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Case Report

Vestibular Function in Children With Von Hippel–Lindau Disease

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Von Hippel–Lindau disease (VHL) is a rare autosomal dominant disorder. It is caused by a mutation in the tumor suppressor gene localized at 3p25-26. Endolymphatic sac tumors (ELSTs) are rare low-grade adenocarcinomas which can occur sporadically but are more commonly found in association with VHL disease. In this paper, we present 3 siblings who underwent comprehensive vestibular assessment following a genetic diagnosis of VHL, and review the literature on audiovestibular findings in VHL/ELST in children. This is the first time that newer objective vestibular function tests like the video head impulse test (vHIT), the suppression head impulse test (SHIMP), and the cervical vestibular evoked myogenic potential test (cVEMP) have been performed in children with VHL to yield meaningful information about vestibular function. Monitoring audiological function has been suggested for early detection of ELSTs. It remains to be seen whether monitoring of vestibular function in patients with VHL from an earlier age may yield valuable information about progression of the disease.

KEYWORDS: Von Hippel–Lindau disease, endolymphatic sac tumors, vestibular function, video head impulse test, suppression head impulse test, vestibular evoked myogenic potential test

INTRODUCTION

Von Hippel–Lindau disease (VHL) is a rare autosomal dominant disorder caused by a mutation in the tumor suppressor gene at 3p25-26[1,2], affecting 1 in 35 000-40 000 of the population.[3]

Endolymphatic sac tumors (ELSTs) are rare low-grade adenocarcinomas occurring sporadically, but are more commonly found in association with VHL.[4,5] Histologically different from other petrous temporal bone lesions[6], ELSTs affect between 3.6% and 15% of VHL patients and are bilateral in 14%,[1,4,6] originating from the endolymphatic duct/sac epithelium in the vestibular aqueduct.[6] ELST was the initial presentation in VHL in about a third of patients[6] and with a younger age female predominance.[7] While histologically benign, ELSTs can behave aggressively[8] (Figure 1).

Information regarding vestibular status in VHL is lacking. In this paper, we present 3 siblings who underwent comprehensive vestibular assessment following a genetic diagnosis of VHL, and review the literature on audiovestibular findings in ELST in children. This is the first time that newer objective vestibular function tests like video head impulse test (vHIT), suppression head impulse test (SHIMP), and cervical vestibular evoked myogenic potential test (cVEMP) have been performed in children with VHL to yield meaningful information about vestibular function.

CASES

Three children with genetic diagnosis of VHL were referred for routine audiometric surveillance in a tertiary hospital. All 3 siblings and their mother were heterozygote carriers of a deletion of exon 1-3 of the VHL gene. After detailed anamnesis, the children underwent peripheral audiological assessment with pure-tone audiometry (PTA)/tympanometry/acoustic reflexes. A comprehensive vestibular assessment was performed with videonystagmography with/without optic fixation, vHIT, SHIMP, cVEMP, static posturography, and optokinetic tests. Informed signed consent was obtained from the children and their mother to report the cases.

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Direction of growth	Structures involved	Possible additional presenting symptoms
Posterior	Cerebellopontine angle and posterior fossa	Vestibular symptoms, headache, possible compressive symptoms
Lateral	Middle ear and mastoid	Facial nerve involvement, symptoms mimicking chronic otitis media or Eustachian tube dysfunction, mass in external auditory meatus
Superior	Semi-circular canals and middle fossa	Imbalance and disequilibrium
Anterior	Petrous ridge, clivus, cavernous sinus, sphenoid sinus	Intracranial symptoms. Vascular compromise

Figure 1. Symptoms of ELST with regard to surrounding structures.

Case 1

Nine years old, Twin 1 presented with no audiovestibular symptoms. Peripheral hearing assessment and screening MRI of brain/spine were normal. Vestibular assessment highlighted an abnormal cVEMP showing a left-sided weakness (42% asymmetry, Figure 2).

Case 2

Nine years old, Twin 2 presented with no audiovestibular symptoms. Peripheral hearing assessment and screening MRI of brain/spine were normal. Vestibular assessment identified an absent response on cVEMP on the left side, with normal response on the right (Figure 3).

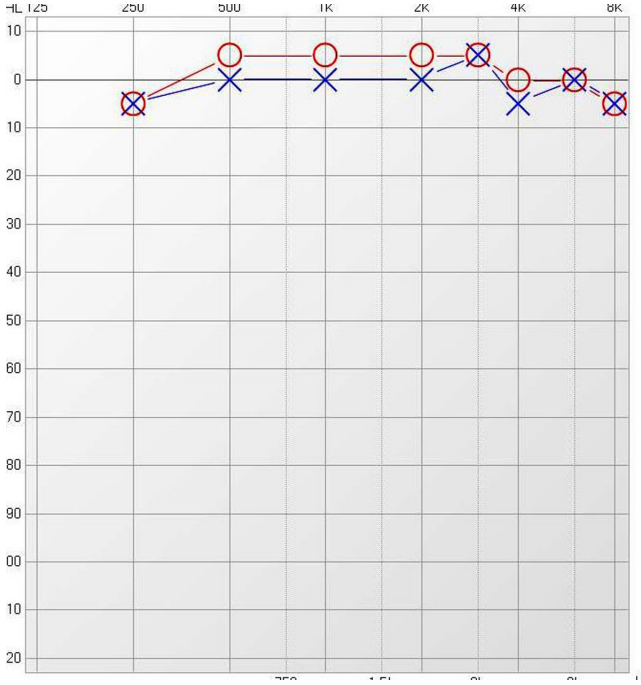


Figure 2. Case 1: (A) PTA, Normal; (B) VHIT, Normal; (C) SHIMP, Normal; (D) Cvemp, 42% asymmetry Left < Right.

Case 3

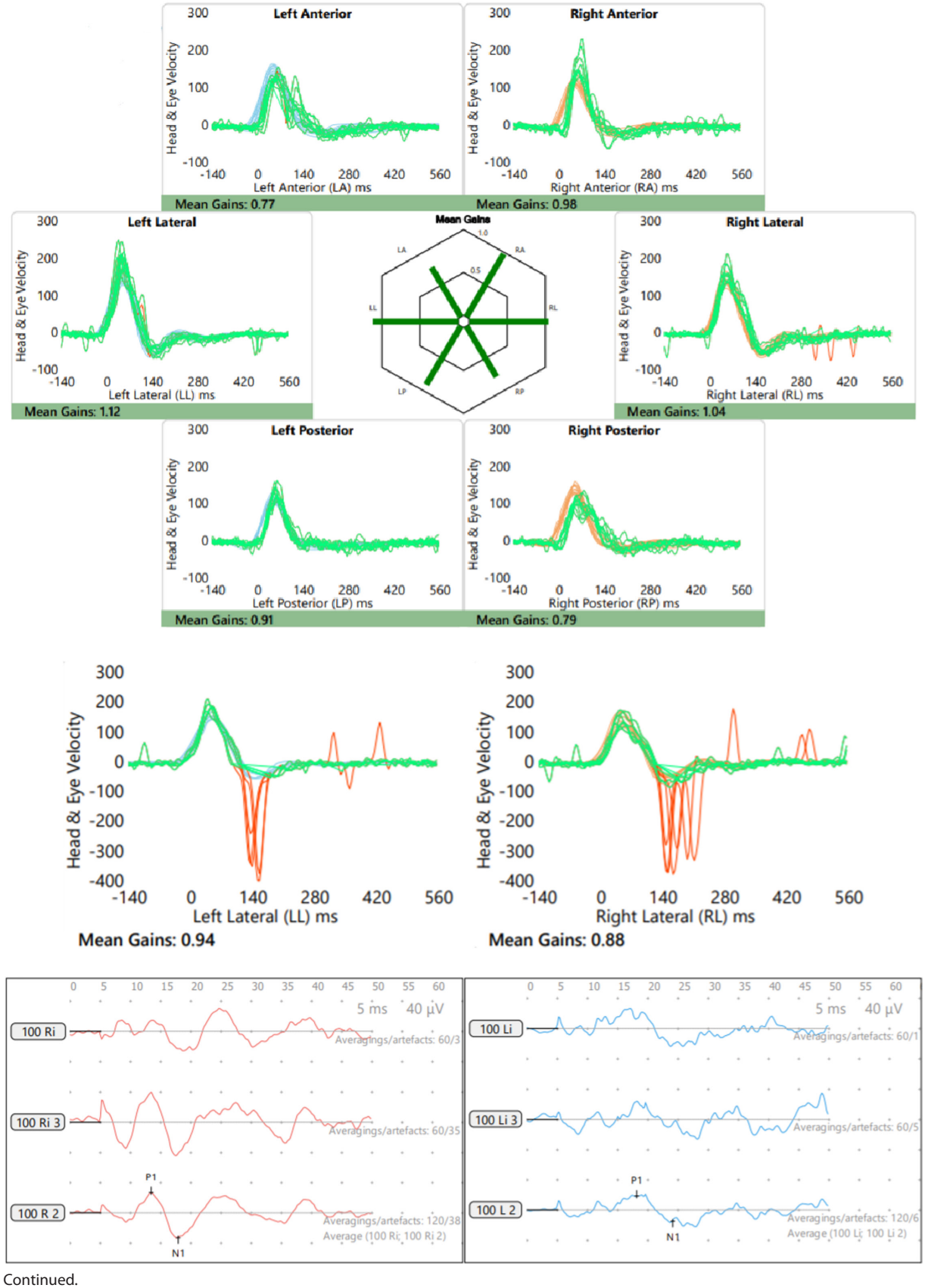
The 16-year-old presented with no audiovestibular symptoms. Peripheral hearing assessment and screening MRI of brain/spine were normal. Vestibular assessment highlighted covert saccades in the left posterior semicircular canal on vHIT with normal gain. SHIMP showed significant asymmetry (38%) with a weaker right side (Figure 4).

DISCUSSION

ELST presents with sensorineural hearing loss (95%), tinnitus (92%), vertigo/disequilibrium (62%),[6](7) and aural fullness (29%)[9](10). The pattern of symptoms in ELSTs may mimic Meniere's disease,[8](9) leading to delays in diagnosis.[10](11)

Currently, biennial audiological testing is performed for all patients with VHL from the age of 5 years and biennial MRI imaging of the brain, spine, and inner ear from the age of 8 years, to monitor for tumors including ELSTs.[2](2) Surveillance MRI can pick up ELSTs at an early, asymptomatic stage.[6] Early detection leads to complete/less complex surgery and hence better outcomes.[6,8](7, 9) Our cases are undergoing this screening process, which is normal so far.

Vestibular symptoms can present with either acute-onset symptoms due to intralabyrinthine hemorrhage, often followed by central compensation; or more insidious-onset symptoms in keeping with slowly developing endolymphatic sac tumors without otic capsule invasion.[11] Vestibular symptoms may coincide with periods of most active hearing loss.[5,9] Similar to auditory symptoms, tumor size was found to be unrelated to vestibulopathy.[11]



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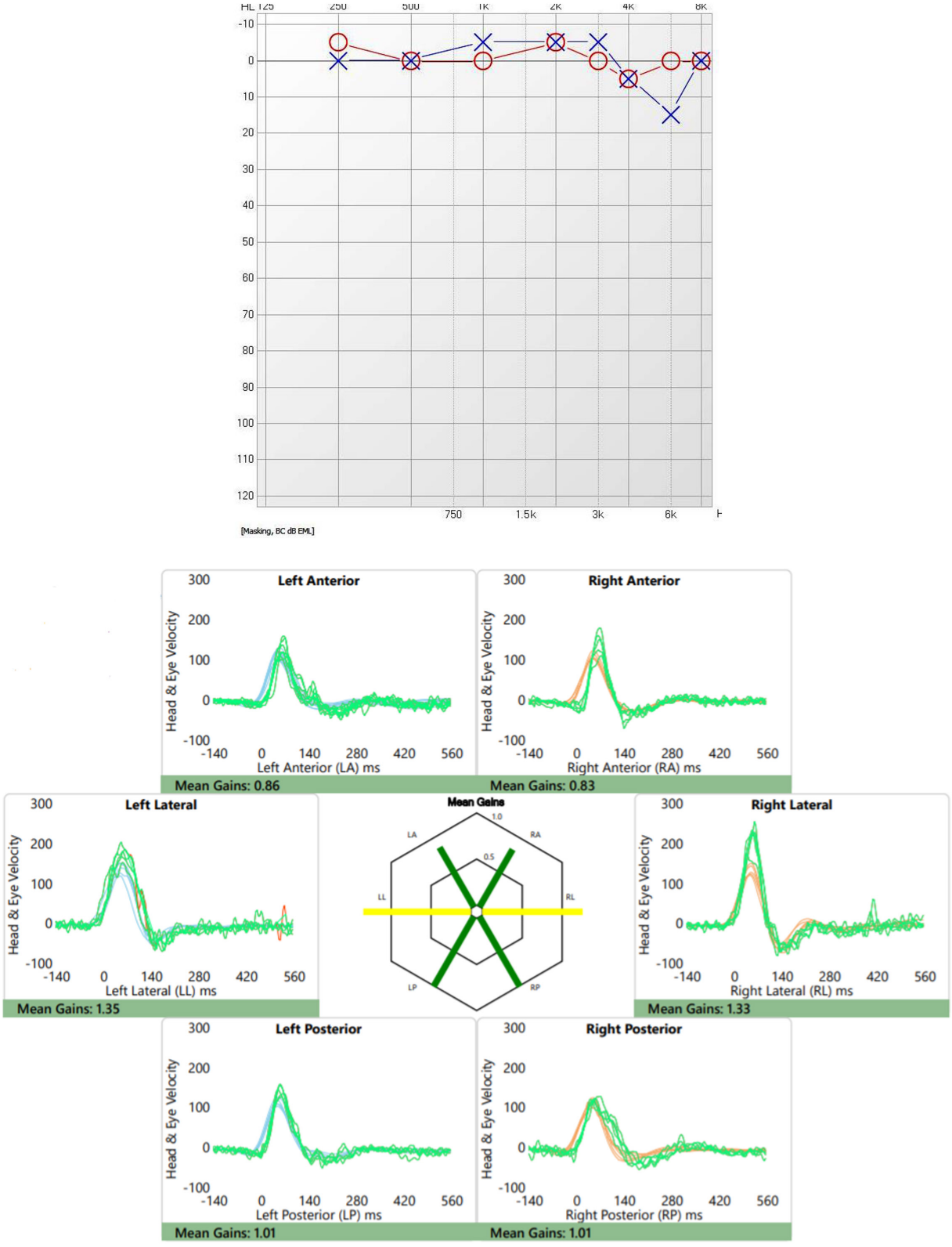

Figure 3. Case 2: (A) PTA, Normal; (B) VHIT, Normal; (C) SHIMP, Normal; (D) Cvemp, Absent response in left ear, normal response in right ear.

The only study investigating vestibular function in VHL/ELST[10] reported formal vestibular diagnostics in 2 cases. The first was a child who showed negative Romberg's/normal calorics/increased gaze positional/vertical optokinetic nystagmus/lowered horizontal optokinetic nystagmus. MRI confirmed an ELST with extension into the interior vestibule/semicircular canals. The second case was an adult with vestibular symptoms but normal electronystagmography/calorics /Romberg test without invasion of the semicircular canals(11).

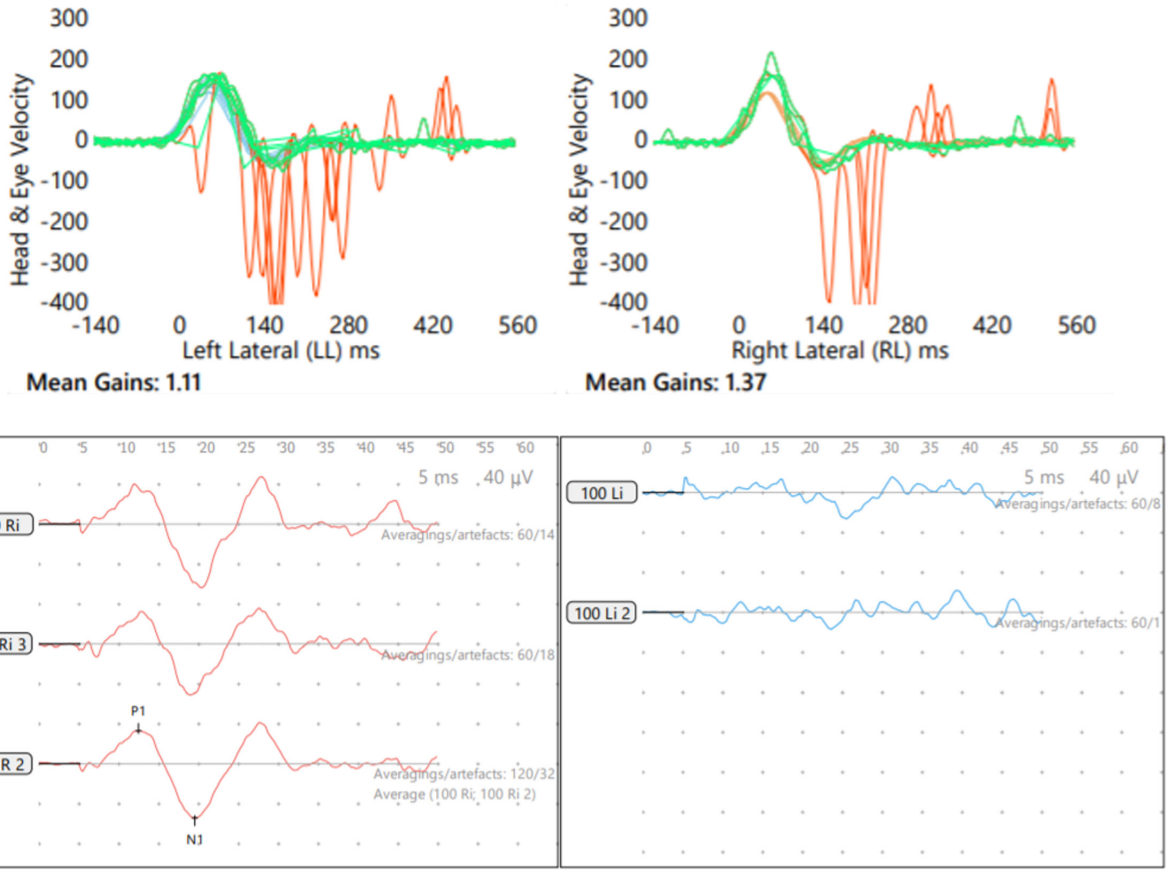

Figure 3. Continued.

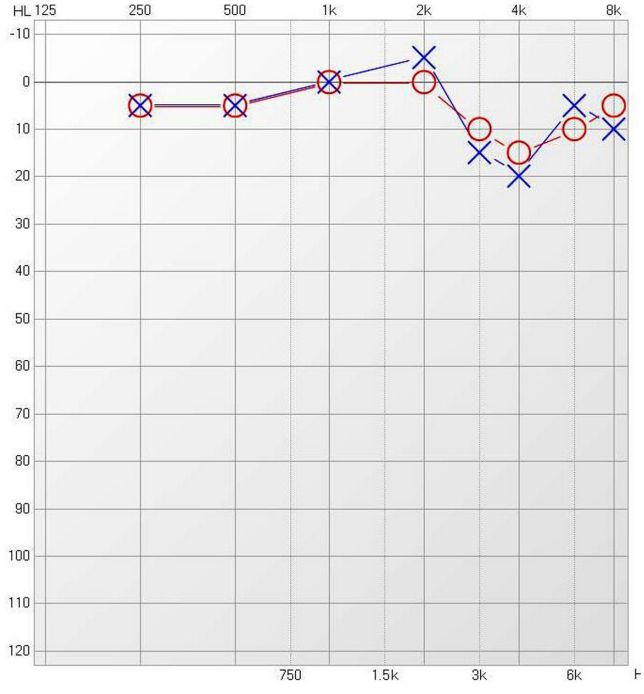

Figure 4. Case 3: (A) PTA, Normal; (B) VHIT, Covert saccades in left posterior semicircular canal (normal gain); (C) SHIMP, Asymmetry of responses 38% (Left > Right); (D) Cvemp, Normal responses.

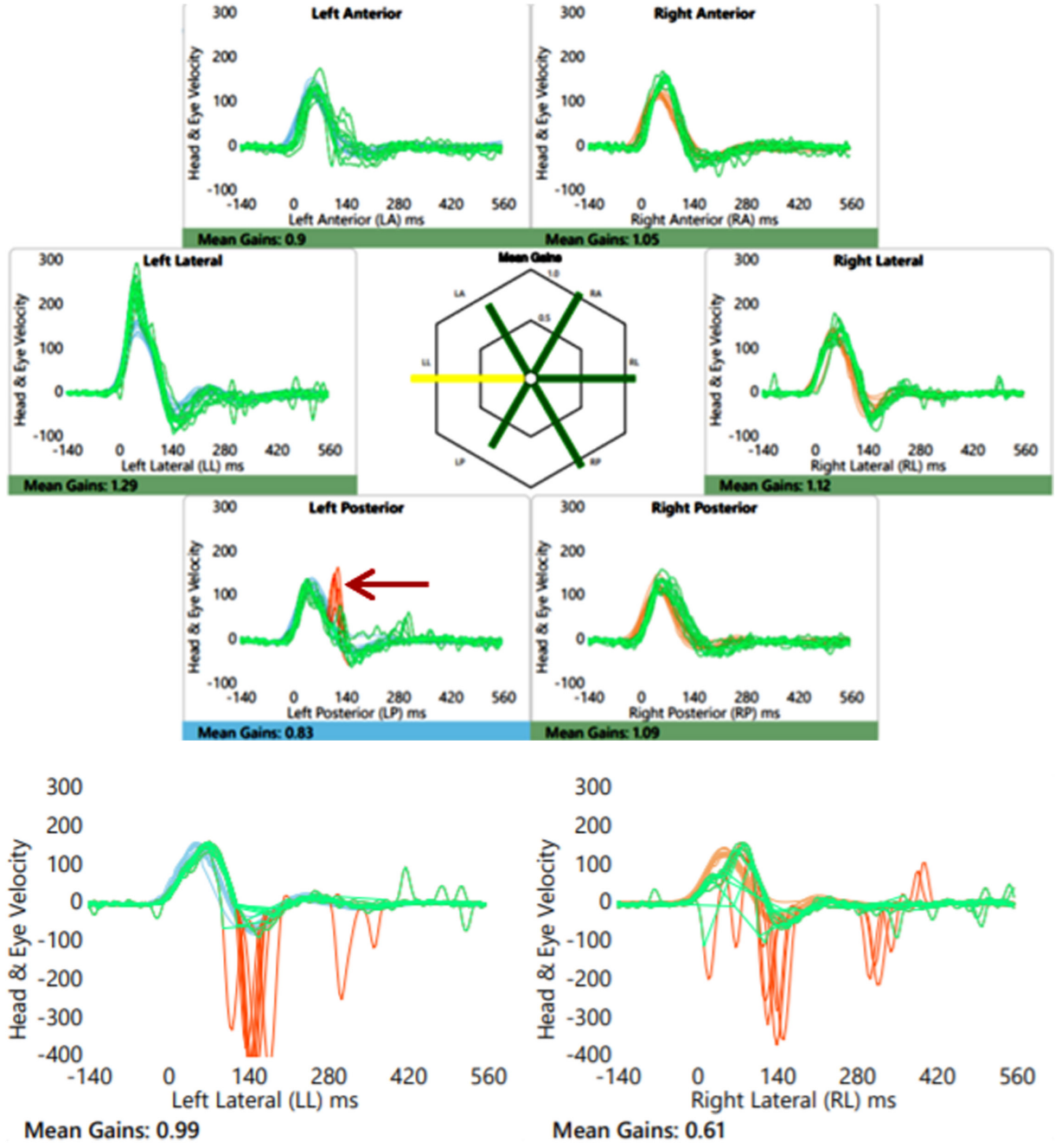

Figure 4. Continued.

(14)Newer objective measurements of vestibular function in children have not been extensively studied. Tests like the vHIT and VEMP in the pediatric population are reliable indicators of vestibular function[12] in children. In our cases, these tests suggested some vestibular hypofunction in all the children in the series. They were asymptomatic due to central compensation.

Cases 1 and 2 showed absence or asymmetry of cVEMPS, suggesting weakness in the saccule/inferior vestibular nerve function. Case 3 showed covert saccades in the posterior semicircular canal on VHIT with normal vestibulo-ocular reflex (VOR) gain, indicating canal weakness. Saccades if present, with normal VOR gain, suggest well compensated vestibular weakness.[13]

The SHIMP test, a new test in objective vestibulometry, indicates compensated vestibular function. As an abnormal SHIMP test is always accompanied by an abnormal lateral semicircular canal, the normal lateral canal vHIT in Case 3 with a significant SHIMP asymmetry is likely to be artifactual.[14]

In all 3 cases, the affected structures are anatomically close to the endolymphatic sac. The scans themselves did not show any ELST, yet the vestibular system showed partial weakness. This could be due to subtle intravestibular endothelial abnormalities including tiny cysts or hemangiomas associated with VHL, or even a very early ELST yet to show up on the scan.

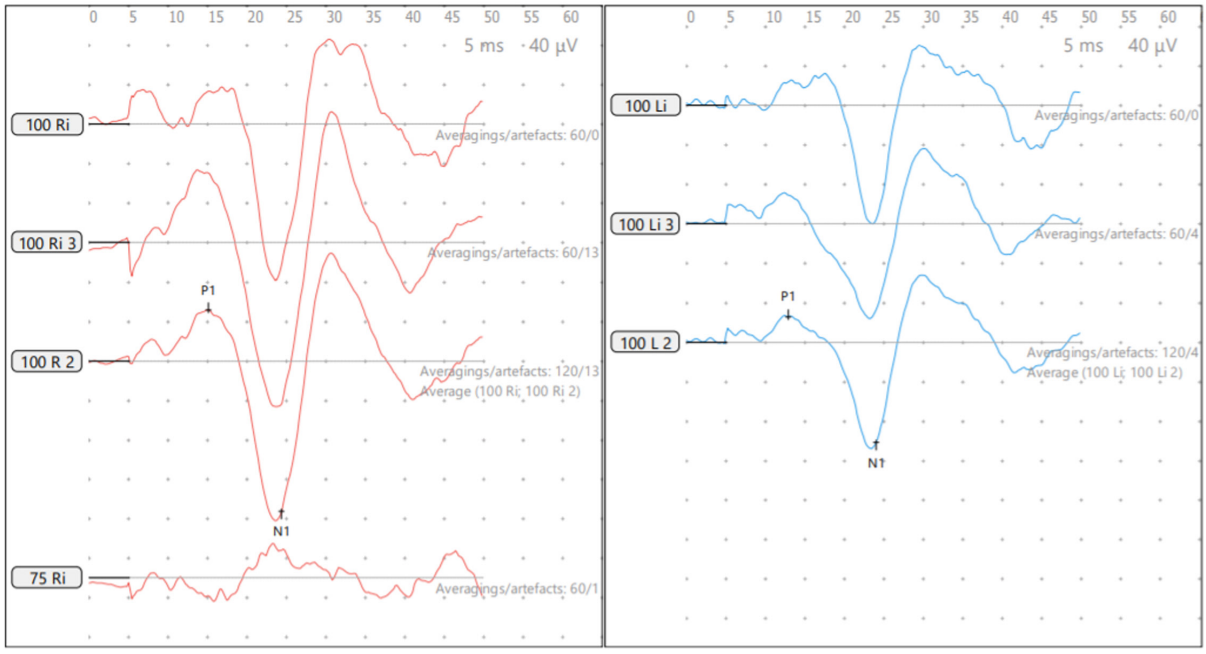

Figure 4. Continued.

Vestibular diagnostics in VHL and in early and evolving ELSTs have not been studied. Hence it is difficult to state the relevance of the abnormalities found in our series with the current level of evidence. From this angle alone, our study is quite unique in identifying objective vestibular hypofunction in VHL in children, and we aim to follow these children up as they mature.

CONCLUSION

We present 3 children with VHL, all showing abnormalities on vestibular diagnostic assessment. While it is known that audiovestibular symptoms may predate imaging findings of ELSTs, it is not known whether vestibular diagnostic assessment may give even earlier clues. Early identification would have a great impact on the treatment and outcome, and hence further study is of interest.

Informed Consent: Verbal/Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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

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