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Case Report

Audio-vestibular Findings in a Patient with Pelizaeus–Merzbacher Disease

Pradeep Yuvaraj[1], Suman Narayana Swamy[1], Kallahalli Chethan[1], Ragavendra Kenchaiah[2], Gautham Arunachal Udupi[3], Aravind Kumar Rajasekaran[1]

[1]Department of Speech Pathology and Audiology, NIMHANS, Bengaluru, Karnataka, India
[2]Department of Neurology, NIMHANS, Bengaluru, Karnataka, India
[3]Department of Human Genetics, NIMHANS, Bengaluru, Karnataka, India

ORCID iDs of the authors: P.Y. 0000-0002-9199-1019, S.N.S. 0000-0002-2668-5832, K.C. 0000-0003-1770-9545, R.K. 0000-0002-3984-0379, G.A.U. 0000-0001-9985-7028, A.K.R. 0000-0002-0387-3435.

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Pelizaeus–Merzbacher disease (PMD) is an X-linked recessive rare disease condition in which audiological deficit is also observed. A 4-year-old male child with PMD underwent an audiological evaluation. The results suggested normal middle ear and outer hair cells functioning, with only peak I of the auditory brainstem response present until 30 dBnHL. Further, the cervical vestibular evoked myogenic potential showed delayed latencies with normal amplitudes. In this case report, we attempt to explain the audio-vestibular test results and correlate them with the pathophysiology. This is the first report on the cervical vestibular myogenic potentials in patients with PMD.

KEYWORDS: Demyelination, hypomyelinating leukodystrophies, Pelizaeus–Merzbacher disease, vestibular evoked myogenic potential

INTRODUCTION

The Pelizaeus–Merzbacher disease (PMD) is a rare X-linked recessive disease that belongs to the group of hypomyelinating leukodystrophies.[1,2] Pelizaeus–Merzbacher disease is diagnosed based on symptomatology, family history, magnetic resonance imaging, and molecular genetic testing.[3] It is characterized by multi-domain neurodevelopmental delays. Audiological deficits are also observed. On auditory brainstem response (ABR), only peaks I and II are present, whereas later peaks (III and V) are absent.[4] This ABR pattern differentiates PMD from other Pelizaeus–Merzbacher-like diseases (PMLDs), where ABR is normal.[4] Vestibular tests reveal poor smooth pursuit, impaired optokinetic test, and failure in fixation suppression, indicating central vestibular dysfunctions.[1] However, existing studies fail to give a detailed insight into the ABR findings and the vestibular-evoked myogenic potentials are not explored in PMD. In this case report, we discuss the ABR test results in detail and further present the cervical vestibular evoked myogenic potential (cVEMP) findings in a patient with PMD.

CASE PRESENTATION

A 4-year-old boy was brought to a tertiary neuropsychiatric hospital with complaint of developmental delay and visual impairment. He was born out of a non-consanguineous marriage and was delivered through a lower (uterine) segment C-section 2 weeks prior to term due to uncontrolled gestational hypertension. The birth cry was delayed, with neonatal jaundice requiring phototherapy for a short duration. Since early infancy (parents reported) child had continuous head nodding movements when made to sit upright with support. Neurological examination demonstrated impaired visual fixation, pale optic disc with horizontal pendular nystagmus with revealed axial and appendicular hypotonia, brisk reflexes, along with bilateral extensor response to plantar reflex. Magnetic resonance imaging revealed diffuse altered signal intensity (hypointense on T1 and hyperintense on T2) change in the white matter of both the cerebral hemispheres without any evidence of diffusion restriction or blooming or contrast enhancement. In addition, bilateral dentate nuclei and cerebellar hemispheric white matter showed similar signal changes along with thinning of corpus callosum and symmetrical T2/FLAIR hyperintensity of bilateral corticospinal tracts and symmetrical central tegmental tract

Corresponding author: Kumar Rajasekaran A, e-mail: raravindk@gmail.com
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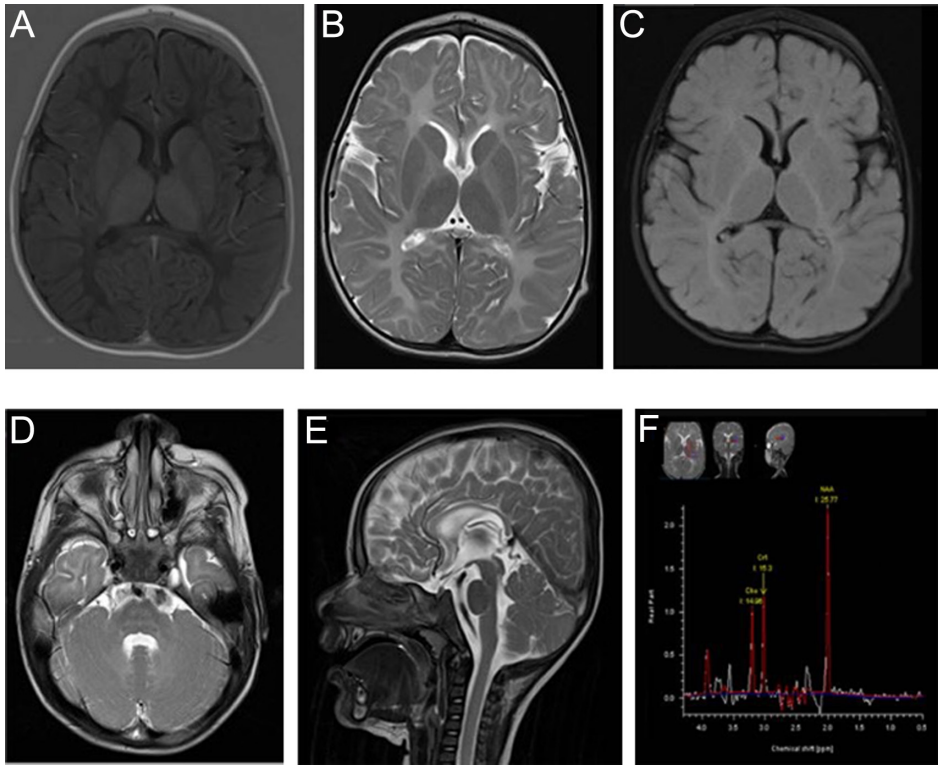

Figure 1. MRI images showing diffuse altered signal intensity change hypointense on T1 (A), hyperintense on T2 (B), FLARE in the white matter of both the cerebral hemispheres (C), both dentate nuclei and BILATERAL (B/L) cerebellar hemispheric white matter (D). Subtle symmetrical T2/Fluid-attenuated inversion recovery (FLAIR) hyperintensity is also seen along both the corticospinal tract (CST) in the pons, median pontine raphe and B/L CTT (D). Thinning of the corpus callosum with (F) MRS showing increased N-acetylaspartate (NAA) peak (E). CTT, central tegmental tract; MRI, magnetic resonance imaging.

(CTT) in the pons, median pontine raphe and bilateral CTT. Magnetic resonance spectroscopy demonstrated an increase in the *N*-acetyl aspartate peak with decreased choline suggesting hypomyelination in affected areas (Figure 1). These findings were suggestive of PMD or PMD-like disease, and the patient underwent chromosomal microarray and whole exome analysis. Both of the technologies revealed a pathogenic copy number gain in Xq22.2 of size 158Kb (ISCN nomenclature: arr[GRCh37] Xq22.2(102905501_103063736)x2). The duplication encompasses 3 OMIM genes, namely, PLP1, MORF4L2, and TMEM31 confirming the clinical diagnosis of PMD. The overall clinical and radiological finding were suggestive that patient was having moderate PMD. Pertaining to speech and language delay, a routine audiological evaluation was performed. Informed consent was obtained from the parents prior to evaluation. This study was approved by the Institute Ethics Committee of NIMHANS (Approval No: NIMHANS/IEC/2023; Date: April 3, 2023).

Methods

The audio-vestibular test battery included tympanometry (GSI-tympstar Pro), distortion product otoacoustic emission (DPOAE), ABR, cVEMP (Intelligent Hearing Systems Inc). The routine protocol was followed to record DPOAEs, ABR (rarefaction and condensation stimulus), and cVEMP[5]. The cVEMP testing was carried out with the child lying on the bed in the supine position. A muted video was played in the opposite side to the recording ear, so as to facilitate head turn to the opposite side. It was done to achieve good sternocleidomastoid muscle (SCM) tension. The standard procedures were employed to delineate peak I from cochlear microphonics (CM).[6] The cVEMP amplitude was normalized, and the interaural amplitude asymmetry ratio was calculated.

RESULTS

In both ears, tympanometry showed "A" type with ipsi reflexes present at 500 Hz, 1 kHz, and 2 KHz at 85 dBHL, DPOAEs were present between 1.5 kHz and 6 kHz, and only peak I was observed at 90 dBnHL on ABR. The observed peak I could be tracked till 30 dBnHL with good wave morphology and replicability (Figure 2). Further, ringing cochlear microphonics was observed bilaterally till 70 dBnHL. The cVEMP was present on both sides (Figure 2).

DISCUSSION

Pelizaeus–Merzbacher disease patients present with abnormal audio-vestibular test findings.[4] In the current study, the patient had an "A" type tympanogram and presence of DPOAE's bilaterally, which indicates normal middle ear function[7] and cochlear outer hair cells (OHCs) functioning.[8] Further, the presence of CM and peak I, on ABR reiterated normal functioning of OHCs, inner hair cells, and spiral ganglion (unmyelinated).[6] In these patients, a dysfunctional medial olivocochlear may have led to reduced inhibition of outer hair cells, which enhances CM.[9] The presence of CM presents a unique problem in the correct identification of peak I. The current study employed standard procedures to delineate peak I from CM (Figure 2). Methods employed were: (i) ABR recording with tube clamping, (ii) ABR recording with alternating polarity stimulus, (iii) adding the responses of rarefaction and condensation polarity stimulus, and 4. ABR recording for lower intensities.[6] Clinicians/researchers performing ABR on patients with PMD should be cautious as patients with white matter demyelination may have ANSD.

In the current study, only peak I could be recorded on ABR, while other peaks (III and V) were absent. The site of generation of peak

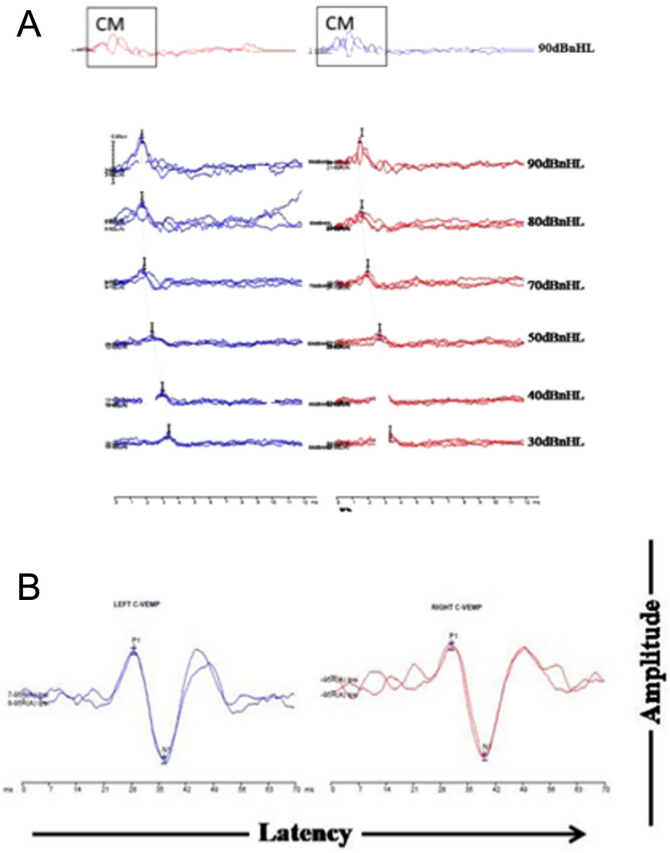

Figure 2. Auditory brainstem recording of both right and left ears with rarefaction and condensation polarity showing CM (at 90 dBnHL) and peak I (from 90 dBnHL to 30 dBnHL) (A) and cervical vestibular evoked myogenic potential for both right and left ears (B).

I is spiral ganglion. It encompasses cell bodies and unmyelinated nerve fibers.[6] As unmyelinated nerve fibers are unaffected in PMD, presence of peak I in the current patient is only expected. In the current patient, the peak I could be tracked till 30 dBnHL bilaterally. Earlier studies also reported presence of peak I on ABR testing.[10] The generators of later peaks are from myelinated portions of the auditory pathway.[11] Hence, absent later peaks in the current patient can be attributed to the demyelination of the white matter in patients with PMD. Substantiating normal hearing based on the presence of ipsi acoustic reflexes, DPOAEs, and consistent response to name call (informal hearing test) would have led to erroneous clinical decision. However, ABR testing revealed the abnormal neural conduction. This highlights the importance of objective hearing assessment in children with genetic abnormalities, even when other tests reveal normal findings.

Studies have reported abnormal Videonystagmography (VNG) test findings indicating vestibular dysfunction in patients with PMD.[1] The cVEMP assesses the vestibulo-collic reflex pathway. This pathway involves the saccule, inferior vestibular nerve, vestibular nucleus, spinal accessory nucleus, spinal accessory nerve, and sternocleidomastoid muscle. In the current patient, cVEMP testing revealed prolonged bilateral P1 and N1 latencies with normal P1-N1 amplitude. A saccular dysfunction may reflect an absent cVEMP or P1-N1 amplitude reduction.[12] However, it was normal in this patient. The latency prolongation can be attributed to vestibular pathways demyelination. Similar latency delay is reported in patients with neurodegenerative conditions like multiple sclerosis.[13] Further, the severity of the demyelination is found to have an impact on the VEMP parameters.[13] Similarly, in the present study, exclusive latency abnormality with normal VEMP amplitude may be related to the severity of the condition (moderate). However, future research on varied PMD severity and VEMP manifestations may shed a clear picture. To our knowledge, this is the first report on cVEMP in patients with PMD.

Overall, the findings of the present study (presence of OAEs, cochlear microphonics and peak I on ABR, normal cVEMP amplitude) aid in understanding the underlying pathophysiology of this condition. This also cautions clinicians to use diagnostic ABR over screening ABR and appropriate methods to correctly identify the peak I when CM is evident.

CONCLUSION

The patient with PMD presents with various audio-vestibular findings, which need to be evaluated cautiously to avoid misinterpretation. In the presence of evident CM, to correctly identify peak I, one should follow the standard procedure mentioned above. It is recommended to use diagnostic ABR over screener ABR as it only detects peak V. In such a group of patients, the absence of peak III and V may be misinterpreted as hearing loss. The cVEMP latency delay strengthens the diagnostic value of demyelination of brainstem structures.

Ethics Committee Approval: This study was approved by the Institute Ethics Committee of NIMHANS (Approval No: NIMHANS/IEC/2023; Date: April 3, 2023).

Informed Consent: Informed consent was obtained from the patients' parent who agreed to take part in the study.

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