrophy, febrile seizures, immunodeficiency, and anemia.

The brain MRI results for the patient indicate the presence of bilateral otitis, as well as mild atrophy in the frontotemporoparietal lobes and an increase in subarachnoid free space. In terms of physical symptoms, the patient experiences difficulties in fully controlling their head movement and swallowing.

The patient failed the newborn hearing screening test in both ears. Auditory Brainstem Response (ABR) were recorded using the Eclipse EP 25 system (Interacoustics, Denmark) and the results showed an absent response at a high sound level of 100 dBnHL to clicks in both ears (Figure 1). The cochlear microphonics (CM) response did not observe.

Otoacoustic emissions (OAE) were negative on both sides (Figure 2a and 2b) and tympanograms of both ears were found to be within normal limits, indicating normal middle ear function. However, the ipsilateral and contralateral acoustic reflexes were absent.

Auditory steady-state response test results for the patient were as follows:

Right ear:

No response at 500, 1000, and 2000 Hz.

Response at 4000 Hz at 85 dBnHL intensity.

Left ear:

No response at 1000 and 2000 Hz.

Response at 500 Hz at 75 dBnHL intensity.

Response at 4000 Hz at 85 dBnHL intensity.

Discussion

In Brown-Vialetto-Van Laere (BVVL) syndrome, sensorineural hearing loss (SNHL) is reported as the second most common presenting symptom following bulbar palsy [3,4]. While the severity of hearing loss can vary from mild to profound, it is most commonly progressive, severe, and often leads to profound SNHL [6]. A study by Menezes et al. documented seven cases of children with RFTV2 deficiency. In most cases, hearing had deteriorated to profound levels, necessitating lip reading within two years of identifying their hearing loss [7].

Our presented case involved a 4-month-old patient who underwent his first hearing test at our clinic, confirming SNHL. Audiological investigations have revealed that the hearing loss observed in BVVL is characteristic of Auditory Neuropathy Spectrum Disorder (ANSD) [7]. Auditory neuropathy spectrum disorder (ANSD) is expected in these patients due to the neurological effects of the disease, as observed in the cases described by Chandran [8] and Mutlu [9]. However, our case did not exhibit the typical

ANSD findings in terms of CM and OAE test results. The precise neurological pathophysiology underlying ANSD associated with BVVL remains uncertain. Nevertheless, disruptions in the SLC52A3 gene have been identified as a known cause, exhibiting a consistent pattern with postsynaptic ANSD [10].

Early-onset SNHL in BVVL cases can worsen over time, often requiring cochlear implant (CI) surgery to address severe hearing impairment. There are limited studies that report the outcomes of CI in patients with BVVL syndrome. The first reported case of CI surgery in a BVVL patient, presented by Sinnathuray et al., unfortunately resulted in a poor response. The authors suggested that the suboptimal CI performance may be attributed to central alterations that affect its effectiveness [6]. Based on our current knowledge, the unsuccessful outcome may be due to ANSD. Menezes et al. have reported successful outcomes of cochlear implantation in patients with BVVL syndrome. The child had severe-to-profound hearing loss in the left ear, and after undergoing cochlear implantation, she showed significant improvement in speech perception [7]. A comprehensive review of BVVL cases showed varying CI performance outcomes, with generally positive results in terms of improved hearing thresholds and speech recognition [11]. In our case, based on test results, bilateral hearing aids were recommended for the patient considering their age. Audiological tests will continue to be conducted, and the results will be carefully evaluated to determine the potential benefits and suitability of a CI.

Recognizing the variety of symptoms and coexisting conditions linked to BVVL, it becomes apparent that standardized testing is challenging. A noteworthy aspect of our case is the early identification of hearing loss. While studies indicate that the typical onset of symptoms occurs in childhood [3], our case occurred at the age of 4 months. Early detection is crucial for timely intervention Mutlu et al. reported positive outcomes in a BVVL case by administering 20 weeks of riboflavin (RF) therapy, resulting in improved satisfaction and benefits from hearing aids [9]. RF therapy aims to supplement reduced RF levels, supporting cellular metabolism and potentially alleviating associated symptoms. The initiation of RF therapy represents a new approach to managing BVVL and holds promise in improving the patient's condition [12]. In our case, treatment with RF therapy has recently commenced following the diagnosis of BVVL. In the future, we will have the opportunity to observe the effect of RF treatment on hearing.

Conclusion

BVVLS is a rare condition that should be considered when neurological symptoms coincide with SNHL, particularly in infants. Audiological test batteries should be employed to evaluate the underlying causes of hearing loss. When a diagnosis of hearing loss is established, it is vital to make appropriate referrals, taking into consideration the patient's physical and mental well-being. Timely recognition and proper management of BVVLS are crucial to offer necessary support and interventions for affected individuals.

References

1. Brown CH. Infantile amyotrophic lateral sclerosis of the family type. Journal of Nervous and Mental Disease. 1894;19(11):707–16.
2. Woodcock IR, Menezes MP, Coleman L, Yaplito-Lee J, Peters H, White SM, et al. Genetic, Radiologic, and Clinical Variability in Brown-Vialetto-van Laere Syndrome. Semin Pediatr Neurol. 2018;26:2–9.
3. Bosch AM, Stroek K, Abeling NG, Waterham HR, Ijlst L, Wanders RJA. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. Orphanet J Rare Dis [Internet]. 2012 [cited 2023 May 21];7(1):83. Available from: /pmc/articles/PMC3517535/.
4. Sathasivam S. Brown-Vialetto-Van Laere syndrome. Orphanet J Rare Dis [Internet]. 2008 [cited 2023 May 20];3(1):9. Available from: /pmc/articles/PMC2346457/.
5. Do Amaral MSA, Massuda ET, Fenólio GHM, Reis ACMB, Hyppolito MA. Cochlear Implant in Brown–Vialetto–Van Laere Syndrome Patient. J Int Adv Otol [Internet]. 2022 Mar 1 [cited 2023 May 21];18(2):192. Available from: /pmc/articles/PMC9450168/.
6. Sinnathuray AR, Fruhstorfer B, Olarte JR, Toner JG. Cochlear Implantation in Brown-Vialetto-Van-Laere syndrome. J Laryngol Otol [Internet]. 2011 Mar [cited 2023 May 21];125(3):314–7. Available from: https://pubmed.ncbi.nlm.nih.gov/20955635/.
7. Menezes MP, O'Brien K, Hill M, Webster R, Antony J, Ouvrier R, et al. Auditory neuropathy in Brown-Vialetto-Van Laere syndrome due to riboflavin transporter RFVT2 deficiency. Dev Med Child Neurol [Internet]. 2016 Aug 1 [cited 2023 Jul 31];58(8):848–54. Available from: https://pubmed.ncbi.nlm.nih.gov/26918385/.
8. Chandran R, Alexander M, Naina P, Balraj A. Auditory neuropathy spectrum disorder with Brown-Vialetto-Van Laere syndrome: challenges in hearing rehabilitation. J Laryngol Otol [Internet]. 2015 May 21 [cited 2023 May 21];129(5):504–8. Available from: https://pubmed.ncbi.nlm.nih.gov/25994385/.
9. Mutlu B, Topçu MT, Çiprut A. A Case with Brown-Vialetto-Van Laere Syndrome: A Sudden Onset Auditory Neuropathy Spectrum Disorder. Turk Arch Otorhinolaryngol [Internet]. 2019 Dec 31 [cited 2023 May 21];57(4):201. Available from: /pmc/articles/PMC7032554/.
10. Gedik Soyuyuce O, Ayanoglu Aksoy E,, Yapici Z. A case report of sudden-onset auditory neuropathy spectrum disorder associated with Brown-Vialetto-Van Laere syndrome (riboflavin transporter deficiency). International Journal of Audiology. 2021;1–7.
11. Chaudhry D, Chaudhry A, Muzaffar J, Monksfield P, Bance M. Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis. J Int Adv Otol [Internet]. 2020 Dec 1 [cited 2023 May 21];16(3):411. Available from: /pmc/articles/PMC7901461/.
12. Manole A, Jaunmuktane Z, Hargreaves I, Ludtmann MHR, Salpietro V, Bello OD, et al. Clinical, pathological and functional characterization of riboflavin-responsive neuropathy. Brain [Internet]. 2017 Nov 1 [cited 2023 May 21];140(11):2820. Available from: /pmc/articles/PMC5808726/.