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Acute unilateral vestibulopathy: Clinical presentation, instrumental patterns, evolution and management

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Acute unilateral vestibulopathy: Clinical presentation, instrumental patterns, evolution and management

Topic editors

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Editorial: Acute Unilateral Vestibulopathy: clinical presentation, instrumental patterns, evolution and management

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KEYWORDS

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Editorial on the Research Topic
Acute Unilateral Vestibulopathy: clinical presentation, instrumental patterns, evolution and management

Acute Unilateral Vestibulopathy: clinical presentation, instrumental patterns, evolution and management Acute Unilateral Vestibulopathy (AUV) represents severe, continuous, and long-lasting vertigo with sudden onset due to acute damage involving either the vestibular nerve or the labyrinthine end-organs. Although most subjects recover spontaneously, several patients develop residual disorders, such as chronic dizziness, disequilibrium, spatial disorientation, and limitations in daily activities. More than a century after the first description, Acute Unilateral Vestibulopathy (AUV) is a syndrome whose etiopathogenesis is still debated. It represents a challenging and intriguing pathology for clinicians from a diagnostic and therapeutic point of view, particularly for the aspects linked to its evolution and the development of vestibular compensation (1, 2).

As the title indicates, this Research Topic entitled "*Acute Unilateral Vestibulopathy: clinical presentation, instrumental patterns, evolution, and management*" covers some of the multiple aspects associated with losing the function of one of the two labyrinths in the light of the latest international guidelines (3, 4).

Two articles in this collection address the issue of the epidemiology and relative etiopathogenesis of AUV. Viberti et al. assessed the epidemiological features of AUV in three different districts in Italy, showing how the estimated incidence is higher than previously reported in the literature. During the COVID-19 pandemic, the epidemiology of several diseases has changed worldwide. The impact of COVID-19 vaccination on AUV development in the setting of a tertiary interdisciplinary neurotology center was retrospectively investigated by Schmid et al..

The video head impulse test (vHIT) is an irreplaceable tool for recognizing the different AUV patterns in an emergency department and following their evolution over time. Alfarghal et al. after a comprehensive literature review, examined the VOR gain assessed using the vHIT in acute vestibular syndromes and proposed a grading scale for the severity of VOR impairment of lateral semicircular canal similar to the current grading for hearing loss based on pure tone audiometry. The clinical implications of vHIT in patients suffering from BPPV secondary to idiopathic sudden sensorineural hearing loss were investigated by Liu et al. who demonstrated that in this subpopulation, the vestibular function and, in particular, the posterior semicircular canal appears to be impaired compared to what was found in patients affected by idiopathic BPPV. The vHIT devices currently in use usually record the track from only one eye. A newer vHIT device allowing a simultaneous record of binocular vHIT has been the subject of a cross-sectional, prospective study by Striteska, Chovanec et al.. The article provided normative values reflecting the conjugacy of eye movement responses to horizontal binocular vHIT in healthy participants.

Vestibular damage and hypofunction could be associated with sudden sensorineural hearing loss since cochleovestibular structures share the same vascularization and are in close anatomical proximity. A retrospective study was conducted by Castellucci et al. to evaluate the specific lesion patterns of vestibular damage in patients presenting with sudden sensorineural hearing loss with or without vertigo and assess the prognostic role of vestibular dysfunctions on hearing recovery, suggesting that vestibular evaluation in SSNHL can provide helpful information on hearing recovery and underlying etiologies.

The ability to compensate and the strategies with which this occurs represent the main question when diagnosing a vestibulopathy. Bedside and instrumental test batteries provide suggestions on each patient's ability to recover, but to date, there needs to be more data on the prognostic value of each test. In a prospective observational case-control study, Striteska, Valis et al. aimed to assess the ability of a head-shaking test (HST) to reflect vestibular compensation in patients after acute vestibular loss, showing how the intensity of nystagmus induced by HST decreased exponentially over time, declining to the value of the control group once vestibular compensation was satisfactory and sufficient for a patient's everyday life. In contrast, well-detectable head-shaking induced nystagmus in subjects with insufficient clinical recovery patients served as an objective indicator of poorly compensated unilateral vestibular loss. Vestibular compensation is strictly linked to the level of physical activity practiced after the acute event and reflects the patient's quality of life. The association between the level of physical activity and chronic dizziness was assessed by Van Laer et al. in a retrospective cohort study on 66 patients who underwent vestibular schwannoma resection.

The onset of an acute vestibular syndrome requires urgent pharmacological management due to the critical procession of symptoms accompanying the event, which therapeutic choices and intervention timing can positively or negatively influence. Viola et al. reviewed the pharmacological therapeutic option, correlating them to the differential and, as far as possible, to the etiological diagnosis.

Finally, this Research Topic includes Finally, this Research Topic includes the description of some clinical cases peculiar to rarity and iconography: the ossification of a posterior semicircular canal following an AUV and mimicking inferior vestibular neuritis was reported by Comacchio and Castellucci whereas three cases of cerebellitis in anti-Yo paraneoplastic syndrome were described and discussed by Kherallah et al..

The Editors hope that this Research Topic can represent a valuable contribution for all clinicians involved in otoneurology, particularly those involved in diagnosing and treating patients affected by acute vestibular syndromes.

Author contributions

SM and ACast wrote the manuscript. All editors designed the Research Topic, reviewed the manuscript, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Video Head Impulse Test Findings in Patients With Benign Paroxysmal Positional Vertigo Secondary to Idiopathic Sudden Sensorineural Hearing Loss

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Benign paroxysmal positional vertigo (BPPV) is amongst the most common causes of episodic vestibular syndrome. It can be classified as idiopathic and secondary types according to the causative factors, and the underlying mechanism between idiopathic (i-BPPV) and secondary BPPV (s-BPPV) may differ. Idiopathic sudden sensorineural hearing loss (ISSNHL) has been considered as a common inner ear disease that precipitates s-BPPV. Yet, few studies have addressed the functional impairment of the semicircular canal (SCC) system in patients with s-BPPV associated with ISSNHL. Our purpose was to explore the pathophysiological mechanism and investigate the clinical implications of video head impulse test (vHIT) in these patients. Here, the clinical and laboratory data of patients with BPPV secondary to ISSNHL, including the results of vHIT, were retrospectively reviewed, and compared with those of patients with i-BPPV. Pathological vHIT findings (low vestibulo-ocular reflex gain and re-fixation saccade), which mainly affected the posterior SCC, were more common in the s-BPPV group than in the i-BPPV group (41.9 and 0%, respectively). The incidence of horizontal SCC involvement was also higher in the s-BPPV group (45.16 and 16.67%, respectively). Furthermore, patients with s-BPPV showed lower vHIT gains of the posterior and horizontal SCCs in affected ears than in unaffected ears. Compared to i-BPPV, posterior SCC paresis detected by vHIT is more prevalent in BPPV secondary to ISSNHL. This dysfunction may be associated mainly with vestibular impairments caused by ISSNHL, and not with BPPV *per se*.

Keywords: benign paroxysmal positional vertigo (BPPV), video head impulse test (vHIT), caloric test, idiopathic sudden sensorineural hearing loss (ISSNHL), vestibulo-ocular reflex (VOR)

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is defined as a sensorineural hearing loss of 30 dB or more in at least three consecutive frequencies occurring within 72 hours (1). In most cases, no specific cause for the hearing loss can be identified, and these patients are classified as idiopathic SSNHL (ISSNHL). Numerous etiologies have been proposed, such as vascular insufficiency, viral infection, and immunologic reaction.

Clinically, about 30% of patients with ISSNHL also manifested vestibular symptoms, such as vertigo or imbalance (2). These vestibular symptoms can take the form of an acute vestibular syndrome (similar to vestibular neuritis, VN) (3), or an episodic vestibular syndrome, for instance, benign paroxysmal positional vertigo (BPPV) (4). BPPV is believed to be caused by detached otoconia from the utricular maculae, which migrate into the semicircular canals (SCCs) and may either move freely in the endolymph (canalithiasis) or become attached to the cupula (cupulolithiasis). Although its etiology is still elusive, BPPV falls into idiopathic and secondary categories according to causative factors, the latter include trauma, Ménière's disease, SSNHL, VN, etc. Recently, some studies have explored BPPV associated with ISSNHL, regarding to its possible pathophysiological mechanism, clinical characteristics, treatment outcomes, and prognosis (4, 5).

To examine the pathophysiological features of patients with vestibular impairments associated with SSNHL, many instrumental vestibular evaluations, such as caloric test and vestibular evoked myogenic potentials (VEMPs), have been explored (6, 7). Traditionally, the caloric test evaluates the vestibulo-ocular reflex (VOR) function of the horizontal SCC using non-physiological stimulus within the frequency range of 0.002–0.004 Hz (8). As a newly developed test, the video head impulse test (vHIT) assesses the angular VOR function of six SCCs within the physiological frequency range (5–7 Hz) (9). For ISSNHL patients with acute vertigo, some novel characteristics of vestibular lesions have been detected by vHIT recently (3, 10). Most of these patients exhibited posterior SCC dysfunction (3, 11), which could serve as a specific prognostic tool for predicting poor hearing recovery in patients with ISSNHL (12). VN, another typical variant of acute vestibular syndrome, shows mainly vestibular impairment in the horizontal and anterior SCC (as in superior VN). Infrequently, the posterior SCC may also be involved, which occurs in inferior or total VN (13–15). As for patients with BPPV secondary to ISSNHL, a common episodic vestibular syndrome following ISSNHL, few studies have so far addressed functional impairment in the SCC system (3, 16).

In this study, we retrospectively reviewed the clinical and laboratory data of patients with BPPV secondary to ISSNHL, including the results of vHIT. Our purpose was to investigate the clinical implications of vHIT in these patients.

MATERIALS AND METHODS

Study Population

A single-center retrospective chart review was conducted at the Department of Otorhinolaryngology, Union Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

The clinical data of patients with BPPV secondary to ISSNHL who attended our outpatient clinic from 2016 January to 2021 October were retrospectively reviewed. Inclusion criteria were: (1) the diagnosis of ISSNHL is established according to the clinical practice guideline of sudden hearing loss proposed by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) in 2012 (1); (2) BPPV is diagnosed according to the diagnostic criteria proposed by the Barany Society in 2015 (17), based on the Dix-Hallpike and Roll tests. (3) Patients underwent both the caloric test and vHIT. In addition, a series of consecutive patients with idiopathic BPPV (i-BPPV) were enrolled as control subjects. According to the diagnostic criteria (17), the included BPPV subtypes were: canalithiasis of the posterior canal (PC-BPPV), canalithiasis of the horizontal canal (HC-BPPV-CA), and cupulolithiasis of the horizontal canal (HC-BPPV-CU).

Exclusion criteria were: (1) other concurrent vestibular disorders (Ménière's disease, VN, vestibular migraine, etc.); (2) BPPV secondary to other disease, such as head trauma, VN, and Ménière's disease; (3) middle ear infections (otitis media, mastoiditis, etc.); (4) middle or inner ear anomaly; (5) having received previous ear surgery; (6) retrocochlear lesions; and (7) central nervous system disorders (multiple sclerosis, cerebellar infarction, etc.).

This study was conducted in strict accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from each patient, and the project was approved by the ethical committee of Union hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Examination Procedure

The diagnosis of BPPV was established based on a history of recurrent positional vertigo and the presence of typical positional nystagmus on the Dix-Hallpike and roll test. For patients with secondary BPPV (s-BPPV), comprehensive neurotologic evaluations, including audiometry, videonystagmography, caloric test, and vHIT were conducted on the same day. Alternatively, patients with i-BPPV only received the vHIT. For all patients with ISSNHL, non-contrast routine magnetic resonance imaging (MRI) was performed to rule out retro-cochlear pathology. If a retro-cochlear lesion was suspected, contrast-enhanced MRI would be ordered.

Pure Tone Audiometry

After excluding middle ear pathologies by otoscopic examination and tympanometry test, a pure tone audiometry test was conducted in a sound-proof cabin in the frequency range of 0.25–8 kHz. Pure tone average (PTA) was calculated as the simple arithmetic mean for the frequencies of 0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 kHz. Configurations of initial audiogram were categorized into four types (7): high-frequency hearing loss, low-frequency hearing loss, flat-type hearing loss, and profound hearing loss (a flat audiogram with a threshold shift >90 dB at all frequencies).

Video Head Impulse Test

The vHIT was conducted using an ICS Impulse system (GN Otometrics, Denmark) following the manufacturer's instructions by experienced technicians. Each patient wore a pair of lightweight, tight-fitting goggles equipped with a small video oculography camera to record and analyze the eye movement. Each patient was seated upright facing the wall 1.0 m away and was instructed to fixate a stationary target on the wall. The patient's head was passively and randomly rotated with a low amplitude (5–15°) and at a high peak velocity (150–250°/s) in an abrupt, brief, and unpredictable manner. At least 20 head impulses were delivered in each direction. Refixation saccades

were categorized, against their appearance, as covert and overt. If the velocity of the saccade exceeded 50°/s, they were deemed positive. In the present study, it was considered abnormal if the horizontal vHIT gain <0.8 or vertical vHIT gain <0.7 and refixation saccades appeared.

Caloric Test

The bithermal caloric test was conducted using infrared videonystagmography (Visual Eyes VNG, Micromedical Technologies, Chatham, IL, USA). The subject was placed in a supine position with their head and upper trunk elevated at 30°. Each ear was alternately irrigated with a constant flow of air, with the temperature for warm and cool stimulation set at 50 and 24°C, respectively. The duration of each caloric irrigation lasted 60 s. Upon each irrigation, the maximum slow phase velocity (SPV_{max}) of the caloric nystagmus was measured, and the canal paresis (CP) was calculated by using the Jongkees' formula. In this study, if the interaural asymmetry of the caloric nystagmus was ≥ 25%, CP was considered to be significant in the horizontal SCC, indicating an abnormal caloric response. According to the published criteria, if the summed SPVmax was <20°/s under four stimulation conditions, the caloric response is believed to indicate bilateral vestibular hypofunction. In this case, ice water irrigation (4°C, 1.0 ml) would be used to confirm the caloric unresponsiveness.

Treatment and Follow-Up

Our treatment protocol conforms to the Chinese guideline for diagnosis and treatment of sudden deafness (2015) (18). Prednisolone was administered orally at a dose of 60 mg daily for six consecutive days, followed by a taper of 30, 20, 10, and 5 mg each for 2 days. Patients with lower body weight (<60 kg) were started on 1 mg/kg oral prednisolone daily, with this amount gradually tapered. Additional medication included vasoactive drugs (ginkgo biloba extract) and anticoagulant thrombolytic drugs (fibrinolytic enzyme). If conservative treatment failed, i.e., no hearing improvement after a 2-week conservative therapy, subsequent intratympanic dexamethasone injection (two times weekly for 2 weeks) or hyperbaric oxygen therapy would be suggested.

Canalith repositioning procedures (CRPs) were performed in both the s-BPPV and i-BPPV groups based on the subtypes of BPPV. Patients with PC-BPPV received the Epley procedure, while patients with HC-BPPV received the Gufoni maneuver (19). Patients were scheduled to return to the clinic at intervals of approximately 1 week until symptoms and typical positional nystagmus during the triggering maneuver completely disappeared.

According to the clinical practice guideline (AAO-HNS, 2012) (1), patients with a hearing gain of <15 dB (change in PTA, in decibels) were considered as treatment non-responders (NR), and the patients with a hearing gain ≥15 dB were classified as treatment responders. Treatment responders were further divided into three groups: (1) recovered to a hearing level within 10 dB of the unaffected ear (complete recovery, CR), (2) recovered to at least 50% of the maximum possible recovery (good recovery, GR), and (3) recovered below 50% of the maximum possible recovery (poor recovery, PR). Maximum possible recovery is defined as reaching the hearing level of the contralateral ear, which was considered as the baseline of normal hearing.

TABLE 1 | Demographic and clinical characteristics of patients with s-BPPV and i-BPPV.

	s-BPPV ($n = 31$)	i-BPPV ($n = 30$)
Gender (male/female)	13/18	8/22
Age (yr.)	53.03 ± 12.35	53.20 ± 13.21
Course duration (days)	12 (6, 43)	15.5 (6.5, 30)
Subtype of BPPV (PC-BPPV/HC-BPPV-CA/HC-BPPV-CU)	17/7/7	25/4/1

s-BPPV, secondary benign paroxysmal positional vertigo; i-BPPV, idiopathic benign paroxysmal positional vertigo; PC-BPPV, canalithiasis of the posterior canal; HC-BPPV-CA, canalithiasis of the horizontal canal; HC-BPPV-CU, cupulolithiasis of the horizontal canal.

Statistical Analyses

Statistical analysis was performed with SPSS software (version R26.0.0.2). All continuous variables are presented as means ± standard deviations (SD) or median and interquartile range (IQR 25th to 75th percentiles) after the verification of normal distribution. Quantitative data with normal distribution between subgroups were compared using the independent-sample *t*-test or paired *t*-test. Non-normally distributed data were compared using the Mann–Whitney *U* test or Wilcoxon signed-rank test. The Chi-squared test and Fisher exact test were performed for categorical variables. The values of $p < 0.05$ were assumed as statistically significant.

RESULTS

From 2016 to 2021, a total of 47 patients were diagnosed as BPPV secondary to ISSNHL, and 31 of them completed instrumental vestibular tests battery, including vHIT and caloric test. Additionally, 30 consecutive patients with i-BPPV were enrolled as a control group.

Comparisons Between Patients With s-BPPV and Those With i-BPPV

The demographic and clinical characteristics of the patients with s-BPPV and i-BPPV are summarized in **Table 1**. No differences were observed in terms of gender ($\chi^2 = 1.575$, $p = 0.21$), age ($t = -0.051$, $p = 0.959$), and course duration ($U = 448.5$, $p = 0.812$) between the two groups.

In the s-BPPV group, 13 cases (13/31, 41.9%) showed pathological vHIT findings (low VOR gain and refixation saccade), with the posterior SCC being the most affected (13/13), followed by the horizontal SCC (5/13). Meanwhile, all patients with i-BPPV showed normal vHIT results. Compared to their idiopathic counterparts, patients with s-BPPV had lower vHIT gains in the posterior ($t = -5.280$, $p < 0.001$) and anterior SCC ($t = -4.575$, $p < 0.001$) of the affected side. No significant

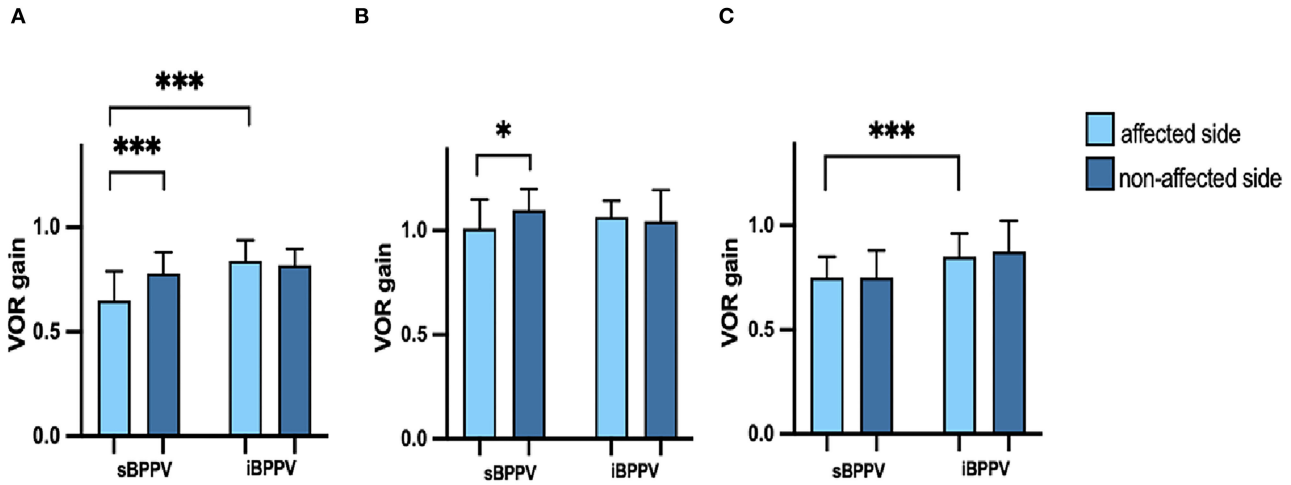

FIGURE 1 | (A) Vestibular-ocular reflex (VOR) gains of the posterior semicircular canal (SCC) in patients with secondary benign paroxysmal positional vertigo (s-BPPV) and idiopathic BPPV (i-BPPV); **(B)** VOR gains of horizontal SCC in patients with s-BPPV and i-BPPV; **(C)** VOR gains of the anterior SCC in patients with s-BPPV and i-BPPV. An upper end of the box is the median. The whisker is the interquartile range (IQR). *$p < 0.05$; ***$p < 0.001$.

difference was demonstrated between the two groups regarding vHIT gain in the horizontal SCC ($t = -1.320$, $p = 0.192$) (**Figure 1**).

The mean VOR gains for the anterior, horizontal, and posterior SCC of both affected and non-affected ears are shown in **Table 2**. In the s-BPPV group, VOR gains of the horizontal ($t = -2.566$, $p = 0.016$) and posterior SCC ($t = -5.673$, $p < 0.001$) in the affected ears were lower than those in the unaffected ears, respectively (**Figure 1**). No interaural difference for VOR gains of the anterior SCC was observed in either group (**Figure 1**).

There were 17 PC-BPPV (17/31, 54.84%), seven HC-BPPV-CA (7/31, 22.58%), and seven HC-BPPV-CU cases (7/31, 22.58%) in the s-BPPV group. And, the i-BPPV group consisted of 25 patients with PC-BPPV (25/30, 83.33%), four patients with HC-BPPV-CA (4/30, 13.33%), and only one patient with HC-BPPV-CU (1/30, 3.33%) (**Table 1**; **Figure 2**). The proportions of BPPV subtypes was significantly different between the two groups ($\chi^2 = 7.407$, $p = 0.026$). Pairwise comparison revealed that the proportion of PC-BPPV in the s-BPPV group was lower than that in the i-BPPV group. And, the HC-BPPV-CU was more prevalent in the s-BPPV group than in the i-BPPV group. If HC-BPPV-CA and HC-BPPV-CU were collectively classified as HC-BPPV, horizontal SCC was more susceptible to BPPV pathology in the s-BPPV group (14/31, 45.16%) than in the i-BPPV group (5/30, 16.67%) ($\chi^2 = 5.772$, $p < 0.05$).

In our s-BPPV group, most patients (27/31) suffered an acute vertigo attack simultaneously with a sudden hearing loss, lasting about 1–3 days. As acute vestibular symptoms gradually subsided, episodic positional vertigo became evident (**Table 3**). The remaining four patients with s-BPPV had no concomitant vestibular symptoms at the time of sudden hearing loss. Positional vertigo developed within 4 days after the onset of hearing loss. The median interval between the onset of postural vertigo and the diagnostic positional tests for patients with s-BPPV and those with i-BPPV was 12 and 15.5 days, respectively (**Table 1**).

TABLE 2 | vHIT gains of the anterior, horizontal, and posterior semicircular canals in patients with s-BPPV and i-BPPV.

SCCs		vHIT gains	
		s-BPPV	i-BPPV
Anterior SCC	Affected side	0.73 ± 0.14	0.88 ± 0.11
	Non-affected side	0.75 (0.70, 0.88)	0.89 ± 0.18
Horizontal SCC	Affected side	1.01 ± 0.21	1.07 ± 0.12
	Non-affected side	1.10 ± 0.12	1.07 ± 0.20
Posterior SCC	Affected side	0.61 ± 0.20	0.84 ± 0.12
	Non-affected side	0.78 (0.72, 0.88)	0.83 ± 0.11

s-BPPV, secondary benign paroxysmal positional vertigo; i-BPPV, idiopathic benign paroxysmal positional vertigo; SCC, semicircular canal; vHIT, video head impulse test.

Comparison Between s-BPPV Patients With Normal vHIT and Those With Abnormal vHIT

There were 13 patients with abnormal vHIT and 18 patients with normal vHIT in the s-BPPV group. The demographic and clinical characteristics of these two subgroups are illustrated in **Table 3**. Age ($\chi^2 = 0.111$, $p = 0.739$), gender ($t = -0.215$, $p = 0.831$), and course duration ($U = 106.5$, $p = 0.674$) did not differ between patients with abnormal and normal vHIT findings.

No differences were observed between these two subgroups in the incidence of acute vertigo ($p = 0.120$), audiogram configurations ($p = 0.099$), hearing outcome ($p = 0.183$), and incidence of spontaneous nystagmus ($p = 0.052$).

Compared to patients with normal vHIT, those with abnormal vHIT showed a significantly increased CP value in the caloric test ($t = 5.854$, $p < 0.001$). Patients with abnormal vHIT were more likely to have an abnormal caloric response ($p < 0.001$).

The VOR gains of the horizontal SCC ($t = -4.432$, $p < 0.001$) and posterior SCC ($t = -5.752$, $p < 0.001$) in the affected ears were significantly lower in the abnormal vHIT group than in the normal vHIT group, respectively. VOR gains of the anterior SCC in affected ears did not differ between the two subgroups ($t = -1.066$, $p = 0.295$) (**Figure 3**).

All patients were given a CRP according to BPPV subtypes. Three patients in the s-BPPV group and five patients in the i-BPPV group adhered to regular follow-up visits on weekly basis, and others were lost to follow-up. In two of the three s-BPPV patients, three CRP sessions were needed to completely resolve the positional vertigo and nystagmus, and in one of the five patients with i-BPPV, two CRP sessions were needed. Due to inadequate data, the number of CRPs in the two groups was not compared in this study.

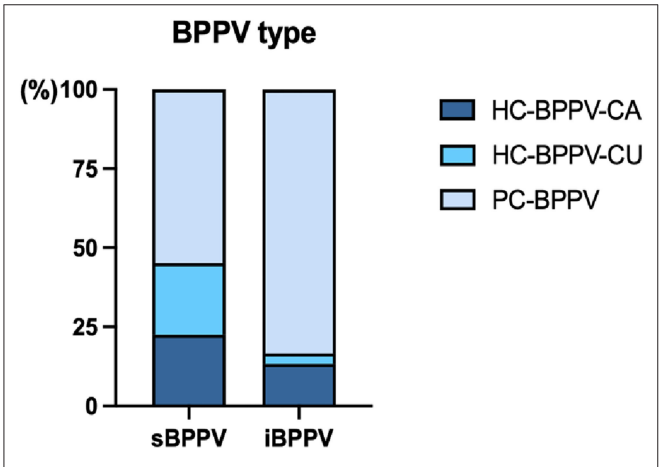

FIGURE 2 | The proportion of posterior semicircular canal canalithiasis (PC-BPPV), horizontal semicircular canal canalithiasis (HC-BPPV-CA), or cupulolithiasis (HC-BPPV-CU) in patients with idiopathic BPPV ($n = 30$) and BPPV secondary to ISSNHL ($n = 31$).

DISCUSSION

Comparisons Between Patients With s-BPPV and Those With i-BPPV

In this study, pathological vHIT response was common in the s-BPPV group, and the posterior and horizontal vHIT gains were lower in the affected side than those in the contralateral side. However, all patients in the i-BPPV group had normal vHIT, and VOR gains in the corresponding SCCs did not differ between the affected and non-affected sides. These results indicated that the pathological vHIT response in BPPV secondary to ISSNHL were mainly attributed to the vestibular impairments caused by ISSNHL, not BPPV *per se*.

In 2004, Rambold et al. for the first time, assessed the high-frequency VOR function in two patients with horizontal BPPV and ipsilateral hearing loss by using the three-dimensional scleral search coil technique. They reported vHIT gain deficit in the posterior and horizontal SCCs ipsilateral to the hearing loss ear (16). In a recent meta-analysis, by comparing the VOR gains of the three SCCs on the affected side relative to those in the contralateral side, and/or healthy controls, Elsherif et al. (20) detected a significant reduction of the posterior vHIT gain in patients with BPPV. Several explanations have been proposed. Disturbance of endolymphatic hydrodynamics in the posterior SCC due to free-floating particles (canalithiasis) has been suggested (21), but this hypothesis remains controversial as other investigators found no significant impairment of VOR gain for the affected posterior SCC in patients with PC-BPPV involving the ampullary arm (22, 23). Canalith jam, either partial or complete type, could lead to decreased VOR gain in response

TABLE 3 | Demographic and clinical characteristics of patients with s-BPPV with abnormal vHIT results and those with normal vHIT results.

		Abnormal vHIT ($n = 13$)	Normal vHIT ($n = 18$)	Test statistics	*P*-value
Gender (male/female)		5/8	8/10	$\chi^2 = 0.111$	0.739
Age (yr.)		52.46 ± 13.59	53.44 ± 11.77	$t = -0.215$	0.831
Course duration (days)		8 (3.5, 57.5)	14 (6, 33.25)	U = 106.5	0.674
Accompanied symptom (with/without vertigo)		13/0	14/4	-	0.120
Audiogram configurations (up/down/flat/profound)		0/8/0/5	1/4/3/10	-	0.099
Outcome of hearing (CR/GR/PR/NR)		0/0/3/10	0/4/5/9	-	0.183
Rate of SN		53.85% (7/13)	16.67% (3/18)	-	0.052
Caloric test	CP value	53.85 ± 22.74	16.89 ± 12.17	$t = 5.854$	<0.001
	Abnormal rate	92.31% (12/13)	27.78% (5/18)	-	0.001
Type of BPPV (PC-BPPV/HC-BPPV-CA/HC-BPPV-CU)		5/3/5	12/4/2	$\chi^2 = 3.487$	0.168
vHIT gains of affected side	Anterior SCC	0.70 ± 0.16	0.75 ± 0.12	$t = -1.066$	0.295
	Horizontal SCC	0.86 ± 0.20	1.13 ± 0.14	$t = -4.432$	<0.001
	Posterior SCC	0.44 ± 0.17	0.74 ± 0.12	$t = -5.752$	<0.001

SCC, semicircular canal; vHIT, video head impulse test; CR, complete recovery; GR, good recovery; PR, poor recovery; NR, non-responder; SN, spontaneous nystagmus; CP, canal paresis. Up-sloping and down-sloping audiogram configurations correspond to low-frequency and high-frequency hearing loss, respectively.

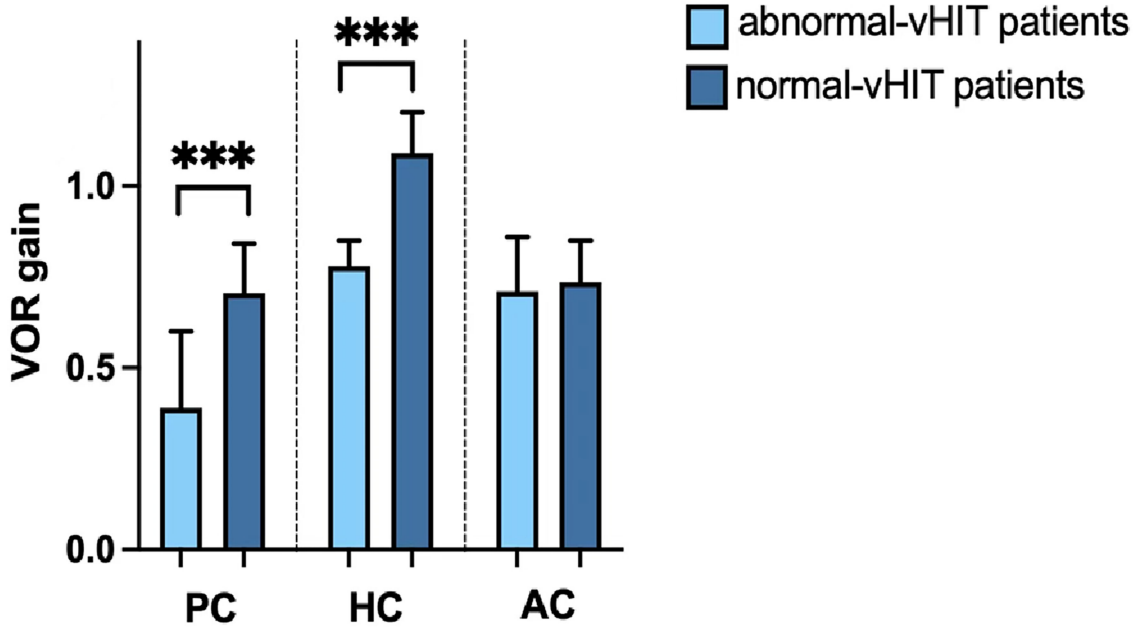

FIGURE 3 | vHIT gains for the posterior canal (PC), horizontal canal (HC), and anterior canal (AC) of patients with s-BPPV with abnormal vHIT results and those with normal vHIT results. ***$p < 0.001$.

to vHIT. The mechanical occlusion of the narrow portion of SCC and resultant blockage of the endolymphatic flow may temporarily inhibit dynamic responses of cupular receptor to high-frequency stimulation (24). The jam also could produce a persistent transcupular pressure gradient and cause cupula deflection in either excitatory or inhibitory direction (25, 26). This cupular deflection may bias the optimal operating point of vestibular hair cells, thus decrease the cupular sensitivity to high-frequency stimulation, resulting in reduced VOR gain for vHIT (27, 28). In addition, a neuropathic mechanism of BPPV should be considered. A quantitative temporal bone study revealed significant neurodegeneration (over 50% of cell loss) in both the superior and inferior vestibular ganglion of patients with documented BPPV (29, 30). However, the etiology of BPPV, i.e., idiopathic or secondary, has not been specified in most of the included studies in this meta-analysis (21, 31–34). Our study showed that, compared with their idiopathic counterparts, patients with s-BPPV showed an obvious interaural difference in vHIT gains in the corresponding SCCs, which indicated that the underlying causes (idiopathic or secondary to ISSNHL) of BPPV may significantly impact the high-frequency VOR function.

We found that the abnormal vHIT response occurred most frequently in the posterior SCC, followed by the horizontal and anterior SCC. These findings were in line with previous studies, which have demonstrated that the reduced vHIT gain was most prevalent in the posterior SCC in the ISSNHL patients with acute vertigo (3, 10, 35). Anatomically, the shared susceptibility of posterior SCC and cochlea (and possibly saccule) may likely reflect the common vascular supply of the pars inferior of the labyrinth given by the common cochlear artery (36). On the other hand, inferior vestibular nerve innervates posterior SCC and saccular macula. Therefore, the lesion pattern might provide clues on a neural vs. vascular etiology in an acute setting. It has been suggested that posterior SCC paresis associated with ipsilateral sudden hearing loss could possibly be caused by ischemia of the common cochlear artery (37), while the lesion pattern of hearing loss and ipsilateral paresis of the posterior and horizontal SCCs may indicate viral neurolabyrinthitis (16). Recently, a selective vHIT gain reduction of the ipsilateral posterior SCC in a SSNHL patient with acute vertigo has been reported, in which posterior SCC fibrosis has been detected by inner ear MRI, thus lend further support to vascular etiology (38). Although recent application of instrumental testing (vHIT and VEMP) can facilitate topographical diagnosis of selective dysfunction of inner ear end-organs, the underlying mechanisms require further investigations for patients with vertigo in SSNHL (3, 38).

In our series, BPPV involving posterior SCC predominated in patients with i-BPPV (83.3%, 25/30). Meanwhile, posterior (PC-BPPV) and horizontal SCC (HC-BPPV-CA and HC-BPPV-CU) were almost equally affected in patients with s-BPPV [54.8% (17/31) and 45.2% (14/31), respectively]. Our findings were in agreement with those of Hong and Yeo, who reported that the most commonly involved canal was horizontal SCC in patients with both ISSNHL and BPPV (4). Additionally, multi-canal involvement was not uncommon in patients with BPPV secondary to ISSNHL (6, 39). In our series, no multiple SCCs involvement was identified, probably due to the relatively small sample size.

Notably, in the s-BPPV group, there is an inconsistency between SCC involvement by BPPV pathology and abnormal vHIT findings, that is, BPPV predominantly affected horizontal

SCC while the pathological vHIT response usually occurred in posterior SCC. Conversely, VN patients are more likely to develop s-BPPV involving posterior SCC (40, 41) and to have pathological vHIT findings in horizontal SCC (13). It is suggested that VN could directly damage the utricular macula or disrupt nerve afferentiation (mainly in superior vestibular nerve), leading to otoconia detachment, but relatively spare the posterior SCC and inferior vestibular nerve function (42). Further in-depth study was warranted to explore the pathophysiological mechanisms underlying this BPPV pathology-vHIT inconsistency in patients with BPPV secondary to ISSNHL.

Comparisons Between s-BPPV Patients With Normal vHIT and Those With Abnormal vHIT

No significant differences in the audiogram configurations and hearing outcomes were observed between patients with normal and those with abnormal vHIT results. In contrast, Byun et al. (12) found that abnormal vHIT gain in the posterior SCC appears to be a specific prognostic factor for unfavorable hearing recovery in ISSNHL. This discrepancy may be ascribed to the different inclusion criteria and smaller sample size of our study.

Compared with the caloric test, vHIT is a low-sensitivity, high-specificity test for detecting horizontal VOR pathology. It has been reported that horizontal canal vHIT is typically normal until a unilateral weakness score on caloric test of >62.5% is reached (43). In a series of patients complaining of vertigo or dizziness in a community hospital, Mahringer and Rambold (44) found that a pathological vHIT was dependent on the severity of unilateral weakness on caloric examination. We also demonstrated a significantly higher incidence of caloric weakness and CP value in patients with s-BPPV with abnormal vHIT results, which indicated more serious vestibular impairments in this subgroup. Furthermore, of the 13 vHIT- positive cases, 5 (38.5%) had abnormal horizontal vHIT results, while 12 (92.3%) had an abnormal caloric response. This horizontal vHIT-caloric dissociation may be attributed to vestibular compensation. Rapid angular head movements are frequent in daily activities. Considering a median 12-day clinical course, the response to rapid head movements may be better adapted than to non-physiological caloric stimuli (8).

In this s-BPPV series, the incidence of posterior and horizontal SCC involvement by BPPV pathology was not different between patients with normal and abnormal vHIT. This result may indicate that, for patients with BPPV secondary to ISSNHL, the severity of high-frequency VOR impairment may not be related to the involvement of SCCs. The relationship between the severity of vestibular damage and SCC involvement in BPPV secondary to ISSNHL needs to be further studied, as the small sample size may limit the generalizability of our findings.

This study is subject to the following limitations. Firstly, due to the small sample size, some uncommon subtypes of BPPV, such as multi-canal BPPV, were not identified in this series. Additionally, confounding factors were not investigated, as the number of patients with an abnormal vHIT response and those with a normal vHIT response in s-BPPV was small, although univariate analysis revealed no baseline differences between the two subgroups. Secondly, the horizontal apogeotropic positional nystagmus might be caused by cupulopathy of the horizontal SCC due to other etiologies, such as biochemical alteration of the inner ear fluids during the course of SSNHL or blood debris attaching to the cupula due to inner ear hemorrhage (37, 45, 46), because many patients were not followed up regularly as suggested by their physicians and the nystagmus conversion might be missed. Moreover, the treatment outcomes of CRP could not be statistically analyzed due to incomplete follow-up data. Several studies have shown that patients with s-BPPV need more CRPs for complete recovery than their idiopathic counterparts (6, 39). Therefore, the impact of pathological vHIT on the treatment outcomes of CRP in patients with s-BPPV warrants further investigations with large samples and long-term follow-up.

CONCLUSIONS

Compared to i-BPPV, posterior SCC dysfunction detected by vHIT is more prevalent in BPPV secondary to ISSNHL. This dysfunction is mainly associated with vestibular impairments caused by ISSNHL rather than BPPV *per se*.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Material preparation and data collection were performed by YLi, RZ, JL, and HW. Data analysis was performed by YLi and KX. The first draft of this manuscript was written by YLe and BL. A critical review of this manuscript was performed by YLe, HX, and BL. All authors contributed to the study conception and design, read, and approved the final manuscript.

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Acute Unilateral Peripheral Vestibulopathy After COVID-19 Vaccination: Initial Experience in a Tertiary Neurotology Center

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Objective: The aim of the present study was to identify patients who developed acute unilateral peripheral vestibulopathy (AUPVP) after COVID-19 vaccination.

Methods: For this single-center, retrospective study, we screened the medical records of our tertiary interdisciplinary neurotology center for patients who had presented with AUPVP within 30 days after COVID-19 vaccination (study period: 1 June–31 December 2021). The initial diagnosis of AUPVP was based on a comprehensive bedside neurotological examination. Laboratory vestibular testing (video head impulse test, cervical and ocular vestibular evoked myogenic potentials, dynamic visual acuity, subjective visual vertical, video-oculography, caloric testing) was performed 1–5 months later.

Results: Twenty-six patients were diagnosed with AUPVP within the study period. Of those, $n = 8$ (31%) had developed acute vestibular symptoms within 30 days after COVID-19 vaccination (mean interval: 11.9 days, SD: 4.8, range: 6–20) and were thus included in the study. The mean age of the patients (two females, six males) was 46 years (SD: 11.7). Seven patients had received the Moderna mRNA vaccine and one the Pfizer/BioNTech mRNA vaccine. All patients displayed a horizontal(-torsional) spontaneous nystagmus toward the unaffected ear and a pathological clinical head impulse test toward the affected ear on initial clinical examination. Receptor-specific laboratory vestibular testing performed 1–5 months later revealed recovery of vestibular function in two patients, and heterogeneous lesion patterns of vestibular endorgans in the remaining six patients.

Discussion and Conclusions: The present study should raise clinicians' awareness for AUPVP after COVID-19 vaccination. The relatively high fraction of such cases among our AUPVP patients may be due to a certain selection bias at a tertiary neurotology

center. Patients presenting with acute vestibular symptoms should be questioned about their vaccination status and the date of the last vaccination dose. Furthermore, cases of AUPVP occurring shortly after a COVID-19 vaccination should be reported to the health authorities to help determining a possible causal relationship.

Keywords: acute unilateral peripheral vestibulopathy, vestibular neuritis, COVID-19, SARS-CoV-2, vaccination, herpes simplex virus, autoimmune cross-reactivity

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with 489,678,203 confirmed cases and 6,149,250 deaths to date (2 April, 2022) (1). An unprecedented worldwide vaccination program has been rolled out since December 2020 to combat this devastating disease. The vaccines most commonly used in Switzerland, the European Union and the United States are based on mRNA technology (Cominarty® by Pfizer/BioNTech; Spikevax® by Moderna) or adenovirus vectors (COVID-19 vaccine Janssen® produced by Johnson and Johnson; Vaxzevria® by Oxford/AstraZeneca) (2) and induce an immune response against the spike glycoprotein of SARS-CoV-2, which is pivotal for viral invasion of host cells (3). Vaccination is an effective tool to prevent infection with the virus, to ameliorate the course of the disease and to reduce the death toll of COVID-19 (4, 5).

Since the beginning of the vaccination program, an increasing number of adverse medical events following administration of the vaccine has been reported. While temporal association does not prove causality, it is nevertheless important to make note of such cases and report them to the health authorities. Based on these data, large-scale post-authorization studies can be conducted to re-evaluate the safety of a vaccine and to re-weigh the risk-benefit-ratio of vaccinations for specific subgroups of the population (6, 7).

A wide spectrum of new-onset neurological disorders following COVID-19 vaccination has been reported so far, including disorders of the brain (e.g., venous sinus thrombosis, acute demyelinating encephalomyelitis), the spinal cord (acute transverse myelitis), the peripheral nervous system (Guillan-Barré syndrome), the muscles (myositis) and the cranial nerves (olfactory dysfunction, optic neuritis, abducens and facial nerve palsies) (8). Reports of sudden sensorineural hearing loss (SSNHL) and tinnitus following COVID-19 vaccination have raised the question whether the eighth cranial nerve and/or the inner ear might also be affected by processes following COVID-19 vaccination. Possible pathomechanisms discussed in this context comprise autoimmune cross-reactivity between pathogen and host proteins, deposition of immune complexes in the inner ear and reactivation of herpes simplex virus (HSV) or varizella zoster virus (VZV) in the ganglia of the eighth cranial nerve (9, 10).

While cochlear symptoms (e.g., SSNHL) have been described in several case reports and cohort studies [see (11) for summary], only two cases of acute unilateral peripheral vestibulopathy (AUPVP) following COVID-19 vaccination could be found in the medical literature so far (2 April, 2022) to the best of our knowledge (12, 13). AUPVP (often also called vestibular neuritis) is an acute vestibular syndrome (AVS) characterized by (i) a horizontal or horizontal-torsional spontaneous nystagmus (SN) following Alexander's law, beating toward the contralateral - i.e., unaffected - ear, (ii) a positive clinical head impulse test of the horizontal semicircular canal (h-HIT) toward the affected ear, (iii) and the absence of concomitant hearing loss or other neurological signs and symptoms (14). AUPVP affects endorgans of the superior vestibular nerve (lateral and anterior semicircular canals, utricle) more frequently than those of the inferior portion of the nerve (posterior semicircular canal, saccule) (15). It is not clear to date whether the disorder is caused by intralabyrinthine lesions, an inflammation of the nerve ("vestibular neuritis") or both (16, 17). Possible underlying pathomechanisms include HSV reactivation, autoimmune response or microvascular ischemic insults to the vestibular labyrinth (18).

The case report about AUPVP after COVID-19 vaccination by Jeong (12) presents detailed results of the bedside neurotological examination and vestibular testing that allow to exclude other causes of AVS, while Canales Medina and Ramirez Gómez (13) only describe a spontaneous nystagmus without differentiating further between a peripheral and a central acute vestibular disorder, e.g., by application of the HINTS (head impulse, nystagmus, test of skew) paradigm (19). Likewise, many case reports about AUPVP or labyrinthitis in patients with SARS-CoV-2 infection are rather based on symptoms and exclusion of other disorders than on clinical and laboratory vestibular testing (20–23). Thus, it remains questionable whether the patients' vertigo was really caused by an acute unilateral peripheral vestibulopathy (24, 25).

Therefore, the aim of the present study was to identify patients with AUPVP after COVID-19 vaccination based on bedside neurotological examination and receptor-specific vestibular laboratory testing. These data are important to establish a realistic risk-benefit ratio of COVID-19 vaccines regarding vestibular disorders and, hence, are not intended to discourage vaccination (7, 9).

PATIENTS AND METHODS

This single-center, retrospective study was carried out at an interdisciplinary tertiary neurotology center. The main catchment area of our institution is the Kanton Zurich with currently 1.56 million inhabitants (26).

TABLE 1 | Patient demographics and vaccination status.

Patient nr.	Age (years)	Gender	Vaccine (date)			AUPVP onset	Interval vaccine - AUPVP
			1st dose	2nd dose	Booster		
#1	37	m	Moderna (2 May, 2021)	Moderna (1 Jun, 2021)	–	7 Jun, 2021	6 days
#2	58	m	Moderna (12 May, 2021)	–	–	1 Jun, 2021	20 days
#3	35	m	Moderna (3 Jul, 2021)	–	–	12 Jul, 2021	9 days
#4	34	f	Moderna (26 Jun, 2021)	–	–	6 Jul, 2021	10 days
#5	44	m	Moderna (10 Jun, 2021)	Moderna (1 Jul, 2021)	–	7 Jul, 2021	7 days
#6	66	m	Moderna (7 May, 2021)	Moderna (4 Jun, 2021)	–	14 Jun, 2021	10 days
#7	53	m	Pfizer (14 Jan, 2021)	Pfizer (11 Feb, 2021)	Pfizer (27 Nov, 2021)	15 Dec, 2021	18 days
#8	53	f	Moderna (12 May, 2021)	Moderna (08 Jun, 2021)	Moderna (16 Dec, 2021)	31 Dec, 2021	15 days

"age", age at symptom onset; AUPVP, acute unilateral peripheral vestibulopathy; "interval", time interval between last dose of COVID-19 vaccine and onset of AUPVP symptoms.

Patients

Within the study period (1 Jun to 31 Dec, 2021), a total of 26 patients were diagnosed in our institution with AUPVP based on the following criteria: (i) horizontal or horizontal-torsional SN following Alexander's law, beating toward the contralateral - i.e., unaffected - ear, (ii) a positive h-HIT toward the affected ear, (iii) absence of concomitant hearing loss or other neurological signs and symptoms, and (iv) symptoms not better accounted for by any other vestibular disorder (14). Only those patients with AUPVP who had developed acute vestibular symptoms within 30 days after a COVID-19 vaccination (n = 8) were included into the present retrospective study (**Table 1**). Patients #2 and #6 had initially been diagnosed with AUPVP *alio loco* before they were referred to our center. The other six patients presented to us shortly after the acute onset of symptoms.

The 30-day interval was based on an extensive literature research about the onset of the following disorders following a COVID-19 vaccination: (i) AUPVP and autoimmune vestibulopathy (2 days to 1 month) (12, 13, 27), (i.) sudden sensorineural hearing loss (0–30 days) (9, 11) (iii) HSV or VZV reactivation (1–16 days) (8, 28–31), and (iv) new-onset neurological disorders (0 days to 1 month) (8, 32).

Exclusion criteria for the present study were: (i) a positive history of SARS-CoV-2 infection before the onset of AUPVP, (ii) onset of acute vestibular symptoms before vaccination, (iii) acute onset of hearing loss after COVID-19 vaccination or (iv) better explanation of symptoms by another vestibular disorder. Of note, no patient presented to our institution with an acute cochleovestibular syndrome within 30 days after COVID-19 vaccination during the study period.

The study was carried out according to the recommendations of the Cantonal Ethics Committee Zurich and in accordance with the Declaration of Helsinki. All clinical and laboratory examinations were part of the clinical routine at our hospital. All patients included into the study provided prior informed consent.

Bedside Neurotological Examination

On initial presentation with AVS, all patients except #2 and #6 (referral after diagnosis of AUPVP had been made *alio loco*) underwent a comprehensive bedside neurotological examination by a neurologist or an otorhinolaryngologist, as described by Straumann (33), including: examination of horizontal and vertical smooth pursuit and saccades; alternating cover test for detection of skew deviation; h-HIT; exploration of spontaneous, gaze-evoked and head-shaking nystagmus (with and without Frenzel goggles), bilateral Dix-Hallpike and supine roll maneuvers with Frenzel goggles; testing of cerebellar coordination (diadochokinesis, finger-to-nose test), Romberg and Romberg-on-foam test ("FRomberg") for examination of postural control (**Table 2**). The HINTS paradigm (head impulse, nystagmus, test of skew) was applied in each patient to disclose a potential central origin of the AVS (19).

Vestibular Laboratory Testing

After the diagnosis of AUPVP had been made, all patients were scheduled for clinical follow-up and vestibular laboratory testing after 1 month according to the routine clinical protocol of our institution for patients with AUPVP (**Table 3**). As patients #2 and #6 were referred from different healthcare providers, vestibular testing was performed with a latency of 5 (#2) and 4 months (#6) after the acute event. The following tests were applied for a detailed analysis of semicircular canal, utricular and saccular function.

Semicircular Canal Function

High-frequency function for all three semicircular canals (SCCs) was assessed by the video head impulse test (vHIT; Otometrics, Natus Medical Denmark, Taarstrup, Denmark) as described previously (34). SCC hypofunction was defined by a reduced vestibulo-ocular reflex (VOR) gain (<0.8 for the horizontal canal (HC) and <0.7 for the anterior (AC) and posterior (PC) canals) with the additional presence of corrective saccades (35–37). Repetitive vHIT measurements during the recovery process of AUPVP have revealed that corrective saccades may still be present after VOR gain values have already normalized (38, 39). Therefore, we also analyzed the presence of covert saccades (CS) and overt saccades (OS) for all SCCs tested (**Table 3**).

In addition, the response of the horizontal SCCs to low-frequency vestibular stimuli was evaluated by caloric irrigation of

TABLE 2 | Bedside neurotological examination on initial presentation and on follow-up examination (same day as laboratory vestibular testing, see **Table 3**).

Patient nr.	SP	SAC	SD	h-HIT	SN	GEN	HSN	Positioning maneuvers	Cerebellar coordination	Romberg	FRomberg	Diagnosis
#1 (initial)	Super-imposed by SN	N	no	**R**	**L II°** (Alexander's law, suppressed by fixation)	No	**L**	n.d.	N	**Sway to R**	n.d.	R AUPVP
#1 (1 month)	N	N	No	N	No (±Frenzel goggles)	No	No	N	N	N	N	Clinical recovery of R h-VOR
#2 (initial)	N	N	No	**R**	**L III°** (Alexander's law, suppressed by fixation)	No	**L**	**L nystagmus (like SN)** in all positions	N	**Not able to stand with eyes closed**	n.d.	R AUPVP
#2 (5 months)	N	N	No	**R**	no (±Frenzel goggles)	No	No	N	N	N	N	R h-VOR hypofunction
#3 (initial)	N	N	No	**R**	**L III°** (Alexander's law, suppressed by fixation)	No	**L**	n.d.	N	**sway to R**	n.d.	R AUPVP
#3 (1 month)	N	N	No	N	no (±Frenzel goggles)	No	No	N	N	N	N	Clinical recovery of R h-VOR
#4 (initial)	N	N	No	**R**	**L III°** (Alexander's law, suppressed by fixation)	No	**L**	**L nystagmus (like SN)** in all positions	N	**Sway to R**	n.d.	R AUPVP
#4 (1 month)	N	N	No	**R**	No (±Frenzel goggles)	No	**L**	N	N	N	N	R h-VOR hypofunction
#5 (initial)	N	N	No	**L**	**R** (Alexander's law, suppressed by fixation)	No	n.d.	n.d.	N	**Slight sway to L**	n.d.	L AUPVP
#5 (1 month)	N	N	No	**L**	no (±Frenzel goggles)	No	No	N	N	N	N	L h-VOR hypofunction
#6 (initial)	N	N	No	**L**	**R** (Alexander's law, suppressed by fixation)	No	**R**	n.d.	N	**sway to L**	n.d.	L AUPVP
#6 (4 months)	N	N	No	**L**	no (±Frenzel goggles)	No	**R**	N	N	N	N	L h-VOR hypofunction

(Continued)

TABLE 2 | Continued

Patient nr.	SP	SAC	SD	h-HIT	SN	GEN	HSN	Positioning maneuvers	Cerebellar coordination	Romberg	FRomberg	Diagnosis
#7 (initial)	N	N	No	**R**	**L III**° (Alexander's law, suppressed by fixation)	No	**L**	n.d.	N	**Not able to stand with eyes closed**	n.d.	R AUPVP
#7 (1 month)	N	N	No	**R**	**L II**° (only with Frenzel goggles)	No	**L**	N	N	N	n.d.	R h-VOR hypofunction
#7 (3 months)	N	N	No	N	no (±Frenzel goggles)	No	No	N	N	N	N	Clinical recovery of R h-VOR
#8 (initial)	N	N	No	**L**	**R III**° (Alexander's law, suppressed by fixation)	No	**R**	n.d.	N	**Sway to L**	n.d.	L AUPVP
#8 (1 month)	N	N	No	N	no (±Frenzel goggles)	No	No	n.d.	N	N	N	Clinical recovery of L h-VOR

Pathological findings are printed in bold.

SP, smooth pursuit; SAC, saccades; SD, skew deviation; h-HIT, clinical head-impulse test for the horizontal semicircular canal ("R/L": positive for head turns to the right/left side); SN, spontaneous nystagmus; GEN, gaze-evoked nystagmus; HSN, head-shake nystagmus; positioning maneuvers, Dix-Hallpike and supine roll maneuvers to both sides; N, normal; n.d., not done; AUPVP, acute unilateral peripheral vestibulopathy; h-VOR, vestibulo-ocular reflex of the horizontal semicircular canal.

the external ear canals with warm (44°C) and cold (30°C) water (Atmos Variotherm plus, Lenzkirch, Germany) (40–42). A caloric paresis (CP) factor >25% calculated by the Jongkees formula (43) was employed as a measure for relative unilateral caloric hypofunction. In the present study, positive values represent right-sided and negative values left-sided caloric hypofunction (**Table 3**).

Dynamic visual acuity (DVA) was used to determine functional integrity of the VOR of the horizontal SCCs (44, 45). In detail, visual acuity was measured in logMAR (decadic logarithm of the mean angular resolution), with the DVA value representing the decrement from static to dynamic visual acuity. Abnormal DVA values were determined by comparison with age-related normative values from our lab.

Nystagmus analysis was performed with video-oculography (VOG) in the dark (Interacoustics, Middelfart, Denmark) (40, 42). Nystagmus direction was defined by the direction of the quick phase. The presence of a spontaneous nystagmus (SN) with a slow phase velocity (SPV) >3°/s or a head-shaking nystagmus (HSN) in the same direction as the SN were interpreted as signs of incomplete central compensation of SCC function after AUPVP (42). Vibration-induced nystagmus (VIN) was tested by applying a 100 Hz vibration stimulus (VestiVIB, Autronic, Hamburg, Germany) to either mastoid as described by Dumas et al. (46). Presence of a VIN >2.5°/s SPV indicated asymmetrical SCC function between the right and the left side with the quick phase of the nystagmus beating toward the side with the higher vestibular activity (47). Positional nystagmus was evaluated during the Dix-Hallpike maneuver and the supine roll maneuver to either side using either VOG or Frenzel goggles.

Otolith Function

Dynamic (transient) utricular and saccular function was tested by ocular and cervical vestibular evoked myogenic potentials (o- and cVEMPs), respectively, using an Eclipse platform (Interacoustics, Middelfart, Denmark) with the stimulation parameters and recording procedures described by Tarnutzer et al. (48). An asymmetry ratio (AR) ≥0.3 indicated asymmetrical otolith function for both o- and cVEMPs based on normative values of our lab. In **Table 3**, a positive AR indicates right-sided relative hypofunction, and a negative AR left-sided relative hypofunction.

Cervical VEMPs were primarily recorded in response to monaural air-conducted sound (ACS) at 500 Hz and 100 dB normal hearing level (nHL) presented *via* headphones (Telephonics TDH-39P; Telephonics Corp., Farmingdale, NY, USA). ACS cVEMPs are very sensitive to middle ear dysfunction with air-bone gaps as small as 8.75 dB able to diminish or cancel the response (49). Therefore, we performed an additional cVEMP recording using bone-conducted vibration (BCV) to Fz (midline of the forehead at the hairline) in those patients with asymmetrical ACS cVEMP responses in order to determine whether a reduced cVEMP amplitude was rather due to middle ear dysfunction (asymmetrical ACS cVEMPs and symmetrical BCV cVEMPs) or saccular hypofunction (asymmetrical ACS and BCV cVEMPs), as described before (48). Dynamic saccular hypofunction was diagnosed if both ACS and BCV cVEMPs yielded an AR ≥0.3. The BCV

TABLE 3 | Vestibular laboratory testing 1 to 5 months after onset of acute peripheral vestibulopathy (AUPVP).

Patient nr.	Side affected	vHIT gain			oVEMP AR	cVEMP AR		DVA	SVV	VOG (SPV)	CP	Interpretation (summary)
		HC	AC	PC		ACS	BCV					
#1 (1 month)	R	1.0	0.9	0.7	−0.01	0.01	n.d.	0.1	−0.2°	**VIN R** (3°/sec) (recovery nystagmus)	n.d.	Recovery of R vestibular function
#2 (5 months)	R	**0.7 (CS, OS)**	0.8	1.1	**0.42**	0.26	n.d.	**0.8**	**2.3°**	**VIN L** (3°/s)	19%	Hypofunction R HC and utricle
#3 (1 month)	R	1.1	1.0	1.3	−0.07	0.07	n.d.	0.2	−0.1°	no significant nystagmus	−14%	Recovery of R vestibular function
#4 (1 month)	R	**0.3 (CS, OS)**	0.8	1.0	n.d.	n.d.	n.d.	**1.2**	**3.1°**	n.d.	n.d.	Hypofunction R HC and utricle (saccule not tested)
#5 (1 month)	L	**0.6 (OS)**	1.3	1.0	n.d.	n.d.	n.d.	0.3	n.d.	n.d.	n.d.	Hypofunction L HC (utricle and saccule not tested)
#6 (4 months)	L	**0.6 (CS, OS)**	1.1	**0.6 (CS,OS)**	−0.14	**–1**	**–1**	0.4	0.9°	**HSN R** (6°/s), **VIN R** (6°/s)	**–80%**	Hypofunction L HC, PC and saccule
#7 (1 month)	R	1.0 **(CS, OS)**	0.8 **(CS)**	0.9	0.0	0.28	n.d.	0.5	**7.5°**	**SN L** (3°/s), **HSN L** (6°/s)	**79%**	Hypofunction R HC, (AC) and utricle
#7 (3 months)	R	1.2	1.2	1.1	−0.16	0.05	n.d.	0.4	1.2°	No nystagmus	**45%**	Recovery of R vestibular function apart from CP
#8 (1 month)	L	1.0 **(CS)**	0.8	0.8	−0.26	−0.37	0.03	0.4	**–2.5°**	No significant nystagmus	**–52%**	Hypofunction L HC and utricle

vHIT gains and DVA values are presented for the affected side only (within normal range on the unaffected side for all patients). Pathological values are printed in bold (see "PATIENTS AND METHODS" section for definition of normal values and further details). For o- and cVEMP ARs, SVV and CP, positive values show relative hypofunction on the right side, while negative values indicate relative left-sided hypofunction.

vHIT, video head impulse test; HC, horizontal canal, AC, anterior canal; PC, posterior canal; o-/c-VEMP, ocular / cervical vestibular evoked myogenic potentials; AR, asymmetry ratio; ACS, air-conducted sound; BCV, bone-conducted vibration; DVA, dynamic visual acuity; SVV, subjective visual vertical; VOG, video-oculography; SPV, slow-phase velocity; CP, caloric paresis; R, right; L, left; n.d., not determined; VIN, vibration-induced nystagmus; CS, covert saccades in vHIT; OS, overt saccades; HSN, head shake nystagmus; SN, spontaneous nystagmus.

stimulus was delivered to Fz by a powerful Minishaker (4810, Bruel and Kjaer, Naerum, Denmark) connected to an amplifier (2718, Bruel and Kjaer). Cervical VEMP p13n23 amplitudes were normalized to the muscular background activity of the ipsilateral sternocleidomastoid muscle, resulting in unitless values for corrected cVEMP amplitudes [see (50) for details]. Measurements were discarded if the background muscular activity was $<60\,\mu V$.

For oVEMPs, only 500 Hz BCV stimuli were applied to Fz by the Minishaker. Due to their excitatory nature, oVEMP n10p15 amplitudes do not have to be normalized to background muscular activity of the contralateral inferior oblique muscle and are therefore measured in μV.

Static (sustained) utricular function was determined by measuring the subjective visual vertical (SVV), as described recently (51). Based on normative values of our lab, values up to $\pm 2.2^{\circ}$ were judged as normal (positive value: deviation to the right, negative: deviation to the left). SVV and oVEMP amplitudes/AR do not necessarily correlate as they assess two different channels of otolith function: while oVEMPs probe dynamic (transient) utricular function mainly mediated by type I vestibular hair cells and irregular utricular afferents of the striola, the SVV is an indicator of static (sustained) utricular function determined mainly by peripheral type II vestibular hair cells and regular utricular afferents (51, 52).

Magnetic Resonance Imaging

Two patients (#1 and #7) underwent magnetic resonance imaging (MRI) of the brain and the temporal bone mainly for exclusion of acute stroke 5 days (#1) and 1 day (#7) after the onset of the acute vestibular syndrome. Acquisition and interpretation of the images were performed by the Department of Neuroradiology at Zurich University Hospital. All MR images were acquired on a three Tesla MRI Scanner (Skyra, release E 11, Siemens Healthcare, Erlangen, Germany). The MRI protocol consisted of diffusion-weighted imaging (DWI), fluid-attenuation inversed recovery (FLAIR), T2-weighted (T2w) und T1 non-contrast- and contrast-enhanced sequences. Intravenous Dotarem (gadoterate meglumine, 0.5 mmol/ml) at a concentration of 0.2 ml/kg body weight was used as a contrast agent.

In detail, DWI [acquisition type 2D, read-out segmented echo planar imaging approach, field of view 220 × 220 (mm^2), number of slices 38, voxel size 1.1 × 1.1 × 3.0 (mm^3), slice gap 0.9 (mm), repetition time (TR) 7,340 (ms), echo time (TE) 68 (ms), *B*-values 0 respectively 1,000 (s/mm^2), acquisition time (TA) 4:33 (min:s)], FLAIR [acquisition type 3D, field of view 240 × 233 (mm^2), number of slices 176, voxel size 0.5 × 0.5 × 1.0 (mm^3), TR 4,700 (ms), TE 386 (ms), inversion time (TI) 1,530 (ms), TA 5:59 (min:s)], and T2w [acquisition type 2D, turbo-spin echo approach (TSE), field of view 220 × 220 (mm^2), number of slices 44, voxel size 0.4 × 0.4 × 3.0 (mm^3), slice gap 0.3 (mm), TR 8,180 (ms), TE 100 (ms), TA 3:26 (min:s)] sequences were acquired in transverse orientation.

Furthermore, time-of-flight (TOF) and contrast-enhanced (CE) magnetic resonance angiography (MRA) of cerebral vessels were accomplished with the following parameters: TOF [acquisition type 3D, field of view 190 × 175 (mm^2), number of slices 240, voxel size 0.3 × 0.3 × 0.6 (mm^3), slice gap −4.8 (mm), repetition time (TR) 21.0 (ms), echo time (TE) 3.43 (ms), Flip Angle 20 Deg., TA 5:37 (min:s)]; CE-MRA [acquisition type 3D, field of view 325 × 310 (mm^2), number of slices 88, voxel size 0.8 × 0.8 × 0.9 (mm^3), slice gap −0.18 (mm), repetition time (TR) 3.29 (ms), echo time (TE) 1.26 (ms), Flip Angle 25 DEg, TA 0:22 (min:s)].

RESULTS

Patient Demographics

Within the study period, $n = 8$ patients met the inclusion criteria (diagnosis of AUPVP and symptom onset within the first 30 days after COVID-19 vaccination). The mean interval between the last dose of the vaccine and the beginning of symptoms was 11.9 days (SD 4.8) with a median of 10 days and a range between 6 and 20 days. The demographic data of the patients are summarized in **Table 1**: two were female, six were male, the mean age at onset of symptoms was 46 years (SD 11.7). All patients had received mRNA vaccines ($n = 7$: Moderna, $n = 1$: Pfizer/BioNTech). Three patients developed AVS after the first dose, three after the second, and two after the third ("booster"). Of note, all patients experienced only one episode of acute vestibular symptoms, even those who had received more than one vaccination dose ($n = 5$).

Vestibular Testing

On initial bedside examination, all patients showed a horizontal or horizontal-torsional SN with the quick phase beating toward the contralateral ear following Alexander's law and a positive h-HIT toward the affected side (**Table 2**). For patients #2 and #6, this information was obtained from the medical records of the referring physicians. None of the patients displayed signs and symptoms of any otological disease, central vestibular syndrome or acute herpes zoster.

Table 3 summarizes the results of laboratory vestibular testing at a 1- to 5-month interval after symptom onset. Representative examples are shown in **Figures 1**, **2**. Patient #7 was examined 1 and 3 months after the acute event, while all the other patients were tested only once. Two patients (#1 and #3) displayed no more signs of unilateral vestibular hypofunction after 1 month and reported complete resolution of symptoms. Taking the initial clinical findings from **Table 2** into account (positive h-HIT to the affected side and horizontal-torsional SN to the unaffected side, we concluded that their vestibular function had recovered. Patient #1 yielded a very mild recovery VIN (fast phase directed to the originally affected right side) with a slow-phase velocity of 3°/sec (see Discussion).

For the remaining six patients, the following vestibular endorgans were affected by AUPVP in declining order: HC ($n = 6$), utricle ($n = 4$), PC ($n = 1$), saccule ($n = 1$). Dynamic saccular hypofunction confirmed by both asymmetrical ACS and BCV cVEMPs was detected in only one patient (#6). Left-sided dynamic saccular function was interpreted as normal in patient #8 due to his symmetrical BCV cVEMP response (AR = 0.03). Two patients (#4 and #5) did not undergo o- and cVEMP testing, so we have no information of dynamic utricular and

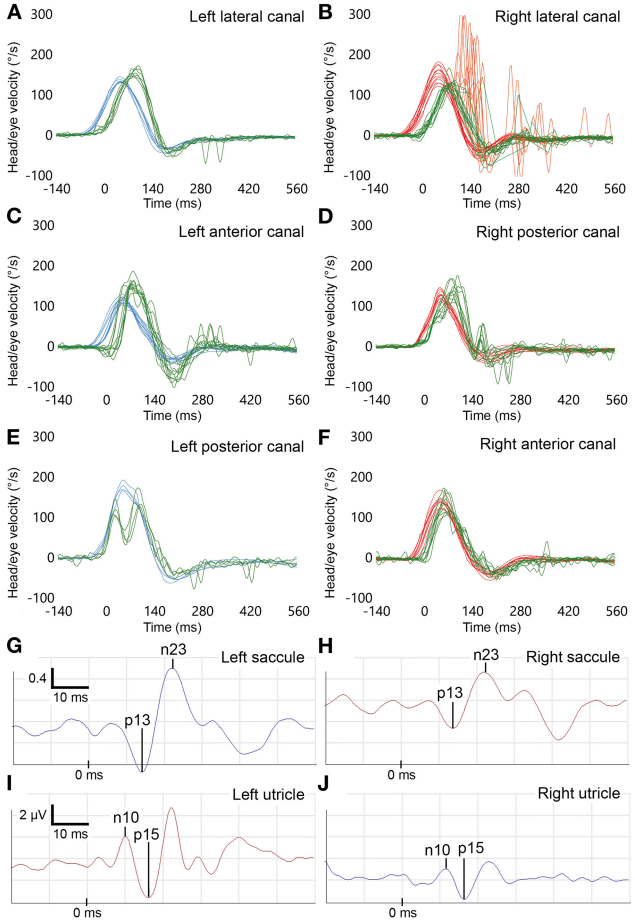

FIGURE 1 | Vestibular function tests in patient #2 (right superior vestibular nerve or its endorgans affected). **(A–F)** Video head impulse test (vHIT) results of all six semicircular canals. Eye velocity is right-left mirrored for better comparison with head velocity. **(A,C,E)** Head impulses stimulating left-sided semicircular canals. Blue traces: head velocity. Green traces: eye velocity of the vestibulo-ocular reflex. **(B,D,F)** Head impulses stimulating right-sided semicircular canals. Red traces: head velocity. Green traces: eye velocity of the vestibulo-ocular reflex. Red traces superimposed on green traces: catch-up saccades. The eye velocity traces indicate hypofunction of the right lateral semicircular canal (gain = 0.7). **(G,H)** Cervical vestibular-evoked myogenic potentials (cVEMPs) in response to air-conducted sound. *Y*-axis indicates the normalized p13n23 amplitude (unitless). The traces show slightly reduced cVEMP responses for the right (red traces) as compared to the left saccule (blue traces), which are still within normal range (asymmetry ratio, AR = 0.26). **(I,J)** Ocular vestibular evoked myogenic potentials (oVEMPs). *Y*-axis indicates absolute amplitude (µV). The response of the right utricle (blue traces – crossed reflex pathway) is smaller compared to the left side (red traces), AR = 0.42. *X*-axis represents time in all graphs.

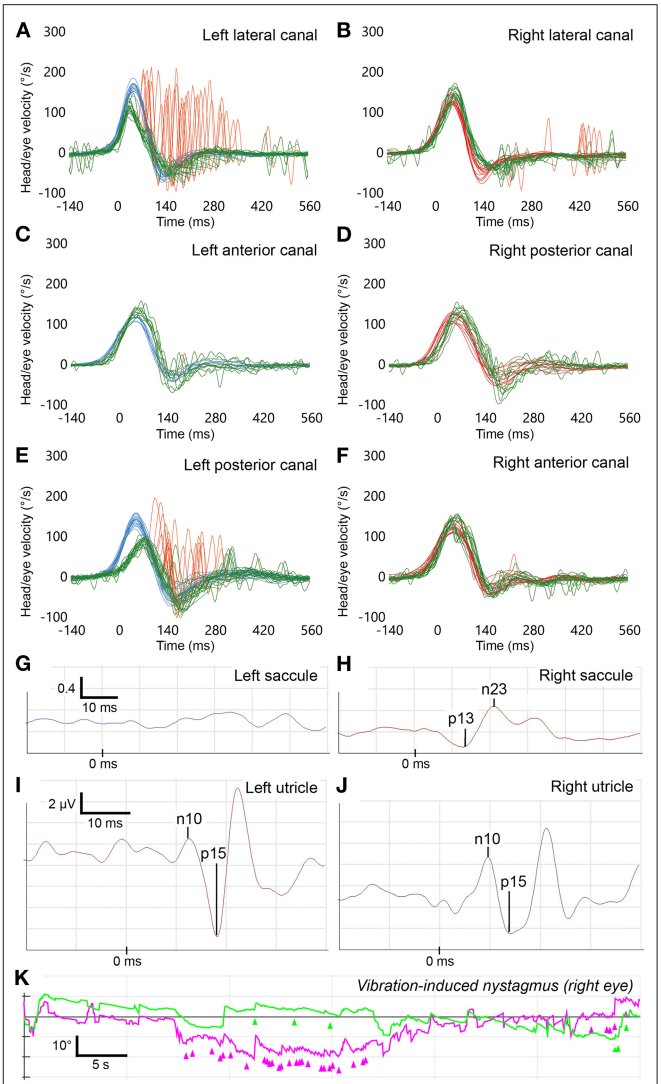

FIGURE 2 | Vestibular function tests in patient #6 (left superior and inferior vestibular nerves or their endorgans affected). See legend of **Figure 1** for general features of **(A–J)**. The vHIT traces indicate hypofunction of the left lateral and posterior semicircular canals (gain = 0.6 each), loss of the cVEMP response of the left saccule (AR = −1) and symmetrical oVEMP responses (AR = −0.14). **(K)** Video-oculography recordings during a 100 Hz vibration stimulus applied to the left mastoid. The magenta trace shows horizontal eye position (°) and the green trace shows vertical shows eye position (°) as indicated on the *y*-axis. Nystagmus quick phases are labeled with arrow heads. The right-beating vibration-induced nystagmus is consistent with hypofunction of the left lateral semicircular canal. *X*-axis represents time in all graphs.

saccular function in them. Only one patient (#7) displayed a possible transient hypofunction of the AC: while corrective covert saccades (CS) with a normal gain (0.8) were present at 1 month after symptom onset, these were no longer detectable after 3 months, indicating recovery of the anterior canal. The endorgan involvement (AC, HC, utricle) of this patient at 1 month was compatible with a selective damage to the supply area of the superior vestibular nerve, while the other five subjects with a vestibular deficit in laboratory testing yielded a heterogeneous pattern of endorgan involvement not fitting exactly with the supply areas of the superior and/or inferior vestibular nerves (**Table 3**). This aspect will be dealt with in detail in the discussion.

MRI Examination

Two patients underwent MRI examination of the brain and the temporal bone in the acute stage of the disease (patient #1 5 days and patient #7 1 day after the onset of symptoms). In patient #1, no T1 hyperintensity was detected in the

right inner ear and the internal auditory canal before and after administration of gadolinium, thus showing no signs of hemorrhage or inflammatory disease. For patient #7, only non-contrast-enhanced sequences were available. Again, there were no signs of right-sided inner ear hemorrhage in T1. In addition, no hyperintensities indicating inflammation were detected in the right inner ear and the internal auditory canal in the FLAIR sequence.

Treatment

All patients received initial symptomatic treatment (i.e., antiemetics and intravenous fluid) and vestibular rehabilitation therapy. All but two patients (#5 and #6) were treated with oral and/or intravenous steroids in the acute phase of the disease. In detail, patients #1 and #7 received one shot of methylprednisolone 1g i.v., followed by prednisone p.o. 100 mg for 3 days and consecutive reduction of the dose by half every 3 days Patients #2, #3 and #4 obtained 50 mg of prednisone p.o. for 5 days.

DISCUSSION

To the best of our knowledge, this is the first study analyzing the occurrence of AUPVP after COVID-19 vaccination in a specialized neurotology center, identifying eight patients within 7 months. The findings of the study are discussed with special regard to the estimated incidence of AUPVP after COVID-19 vaccination, possible underlying pathomechanisms, treatment, strengths/limitations of the study and perspectives for future investigations.

Estimated Frequency of Acute Unilateral Peripheral Vestibulopathy

In total, 26 patients with new-onset AUPVP presented to our institution within the 7 months of the study period, which would correspond to a 1-year-incidence of 3/100,000 for the Kanton Zurich (1.56 million inhabitants), our main catchment area. Of these 26 patients, 31% ($n = 8$) developed acute vestibular symptoms within 30 days after COVID-19 vaccination.

These numbers reflect a certain selection bias for our institution: as we are a tertiary neurotology center, many patients with acute vestibular symptoms are seen by other healthcare providers of the catchment area, which explains the low overall estimated incidence of AUPVP calculated from the numbers of our center as compared to the literature (1-year-incidence of 3.5 to 24/100,000) (53). On the other hand, particularly patients with severe symptoms or complex medical issues are referred to our institution, which may account for the high percentage of patients with AUPVP after COVID-19 vaccination (31%). Considering the 542,860 people who received at least one vaccination dose in the Kanton Zurich within the study period (54), our data suggest 1.47 cases of AUPVP per 100,000 persons within 30 days after vaccination, indicating a low risk. Further possible confounders of the study are discussed in Section Implications For Treatment and Further COVID-19 Vaccinations.

Types of Vaccine

All patients of the present study had received an mRNA vaccine. This does *not* reflect any potential relationship between the type of the vaccine and the occurrence of AUPVP, but is rather a result of local availability. As of 30 March, 2022, only three different vaccines have been authorized in Switzerland: the mRNA vaccines by Pfizer/BioNTech (authorized on 19 Dec 2020) and Moderna (authorized on 12 Jan 2021) and the vector-based vaccine by Janssen (authorized on 22 Mar 2021) (55). In addition, the Swiss health authorities generally recommend mRNA vaccines (56), so that the latter account for >99% of the 8,862,579 million vaccination doses administered in Switzerland within the study period (67.6% Moderna, 31.8% Pfizer), while the vector-based vaccine comprises only 0.6% of vaccination doses (57). Thus, the predilection of AUPVP in patients immunized with the Moderna vaccine rather reflects the distribution of vaccines in the general population than a possible causal relationship.

Interpretation of Results

Results From Selected Patients

Patient #1 displayed a subtle VIN beating toward the initially affected right side (SPV = 3°/s, normal values up to 2.5°/s) on VOG recording 1 month after the onset of symptoms (**Table 3**). At this time, the initial SN to the left and the pathological h-HIT to the right (**Table 2**) had recovered. Therefore, we interpret the subtle VIN to the right as a recovery nystagmus caused by the persistence of a certain degree of central compensation for an initial imbalance in vestibular tone after the need for this amount of compensation was no longer present due to recovery of peripheral vestibular function (58, 59). Similar observations have been made before for patients in the compensation/recovery phase after AUPVP: Dumas et al. (60) described a VIN with the quick phase beating toward the affected side in 11% of patients in the late phase of AUPVP. Likewise, Park et al. (61) reported that an initial paralytic (i.e., beating toward the unaffected side) VIN reversed its direction after 2 months in 10% of patients with AUPVP.

Patient #7 underwent vestibular laboratory testing 1 and 3 months after the onset of symptoms (**Table 3**). After 1 month, the right-sided horizontal and anterior canals displayed refixation saccades, but normal VOR gain values (1.0 for the HC and 0.8 for the AC). On the second assessment 2 months later, these saccades had disappeared. At the same time, the SVV had recovered, no spontaneous and head-shaking nystagmus was detected in the VOG, and caloric paresis of the horizontal canal had recovered from initially 79 to 45%. In summary, these results indicate an ongoing recovery of right-sided vestibular function. The transient presence of refixation saccades despite a normal VOR gain during the compensation/recovery process of AUPVP is in line with the findings reported by MacDougall and Curthoys (62), Manzari et al. (38) and Yang et al. (39). The consecutive vHIT measurements in patients recovering from AUPVP from these studies showed that VOR gain may recover earlier than refixation saccades. As the first vHIT examination was performed 1 month after the onset of symptoms in patient #7, we might well have missed an initial reduction of VOR gain.

A second noteworthy finding in patient #7 is the different time course for recovery of high-frequency (vHIT) and low-frequency function (caloric testing) of the horizontal canal: while vHIT testing displayed only refixation saccades with a normal VOR gain 1 month after symptom onset, there was a high degree of caloric asymmetry (CP = 79%) at that time, which improved up to a CP of 45% within the next 2 months (**Table 3**). This observation is in line with the findings by Zellhuber et al. (63) who attributed the different time courses of HC function recovery as measured by vHIT and caloric testing to the two different aspects of horizontal canal function (high- and low-frequency) assessed by these two tests.

Involvement of Individual Vestibular Endorgans

In summary, hypofunction was detected more frequently for endorgans supplied by the superior vestibular nerve (HC: $n = 6$, utricle: $n = 4$) than those of the inferior vestibular nerve (PC: $n = 1$, saccule: $n = 1$), which is in line with the distribution found by Taylor et al. (15). Comparison between our study and the latter is however limited by two facts: first, vestibular laboratory testing was performed at different timepoints [Taylor et al. (15): within 10 days after symptom onset; present study: 1–5 months after symptom onset]. Therefore, we might have missed initial hypofunction of vestibular endorgans: for instance, the anterior canal showed a reduced VOR gain for 90.7% of patients in Taylor's study (15), while we only detected corrective saccades with a normal VOR gain in one (#7) out of eight patients in the present study. Second, two patients in the present study did not undergo o- and cVEMP testing, so that we cannot make a definite statement about the number of patients affected by dynamic utricular and saccular hypofunction.

There has been a debate in the literature whether all endorgans supplied by one branch of the vestibular nerve must be affected to the same extent in order to qualify for the diagnosis of vestibular neuritis, i.e., a damage to the vestibular nerve rather than the vestibular labyrinth. Uffer and Hegemann (16) reported that this was the case in only 24% of patients with AUPVP tested within 10 days of symptom onset. In the present study, only one (patient #7) out of eight patients (12.5%) displayed an involvement of all endorgans supplied by the superior vestibular nerve (HC, AC and utricle) after 1 month. Again, comparability between our results and the ones by Uffer and Hegemann (16) is limited by the different timepoints of vestibular testing. We found no case where only endorgans of the inferior vestibular nerve were affected, which is in line with the low proportion of an isolated AUPVP of the inferior vestibular nerve and / or its endorgans (saccule, posterior canal) reported in the literature (1.2%−5%) (64).

To date, it is still elusive whether AUPVP is primarily a disorder of the vestibular labyrinth, the vestibular nerve or both (17). In the present study, brain MRIs from the acute phase of the disease were available for two patients (#1 and #7) indicating neither a structural lesion in the vestibular labyrinth or the vestibular nerve. It should, however, be noted that these MRIs were primarily done for detection of stroke and not for evaluation of the inner ear/the internal auditory canal.

Possible Underlying Mechanisms of AUPVP Following COVID-19 Vaccination

Onset of acute vestibular symptoms within 6 to 20 days after administration of a COVID-19 vaccine in the present study is in line with the temporal course of HSV reactivation and autoimmune neurological disorders occurring after vaccination against SARS-CoV-2.

Herpes Simplex Virus Reactivation

A growing body of evidence from anatomical, immunohistological, molecular biological and genetic studies suggests a reactivation of herpes simplex virus hibernating in the neurons of the vestibular ganglia as a possible cause for AUPVP (65–69). Reactivation of latent HSV and VZV infections including dermatological and ophthalmological manifestations has been observed within 1–16 days after COVID-19 vaccinations with different types of vaccine (8, 28–31). A review of 40 dermatological cases described a median latency of 13 days between vaccination and onset of clinical symptoms for HSV reactivation (31), which is in line with the time course observed in the present study (mean latency: 11.9 days, median: 10 days). Reactivation of HSV or VZV is not unique for COVID-19 vaccinations, but has been observed before for hepatitis A and influenza vaccines (70). While a causal relationship has not been proven, immune-modulatory effects of the vaccine are discussed in this context, in particular suppression of cellular immunity (28) by inhibition of distinct Th1 cell populations (8, 29). Reactivation of herpes virus is also supposed to play a role in facial nerve palsy after COVID-19 vaccination (8).

Autoimmune Response

Both mRNA and vector-based vaccines induce an immune response of the host against the spike glycoprotein of SARS-CoV-2 (3). Of note, there is a high degree of structural homology between this protein and the human proteome (molecular mimicry), which may cause a cross-reaction of the vaccine-induced immune response against self-proteins resulting in autoimmune disorders after COVID-19 vaccination (71, 72). Molecular mimicry as an underlying cause for autoimmune reactions in temporal association with vaccinations has been discussed before (e.g., for hepatitis B, influenza or human papillomavirus vaccination) (73), and new-onset autoimmune disorders have been observed after COVID-19 vaccinations, e.g., immune thrombotic thrombocytopenia and Guillan-Barré syndrome (7). A recent study found a median of 11 days between vaccination and onset of autoimmune neurological disorders (32), which corresponds to the start of IgG production between 10 and 14 days after vaccination (9, 74).

The inner ear might also be a target of autoimmune cross-reactivity following COVID-19 vaccination, as its proteome shares immunogenic heptapeptides with the SARS-CoV-2 protein (e.g., peptide sequences of prestin and wolframin) (72). This notion is supported by a recent description of autoimmune inner ear disease (AIED) with bilateral sensorineural hearing loss and bilateral vestibulopathy following COVID-19 vaccination with the Pfizer mRNA vaccine (27).

Summary

The results from the present study do not provide evidence for a specific underlying pathophysiology of AUPVP after COVID-19 vaccination. No patient displayed clinical signs for HSV reactivation (e.g., skin lesions, HSV keratitis) or a systemic autoimmune disorder. Furthermore, the MRIs of the brain and temporal bone in patients #1 and #7 did not indicate a structural lesion of either the vestibular labyrinth or the nerve. Regarding the endorgan lesion patterns in laboratory vestibular testing, a disorder of the superior vestibular nerve - e.g., by reactivation of HSV in the vestibular ganglia - may be suspected in patient #7. All the other patients showed a "patchy" involvement of individual vestibular endorgans that did not fit with a selective damage to the superior or inferior vestibular nerve, which might be due to an autoimmune response against antigens of the vestibular labyrinth or autoimmune vasculitis (17).

Implications for Treatment and Further COVID-19 Vaccinations

Six of eight patients in the present study received systemic steroids in the acute phase of the disease. In retrosptect, this treatment must be re-evaluated critically regarding a potential attenuation of the vaccine-induced immune response against SARS-CoV-2 (12, 75, 76). When the patients presented with acute vestibular symptoms, they usually did not mention that they had received a recent COVID-19 vaccination, and the question about vaccination status was not part of our clinical routine before this study. In the meanwhile, this question has been added to our standardized questionnaire.

To date, it is not clear how systemic corticosteroids affect the immunogenicity of different COVID-19 vaccines. In accordance with guidelines for other inactivated vaccines, it is recommended to wait for at least 2 weeks after vaccination before a high-dose course of systemic steroids is started [Soy et al. (76) and personal information: Dr. Nadia Eberhard-Kuhn, Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich]. As there is currently no high-quality evidence for the efficacy of systemic corticosteroids in AUPVP (77, 78), the potential risks and benefits of starting a treatment should be balanced for each single patient. Consulting an immunologist or infectious disease specialist is useful in this context. As described for SSNHL after COVID-19 vaccinations before (9, 12, 75), intratympanic application of steroids into the affected ear is also an alternative (17).

Our patients were often hesitant to obtain the next vaccination dose. No official recommendations are currently available for such situations. As the risk of contracting a SARS-CoV-2 infection with all its possible complications outweighs the risk of experiencing another episode of acute vestibular syndrome, we encourage our patients to proceed with vaccination. We recommend changing the type of vaccine if possible and to take valaciclovir for 7 days starting 2 days before the vaccination to suppress HSV reactivation (9, 27). Patients are furthermore advised to contact us immediately if they experience vertigo symptoms, so we can diagnose a possible relapse of vestibular dysfunction and start treatment (e.g., by intratympanic steroid injection) as soon as possible.

Strengths, Limitations, and Perspectives

This is the first case series of patients developing AUPVP within 1 month after COVID-19 vaccination. The strength of the study is that all patients underwent a comprehensive bedside neurotological examination at onset of symptoms and that laboratory vestibular testing was performed in all patients.

The major limitation of the study is its retrospective nature. As patients were not included prospectively into the study, not all bedside and laboratory tests were available for all patients. Furthermore, vestibular laboratory examination was only conducted 1 month after the onset of symptoms in most patients because this is part of our routine clinical protocol for AUPVP. This delay had no impact on the diagnosis of AUPVP in the present study because the disorder was defined by clinical criteria. In future prospective studies, laboratory vestibular testing of all five vestibular endorgans should, however, be performed within the first 10 days of symptom onset in order to grasp the full extent of initial vestibular hypofunction and to achieve a better comparability with previous studies on this topic (15, 16).

Another limitation of the study is a possible selection bias of patients who were recruited from a single tertiary neurotology center. On the one hand, the number of patients with AUPVP after COVID-19 vaccination may have been underestimated because not all patients were routinely asked about their vaccination status at the time of the study; on the other hand, a possible temporal association between the two events may have been overestimated due to the high number of 542,860 people in the Kanton Zurich (approximately one third of the inhabitants) who received at least one COVID-19 vaccination during the study period, which makes it more likely that any medical condition, including AUPVP, occurs in temporal association with a vaccination.

To obtain more representative and reliable results about a possible link between COVID-19 vaccination and the rare event of an AUPVP, large-scale, multi-center studies are warranted. In this context, self-controlled case series (SCCS) offer a valuable approach because each subject acts as its own control, thus minimizing the effect of possible confounders (6). Furthermore, these studies should comprise follow-up vestibular laboratory testing in order to determine the prognosis of AUPVP after COVID-19 vaccination as compared to other AUPVP cases. In the present study, results from repetitive vestibular testing were only available for patient #7 (1 and 3 months after the acute event, **Table 3**) indicating a recovery of right-sided vestibular function apart from caloric paresis of the right horizontal canal.

CONCLUSION

This is the first study to report a temporal association between COVID-19 vaccination and AUPVP in several cases of one tertiary neurotology center. Based on our results, the risk of AUPVP within 30 days after the vaccination is very low. Nevertheless, we recommend to ask patients with a new diagnosis of AUPVP about the date of their last vaccination and the type of vaccine they received. Although a causal relationship is not known to date, cases should be reported to health authorities in

order to provide data for future epidemiological investigations on possible side effects of COVID-19 vaccination.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

A formal ethical approval was waived by the local Ethics Committee (Kantonale Ethikkommission, Zurich, Switzerland) in view of the retrospective nature of the study, which is based on single cases, and since all the procedures being performed were part of the routine care. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JD and DS designed the study. MS, DB, DS, and JD collected and analyzed the data. DB created the figures. AP interpreted the MR images. MS and JD wrote a first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Subjective perception of activity level: A prognostic factor for developing chronic dizziness after vestibular schwannoma resection?

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Introduction: A vestibular schwannoma (VS) resection causes an acute unilateral vestibular deafferentation resulting in acute postoperative symptoms. Despite the expected resolution of most of the symptoms, due to central vestibular compensation, more than one out of four patients develop chronic dizziness. Several predictive factors, such as age and tumor size, have been suggested. Despite its potential effect on the process of central vestibular compensation, the level of physical activity after VS resection was not yet considered. Therefore, the association between the level of physical activity and chronic dizziness after VS resection will be investigated.

Methods: This retrospective cohort study included 66 patients who underwent a retro-sigmoid VS resection between October 2001 and February 2007. Patients were assessed before surgery and at 9 weeks and 6 months postoperatively. At 9 weeks, patients were asked to report their level of physical activity (PA) during the past week by using a visual analogue scale and their balance performance was assessed by four standing balance conditions with eyes closed and the Timed Up and Go test (TUG). Based on the Dizziness Handicap Inventory (DHI) score at 6 months, patients were divided in a chronic dizziness group (DHI $>$ 30) and non-chronic dizziness group (DHI-score $\leq$ 30). Age, sex, Koos classification, preoperative vestibular function, treatment group, balance performance, and level of PA were compared between both groups and used as independent variables in linear regression analyses with the DHI score at 6 months as dependent variable.

Results: The chronic dizzy patients revealed to have significantly lower levels of PA ($p < 0.001$) and worse static and dynamic balance performance ($p = 0.023$ and $p = 0.041$, respectively) 9 weeks after surgery. After elimination, the multiple regression analysis resulted in a model with two variables (PA level, TUG) which significantly predicted the DHI score ($F_{2,42} = 6.581$; $R^2 = 0.239$; $p = 0.003$).

Conclusion: This study revealed associations between (1) the level of PA and balance performance in the subacute phase and (2) chronic dizziness after VS resection. Assessment of the level of PA and balance performance during the subacute phase, which can be performed in a non-invasive and non-time-consuming way, might therefore provide prognostic information after VS resection.

KEYWORDS

vestibular schwannoma, physical activity, chronic dizziness, balance, risk factors

Introduction

Vestibular schwannomas (VS) are one of the most common intracranial benign tumors, representing over 80% of cerebellopontine angle tumors (1–3). Symptoms such as hearing loss, tinnitus, vertigo, and/or neuropathies can be present, depending on tumor size and location (3). Different treatments can be considered, of which observation with annual follow-up, resection surgery and radiosurgery or therapy are the most prevailing options (3–5). A VS resection causes an acute unilateral vestibular deafferentation so that postoperative symptoms such as acute dizziness, unsteadiness, and nausea may occur to a greater or lesser extent, depending on the residual vestibular function before surgery (6–10). In case of sudden vestibular function loss, central vestibular compensation is expected to take place after the acute phase, leading to a balanced sensory reweighting and resolution of the majority of the symptoms (11, 12). Despite the expected process of central vestibular compensation, more than one out of four patients develop persistent symptoms of dizziness (28%) (7). When investigating possible influencing factors for developing chronic dizziness, conflicting evidence was found regarding associations between chronic dizziness and age, tumor size, and preoperative vestibular function (7, 13, 14). These factors thus only partially explain the variation in outcome concerning chronic dizziness after VS resection. Another potential influencing factor is the level of physical activity, as it is assumed that repetition of movement is needed to stimulate central vestibular compensation (15–19). The preoperative level of physical activity was previously investigated and it was concluded that a higher level of physical activity before surgery led to better balance performance after VS resection (20, 21). Balance performance was used in these studies as an outcome measure. However, poorer balance performance during the subacute phase might indicate development into chronic dizziness, as an association between balance performance and dizziness in vestibulopathies has previously been reported (22–24). Despite this relation, balance performance was not yet considered as an influencing factor for chronic dizziness after a VS resection. The same applies to the postoperative level of physical activity, which can be more challenging for the patient compared to before surgery, as initially (head) movements will provoke symptoms due to the acute deafferentation (16). This was confirmed by two studies that found a lower variability in head movements, and thus an altered head movement strategy, during gait tasks at 6 weeks after VS resection compared to before (25, 26). Furthermore, patients with chronic vestibulopathies have lower physical activity levels compared to healthy controls (27–29). These results suggest that although physical activity is recommended to stimulate central vestibular compensation, patients might avoid (head) movements. Revealing an association between the level of physical activity and chronic dizziness could lead to additional clinically relevant postoperative measurements and ultimately to changes in the management of patients after a VS resection. Therefore, the hypotheses of this study are whether (1) the subjective level of physical activity differs between chronic dizzy and non-chronic dizzy patients and (2) the subjective level of physical activity influences the development of chronic dizziness.

Materials and methods

Participants

A retrospective cohort study was performed on patients who underwent VS resection *via* a retrosigmoid approach (30) at the Antwerp University Hospital. In the period between 19 October 2001 and 23 February 2007, patient records for which a Dizziness Handicap Inventory (DHI) measurement was available 6 months after surgery were included in the study (31). This study was approved by the ethical committee of the Antwerp University Hospital and the University of Antwerp (18/13/182).

Outcome measures

The objective of this study was to identify influencing factors for developing chronic dizziness after a VS resection. Therefore, the relationship between perceived handicap due to dizziness at 6 months after surgery (dependent variable) and the following independent variables was studied: age, sex, tumor size, preoperative vestibular function, level of physical activity, and balance performance during the subacute phase. At the time, for other research purposes, all patients were given a specific type of treatment. Therefore, treatment protocol was considered an independent variable as well. A complete overview of the clinical assessments performed at different timepoints is presented in Figure 1.

Perceived handicap due to dizziness/instability

The primary outcome measure of this study was the Dutch version of the Dizziness Handicap Inventory (DHI) (32, 33) at 6 months, revealing whether the patient had developed chronic dizziness or not. Twenty-five questions, that can be answered with yes (four points), sometimes (two points) or no (zero points), assess possible functional, emotional, and physical impairments due to dizziness. The higher the score (maximum 100), the worse the perceived handicap is present: 0–30 equals a low handicap, 31–60 a moderate handicap, and over 60 a severe handicap (23).

Koos classification

All VS were diagnosed before surgery by Magnetic Resonance Imaging and tumor size was graded based on the Koos classification (34, 35): grade 1 (small intracanalicular tumor), grade 2 (small tumor with protrusion into the cerebellopontine angle, no contact with the brainstem), grade 3 (tumor occupying the cerebellopontine cistern with no brainstem displacement), and grade 4 (large tumor with brainstem and cranial nerve displacement) (32, 33).

Preoperative vestibular function

Before surgery, the vestibular function was assessed by binaural bithermal caloric testing and the sinusoidal harmonic acceleration test. The complete testing procedure was described elsewhere (31, 36). Based on the slow phase velocity (°/s) of the caloric nystagmus, obtained during the maximal response of a caloric irrigation, Jongkees' formula was used to calculate the percentage of labyrinth asymmetries. Labyrinth asymmetry was considered normal if the difference between both ears was $< 19\%$ (36). Based on the slow phase velocity component during sinusoidal harmonic acceleration, vestibulo-ocular reflex (VOR) gain and VOR phase were calculated. The VOR gain was considered low if < 0.29 and a delay in the system was indicated by a VOR phase above 18°. Based on our normative data, 95% confidence intervals for VOR gain and phase were, respectively, (0.29; 0.87) and (−1.4; 18.1). (36). Labyrinth asymmetry, VOR gain, and VOR phase were used in the statistical analysis.

Treatment protocol

In the period between 2001 and 2007, patients after VS surgery were engaged in three different treatment protocols (31, 37): (1) the General Instructions-group received education concerning the vestibular system and general instructions to be physically as active as possible, (2) the Vestibular Rehabilitation-group received the same content as group 1 with an additional customized vestibular rehabilitation home-exercise program, and (3) the Vestibular Rehabilitation + Baclofen-group received the same content as group 2 with an additional medical therapy program with Baclofen up to 6 weeks after surgery (31, 37). During the follow-up sessions, the patients of treatment groups 2 and 3 were able to ask advice concerning their vestibular rehabilitation program. During the retrospective data collection period, two prospective clinical studies were conducted at the time (31, 37). In the first study, patients were randomly assigned to group 1 or 2 by a closed envelope (31). In the second study, patients were asked to participate in group 3. In case patients refused to participate in group 3, they were assigned to group 2 as this was standard care at the time (37). Patients that were seen in between or after the two studies performed the second treatment protocol (group 2). The vestibular rehabilitation program was the same for both clinical trials. The patients of groups 2 and 3 reported a daily exercise duration of $\sim$ 30 min. Treatment adherence was high up to 9 weeks after surgery but decreased between the 9th and 12th week. We observed that 2 months after surgery, most patients had returned to their daily activities, which probably resulted in less time available and less need to perform the exercise program.

Physical activity level

All patients were advised to be physically as active as possible after surgery. To estimate the patient's actual activity level, 9 weeks after surgery, the patient was asked to subjectively score his or her level of physical activity during the past week. Physical activity was scored using a visual analogue scale, ranging from zero physical activity (0) to vigorous physical activity (100). The following examples were given to the patients to help them score their level of physical activity: 0 means you spend all day in your bed while 100 indicates the highest level of physical activity you can imagine.

Balance performance

Static and dynamic balance performance was assessed 9 weeks post-surgery. Static balance assessment consisted of 4

FIGURE 1
Timeline clinical assessments.

different static balance test conditions with eyes closed: Romberg with Jendrassik maneuver, standing on foam, tandem stance, and single leg stance. The patient was asked to stand in each position for a maximum of 30 s. Timing was stopped earlier, in case of loss of balance or change in foot position. Each condition was repeated three times, unless the maximum score of 30 s was already reached during the first or second trial. A standing balance sum was calculated by adding the best scores, leading to a maximum possible score of 120 s (38). Dynamic balance was assessed using the Timed Up and Go test. Patients were asked to sit on a chair. After the signal "start," patients had to stand up, walk 3 m, turn 180° to walk back to the chair and return to sitting position. The patient was instructed to perform this task in a fast but safe manner. The time (seconds) to complete the task was measured from the "start" signal to the moment the patient sat down again with their back touching the back of the chair. Patients performed the Timed Up and Go test 3 times and the best score (shortest time) was withheld (39).

Statistical analysis

The demographics and study variables were described using means and standard deviations for continuous variables and frequencies for the categorical variables. Afterwards, patients were divided into a group with chronic dizziness (DHI score $>$ 30) and a group without chronic dizziness (DHI score $\leq$ 30) (23, 40, 41). All study variables were compared between both groups by performing independent samples t-tests for the continuous variables (age, preoperative vestibular function (labyrinth asymmetry, VOR gain, and VOR phase), static and dynamic balance performance, and subjective level of physical activity) and Fisher's exact tests for the categorical variables (sex, treatment group, and Koos Classification). Level of significance was set at a p-value of 0.05 and effect sizes (Hedges g) were calculated (42–44). An effect size was interpreted as strong when over 0.5 and the 95% confidence interval did not contain zero (45).

To unravel predictive factors for developing chronic dizziness, a multiple linear regression analysis was performed with the DHI score at 6 months as dependent variable. When taking into account the rule of thumb in regression, a maximum of one independent variable per 10 participants was set, besides intercept and slope (46). For the regression analysis, a complete dataset was available for 44 patients. Data were missing since not all patients were able to attend every session or not all outcome variables were gathered for each patient. Therefore, a maximum of 3 independent variables were used in the regression analysis. To identify the 3 main predictive variables for this model, a univariate regression analysis with DHI at 6 months was performed beforehand for all study variables. Ultimately, the 3 variables with the highest R^2 and a p-value lower than 0.05 were used in the backward multiple regression analysis. Independent variables were removed from the model if the probability of F (p-value) was $\geq$ 0.10. Multicollinearity was controlled for by calculating the variance inflation factor (VIF). A VIF below five was interpreted as no risk for multicollinearity (47). IBM Statistics SPSS 27 for Windows was used to perform all data analyses.

Results

Study participants

A total of 66 patients were included and assessed both preoperatively and after 9 weeks and 6 months. Participants were 50.16 $\pm$ 10.91 years old of which 28 were women and 38 were men. All preoperative tumors were graded based on the Koos classification: grade 1 (9 patients), grade 2 (33 patients

TABLE 1 Comparison of continuous variables between non-chronic dizziness and chronic dizziness groups.

	Non-chronic dizziness group Mean (SD) $N = 49$	Chronic dizziness group Mean (SD) $N = 17$	Independent samples t-test P-value	Effect sizes Hedges g (95% CI)
Age (years)	49.19 (11.30) $N = 49$	52.95 (9.48) $N = 17$	0.224	0.341 (−0.208; 0.889)
Timed Up and Go test (s)	7.78 (1.16716) $N = 45$	8.53 (1.43833) $N = 17$	0.041*	0.588 (0.025; 1.147)*
Standing balance performance (s)	57.41 (20.25) $N = 45$	46.07 (15.29) $N = 17$	0.023*	0.587 (0.024; 1.146)*
Subjective level of physical activity (mm, max 100)	77.16 (16.56) $N = 32$	53.54 (22.06) $N = 13$	<0.001*	1.270 (0.577; 1.952)*
Preoperative vestibular function (labyrinth asymmetry)	45.77 (27.30) $N = 35$	39.17 (20.88) $N = 12$	0.449	0.251 (−0.896; 0.397)
Preoperative vestibular function (VOR gain)	0.45 (0.23) $N = 36$	0.38 (0.20) $N = 14$	0.327	0.307 (−0.305; 0.916)
Preoperative vestibular function (VOR phase)	19.11 (13.41) $N = 36$	18.00 (10.54) $N = 14$	0.782	0.086 (−0.522; 0.694)

N, number; SD, standard deviation; s, seconds; mm, millimeter; max, maximum.
*Significant result.

grade), grade 3 (16 patients), and grade 4 (8 patients). As not all outcome variables were collected for each patient, data were missing concerning preoperative vestibular function (19 patients concerning labyrinth asymmetry and 16 patients concerning VOR gain and VOR phase), treatment group (post-surgery, 2 patients), the level of physical activity (9 weeks, 21 patients), and balance performance (9 weeks, 4 patients).

Comparison between chronic dizzy and non-chronic dizzy patients

The chronic dizziness and non-chronic dizziness groups consisted of 17 and 49 patients, respectively, meaning that 25.8% of the patients developed chronic dizziness. The differences between the two groups concerning the study variables are shown in Tables 1, 2. Three variables, namely level of physical activity ($p < 0.001$), timed up and go test ($p = 0.041$), and standing balance performance ($p = 0.023$), showed significantly better scores in the non-chronic dizziness group. Effect sizes for the continuous variables were presented as well, with strong effect sizes for the level of physical activity (Hedges g = 1.270 [0.577; 1.952]), timed up and go test (Hedges g = 0.588 [0.025; 1.147]), and standing balance performance (Hedges g = 0.587 [0.024; 1.146]).

TABLE 2 Comparison of categorical variables between chronic dizziness and non-chronic dizziness groups.

		Non-chronic dizziness group $N = 49$	Chronic dizziness group $N = 17$	Fischer's exact test P-value
Sex	Male	23	5	0.262
	Female	26	12	
Koos classification	Grade 1	6	3	0.737
	Grade 2	25	8	
	Grade 3	11	5	
	Grade 4	7	1	
Treatment group	General instructions	12	6	0.592
	Customized VR	26	8	
	Customized VR and baclofen	10	2	

VR, vestibular rehabilitation.

Predictive factors for perceived disability due to dizziness at 6 months

The univariate regression analyses revealed that the level of physical activity ($R^2 = 0.166$; b = −0.404; $p = 0.005$),

TABLE 3 Predictive factors for perceived disability due to dizziness at 6 months.

Univariable regression analyses with perceived disability at 6 months as the dependent variable

Independent variable	R^2	Intercept (a)	Slope (b)	Level of significance
Age	0.032	3.022	0.302	$p = 0.153$
Sex	0.031	14.357	6.590	$p = 0.155$
Koos classification	0.009	23.017	−2.072	$p = 0.438$
Preoperative vestibular function (LA)	0.022	21.764	−0.101	$p = 0.324$
Preoperative vestibular function (VOR gain)	0.010	21.374	−8.017	$p = 0.484$
Preoperative vestibular function (VOR phase)	0.001	18.951	−0.053	$p = 0.799$
Treatment group	0.008	20.130	−2.384	$p = 0.494$
Standing Balance Performance*	0.109	35.984	−0.321	$p = 0.009$*
Timed Up and Go test*	0.110	−20.795	5.173	$p = 0.052$*
Subjective level of physical activity*	0.166	47.961	−0.268	$p = 0.081$*

Multiple regression analysis with perceived disability at 6 months as the dependent variable

Model	R^2	$F_{x,y}$	Level of significance
Model after elimination with two variables*	0.239	$F_{2,42} = 6.581$	$p = 0.003$*
Independent variable	**Intercept (a)**	**Slope (b)**	**Level of significance**
Timed Up and Go test	−1.836	−0.268	$p = 0.052$
Subjective level of physical activity		5.173	$p = 0.081$

Perceived disability = DHI-score at 6 months, R^2 = explained variance of the dependent variable, intercept (a) and slope/regression-coefficient (b) in regression formula: Y (DHI-score) = a + bX (independent variable), LA, Labyrinthine asymmetry; VOR, Vestibulo-Ocular Reflex; F, ratio of the mean regression sum of squares divided by the mean error sum of squares, x/y = degrees of freedom.
*Significant result ($p < 0.05$).

timed up and go test ($R^2 = 0.110$; b = 4.929; $p = 0.008$), and standing balance performance ($R^2 = 0.109$; b = −0.321; $p = 0.009$) explained the largest variance in dizziness complaints compared to the other studied variables (Table 3). Thereafter, a multiple backward regression analysis was performed with these 3 variables. After the elimination process, 2 variables (level of physical activity and timed up and go test) remained in the model which significantly predicted the DHI-score at 6 months and explained up to 23.9% of the variance in DHI-score ($F_{2,42} = 6.581$; $R^2 = 0.239$; $p = 0.003$). However, the two variables are not independent prognostic factors for chronic dizziness. A collinearity analysis was performed for the regression model, indicating no risk of multicollinearity (VIF = 1.289 for the level of physical activity, VIF = 1.498 for timed up and go test, and VIF = 1.341 for static balance performance).

Discussion

Summary of the results

The objective of this study was to explore the association between the perceived level of physical activity during the subacute phase among other variables and chronic dizziness after a VS resection. Patients with chronic dizziness 6 months after surgery showed lower levels of physical activity and poorer balance performance 9 weeks after surgery compared to patients who did not become chronically dizzy. Furthermore, the perceived level of physical activity and dynamic balance performance explained up to 23.9% of the variance in the DHI score at 6 months. Other factors such as age, sex, Koos classification, treatment group, and preoperative vestibular function did not show significant associations with chronic dizziness. In summary, these results identify the perceived level of physical activity and balance performance during the subacute phase as possible prognostic factors for developing chronic dizziness after a VS resection.

The majority of the study variables — age, sex, Koos classification, preoperative vestibular function, and treatment group — were not significantly associated with chronic dizziness. In the literature, the relation of these factors with dizziness was studied in patients with dizziness, unsteadiness, or balance problems (48–50). Similar to the previously mentioned studies in patients after VS resection (7, 13, 14), conflicting results were found concerning the relation of these factors with dizziness: one study reported a significant association with sex (48) and two other studies reported no significant

associations with sex (49), age (48, 49), or vestibular function (50). Besides the significant association between dizziness and sex (48), these results are thus similar to what was found in this study. Furthermore, our results confirmed that physical activity and thus exposure to movement is required to stimulate central vestibular compensation after an acute unilateral vestibular deafferentation (15–19). However, the literature revealed that, in the long-term, levels of physical activity in these patients remain lower, compared to physical activity levels in healthy adults (27–29). Our results also unraveled an association between physical activity and the development of chronic dizziness after VS resection. Although in the literature limited information is available concerning this association, physical activity levels in chronic unilateral vestibulopathy-patients correlated moderately ($r > 0.4$ or $r < -0.40$) (51) with vertigo severity ($r = -0.602$) (27), dizziness severity (r = -0.493) (27), dizziness frequency (r = -0.487) (27), and challenging static balance performance (r = -0.452) (28). Combined with the level of physical activity, balance performance during the subacute phase explained a significant amount of variance in dizziness complaints after 6 months. The possible prognostic value of balance performance after VS resection was, however, not investigated before. Instead of balance performance, the predictive value of psychological factors and visual dependency on chronic dizziness were already explored. For example, VS patients revealed to have elevated levels of preoperative psychological burden, related to the number of present symptoms (52), and VS patients with the presence of psychological factors, such as anxiety or depression, show worse balance performance (53, 54). At the time, we did not systematically assess these factors. However, the presence of psychological factors—namely fear avoidance beliefs—might partially explain the association that was found in this study between physical activity and chronic dizziness. In case of fear of movements that provoke symptoms, insufficient exposure to movement will arise, and thus central compensation is not stimulated as needed, to prevent development into chronic dizziness. The relation between the presence of fear-avoidance beliefs and the level of physical activity was recently studied in a group of patients with mixed vestibular disorders, revealing that the presence of fear-avoidance beliefs significantly predicted activity limitations (55). Another interesting possibly predictive factor to explore is the preoperative amount of visual dependency. VS patients relying more on visual cues for balance control, initially show worse balance performance after surgery (56). Therefore, both presence of psychological factors and type of sensory weighting, for example, greater dependence on visual stimuli (12), seem to influence balance performance. This was confirmed by Cousins et al. who identified both anxiety and visual dependency as prognostic factors for clinical recovery (DHI score after 10 weeks) in vestibular neuritis patients (57). However, the impact of these patient-related factors on chronic dizziness in patients after VS surgery has not been investigated so far. Another preoperative treatment approach for VS, which was not applied in our study, is the preoperative deterioration of vestibular function by, for example, intratympanic gentamicin injection. Preoperative deterioration might stimulate preoperative central vestibular compensation and would perhaps allow clinicians to control the above-mentioned patient-related factors better. However, so far only conflicting results regarding the effect on postoperative symptoms were found (58–62). In summary, large prospective cohort studies in patients after VS resection, investigating the association between multiple objectively measured factors — such as level of physical activity and balance performance on top of other factors such as visual dependence and fear avoidance beliefs — and chronic dizziness, is recommended.

Clinical implications

Assessing the level of physical activity and balance performance can be rather easily performed, as described in this study. These measurements were conducted in a standardized and safe manner without invasive or time-consuming procedures. However, in contrast to how physical activity was assessed in this study, objective measures should be preferred, such as accelerometers, heart rate monitors, or even smartphone applications (63). Furthermore, measuring the level of physical activity during the subacute phase could raise awareness concerning the actual physical activity level and lead to additional guidance for patients whose activity levels are low. Vestibular rehabilitation might play an important role in the general activation of these patients (64–66). Besides the type of intervention, the timing of both assessment and intervention seems crucial as well, as the 1st weeks after vestibular deafferentation were identified as the most critical time period to stimulate central vestibular compensation (19). Assessing the level of physical activity after 9 weeks, as performed in this study, could, for example, signal that the intensity of vestibular rehabilitation should be increased rather than decreased. In addition, in case of the presence of psychological factors or visual dependency, components such as cognitive behavioral therapy and visual desensitization therapy may need to be added. In our study, the type of treatment was not significantly associated with the development of chronic dizziness. However, customized vestibular rehabilitation might have indirectly influenced the development of chronic dizziness as both variables that were associated with chronic dizziness were more favorable in the patients that received customized vestibular rehabilitation in the first 9 weeks after VS surgery. Indeed, the TUG scores at 9 weeks were higher in the general instruction group (group 1) compared to the modified vestibular rehabilitation groups (groups 2 and 3). In the elderly patients ($\geq$50 years), the difference in TUG scores was significant between both groups with 9.08 (1.17) seconds for the general

instruction group and 8.06 (1.12) seconds for the vestibular rehabilitation groups; independent samples t-test: $p = 0.03$, while for the entire population this was 8.36 (1.35) seconds for the general instruction group and 7.77 (1.15) seconds for the vestibular rehabilitation groups; independent samples t-test: $p = 0.09$ (31). Furthermore, although not significant, a higher level of physical activity was found in the customized vestibular rehabilitation groups (groups 2 and 3) compared to the general instruction group (group 1) with scores of 72.50 (21.71) and 63.64 (18.14), respectively (independent samples t-test: $p = 0.229$). Again this difference in the level of physical activity was more pronounced in patients older than 50 years of age: 71.64 (21.11) for the vestibular rehabilitation groups and 57.83 (22.26) for the general instructions group; independent samples t-test: $p = 0.17$. The small sample sizes might explain why the differences in TUG and activity level were not significant. In addition, it was observed that after 9 weeks, patients' adherence to the customized vestibular rehabilitation decreased and advice related to vestibular rehabilitation was usually stopped after 12 weeks. One might hypothesize that patients reaching a higher level of activity at 9 weeks stayed active in the following months, thereby partly decreasing the risk of developing chronic dizziness. This might explain why the type of treatment (in the first 9 to 12 weeks after VS surgery) was not associated with the development of chronic dizziness at 6 months. As mentioned before, more research is needed to confirm the influence of physical activity and balance performance on chronic dizziness. Thereafter, research concerning additional assessment and treatment can be performed.

Limitations

This study included a rather small sample size ($n = 66$). However, with 25.8% of the patients developing chronic dizziness, a representative sample was chosen as this number is in line with the literature (7). The small sample size and a varying amount of collected data per patient only allowed 3 independent variables in the regression analysis. At the ENT department, the self-observed level of physical activity was only requested from the patients from November 2002. Therefore, 21 out of 66 data points were missing concerning the level of physical activity at 9 weeks. When comparing the group with and without available perceived physical activity levels, the DHI score at 6 months did not differ between both. Therefore, the results of this study were thought not to be influenced by these missing data. Another limitation was that the measurement of physical activity in our study was patient-reported and therefore subjective. Furthermore, no information concerning the preoperative level of physical activity was gathered. It is possible that patients with higher levels of physical activity post-surgery might have been physically more active before surgery than those with lower physical activity levels. This preoperative level of physical activity, therefore, might influence the development of chronic dizziness as well (20) and was not taken into account in our study. Other possibly influencing variables, such as presence and duration of (vestibular) symptoms before surgery or location of tumor origin, were not assessed for their role on chronic dizziness as these data were not collected in this study. The lack of these variables could clarify why only 23.9% of the variance in DHI score was explained by our regression model. Finally, although an association was found between the level of physical activity and chronic dizziness, based on this study, no conclusion can be made concerning a possible causal relationship between both. Further longitudinal research is necessary to clarify if physical activity is a prognostic factor for the development of chronic dizziness after VS resection.

Conclusion

This study revealed associations between (1) the level of physical activity and balance performance during the subacute phase and (2) chronic dizziness after a VS resection. Despite the fact that only 23.9% of the variance of the DHI score at 6 months was explained by the subjective perception of activity level and functional balance at 9 weeks and that the two variables were not independent factors for chronic dizziness, it seems worthwhile to investigate this further and to determine whether objective measures of physical activity can predict chronic dizziness.

Data availability statement

The data is the property of the University of Antwerp. Requests to access these datasets should be directed to LVa, lien.vanlaer@uantwerpen.be.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the Antwerp University Hospital and University of Antwerp. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LVa: conception, content, design, conduct, analysis and interpretation of data, presentation of the research, and writing of the manuscript. AH and VV: conception,

content, design, interpretation of data, presentation, and critical revision of the research. CD: acquisition of data and critical revision of the research. PV: concept, acquisition of data, and critical revision of the research. LVe: conception, content, design, acquisition and interpretation of data, and presentation and critical revision of the research. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case report: Acute vestibular syndrome and cerebellitis in anti-Yo paraneoplastic syndrome

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Background: We define acute vestibular syndrome (AVS) as a sudden onset vertigo, nausea, vomiting, and head motion intolerance, more frequently associated with an acute peripheral and unilateral vestibulopathy. About 10–20% of all cases with central vestibulopathy are secondary to stroke. We report three patients evaluated over the past decade with an acute AVS along with subtle downbeat nystagmus (DBN), followed by dysarthria and progressive truncal and limb ataxia, as well as increasing DBN intensity.

Methods: All patients underwent neurologic examination, video-oculography, MRI, serum cancer markers, spinal fluid examination, paraneoplastic panel testing, and oncologic workup. With a consolidated diagnosis of cancer/paraneoplastic syndrome, we treated with plasma exchange (PLEX), high-dose steroids, surgery, and oncologic investigation. We additionally provided oncotherapy in one out of three patients.

Results: All three patients had an acute AVS, downbeat nystagmus DBN, and inability to perform tandem gait. Two of three patients had a normal head impulse test (HIT). As acute vertigo, nausea, and vomiting subsided, a progressive cerebellar syndrome ensued characterized by persistent DBN, impaired horizontal and vertical pursuit, impaired VOR suppression, truncal and limb ataxia, and dysarthria. All patients had normal MRI brain studies excluding stroke. CSF studies demonstrated lymphocytic pleocytosis and elevated protein. One patient had confirmed ovarian cancer with high CA-125 serum levels; another had undifferentiated cancer of unknown primary with high CA-125 and one patient with esophageal cancer. All had a positive PCA-1 antibody titer, also known as anti-Yo antibody. In one patient with expeditious immunosuppression, the ataxia progression slowed for 18 months, whereas the other two patients with delayed initiation of treatment had more rapidly progressive ataxia.

Discussion: Paraneoplastic encephalitis related to PCA-1 antibody (Anti-Yo) targets Purkinje cells and cells in the granular layer of the cerebellar cortex. Clinically, our patients had a central AVS characterized by DBN and followed with progressive ataxia and unremarkable neuroimaging studies. Rapid initiation of treatment may offer a greater chance to prevent further neurologic decline. Any patient with an AVS as well as DBN and normal MRI

should have an expeditious workup to rule out metabolic, toxic, and infectious causes just prior to considering prompt treatment with high-dose steroids and plasma exchange (PLEX) to mitigate the risk of rapidly progressive and irreversible neurologic decline.

KEYWORDS

acute vestibular syndrome (AVS), cerebellitis, PCA-1, anti-Yo, paraneoplastic syndrome

Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare neurologic condition most commonly due to anti-Purkinje cell cytoplasmic antibody type-1 (PCA-1), also commonly referred to as anti-Yo antibody, which is typically associated with breast and ovarian cancers (1). Neurologic manifestations often predate diagnosis of malignancy (2). Immune-mediated damage to Purkinje cells (PC) is typically irreversible, often resulting in permanent devastating disability in afflicted patients (3). Typical targets in PCA-1 antibody-mediated damage involve PC and granular cells in the cerebellar cortex, with secondary demyelination of the dentate nucleus (4, 5). Even though there is no specific mention of PC loss in the flocculus, midline uvula, and nodulus, it is predictable that these structures were involved in n =19/55 downbeat (DBN) anti-Yo patients (5). In this report, we highlight a common anti-PCA-1 phenotype with an acute vestibular syndrome (AVS), defined as the sudden onset of vertigo, nausea vomiting, and head movement intolerance (6, 7) due to a central lesion. The main features include subtle DBN while looking straight ahead and rapid progression from grade 1 to grade 3 truncal ataxia, with an inability to stand or sit without support. Nausea, vomiting, and vertigo rapidly improved in all three patients within two weeks. A normal MRI combined with an inflammatory CSF pointed to a diagnosis of acute cerebellitis. The differential diagnosis included an infectious, para-infectious, or paraneoplastic etiology (8). In the largest previous series of 55 anti-Yo antibody syndrome patients, 20 had acute continuous vertigo, only a few had nausea and vomiting, evolving within days to subacute ataxia, and the remaining patients had a picture of acute cerebellitis, and 19 of their 55 patients had DBN (5).

To date, current literature provides evidence for prompt plasma exchange treatment (PLEX) in halting the progression of cerebellar symptoms in some cases (9) with greater survival length and quality of life. Our reported cases and literature reviews suggest that a prompt combination of PLEX and high-dose steroid treatment in patients with characteristic clinical and CSF findings with normal MRI is justified. Here, the goal realistically at this time is rapid treatment initiation to prevent further neurologic decline, even in the absence of confirmed serologic antibodies.

Methods

All patients had video recordings at the bedside performed by trained doctors of Audiology, advanced nurse practitioner, or registered nurse (RN). We initially recorded the VOG with a target placed at 1 m from the patient and used Otometrics (CHARTR 200 goggles). Recordings began with fixation straight ahead and eccentric right, left, up, and down gaze positions, followed by saccade and pursuit eye movements as the patient tracked the examiner's finger. We then lowered the shield of the goggles to study the possibility of suppressed spontaneous nystagmus. In patient 2, we switched the initial goggles to the lighter Otometrics (Natus Video-Head Impulse goggles) to test and record the horizontal (h) head impulse test of the right eye and to screen for skew deviation during alternate cover test, as the patient fixated at a central target (HINTS protocol). We recruited patient 1 in 2010 before we had the ability to quantitate the VOR. We evaluated the second patient in 2017. The third patient in 2022 declined video head impulse testing (vHIT). Patient 1 had a paraneoplastic panel performed by Athena Labs. Patients 2 and 3 had antibodies tested by Western blot, at the Mayo Clinic (Rochester, MN). The paraneoplastic panel included anti-GAD 65 antibodies. All patients had MRI brain neuroimaging and spinal fluid analysis, followed by investigation of an underlying neoplasm, and biopsy of neoplastic tissue after we classified the presenting AVS as the initial phase of a progressive ataxia syndrome.

Patient 1

A 67-year-old woman presented with acute continuous vertigo with associated nausea and vomiting. We admitted the patient for neurologic evaluation due to substantial truncal ataxia and inability to sit without support. Her posture, gait difficulty, evolved over 5 days from an initial wide base stance on admission. Two serial stroke protocol MRI brain studies with gadolinium within 48 h were performed, both

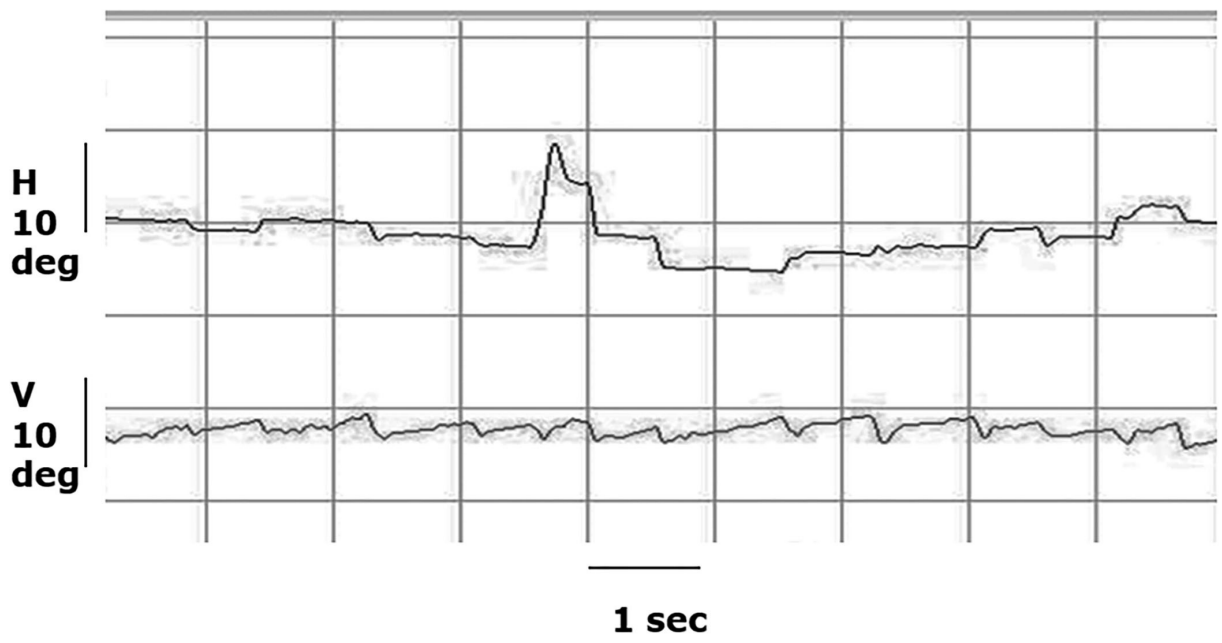

FIGURE 1
Video-oculography (VOG) recording of central fixation. The patient has a primary gaze, low-amplitude downbeat nystagmus with a slow phase velocity of 2 deg/sec and a frequency of 2 Hz, and this nystagmus increases in amplitude and velocity in right and left gaze.

with normal results. Otoneurology consult performed one week after symptom onset (Supplementary Video 1, patient 1) identified low-amplitude DBN best seen with ophthalmoscopy. Furthermore, she had direction-changing horizontal (h) nystagmus in right and left gaze with a downward and oblique direction; she had saccadic h and vertical (v) pursuit (Supplementary Video 1, Figure 1), mostly associated with DBN (Table 1); she had failed to suppress the VOR with visual fixation (VFX). Superimposed DBN on the pursuit tracings interfered with pursuit gain analysis. The head impulse test (HIT) was normal (Table 1, patient 1). We were unable to record the vHIT in 2010. Initially, there was no significant limb dysmetria or dysarthria. CSF studies demonstrated lymphocytic pleocytosis (98 /mm^3) and elevated protein (106 mg/dL). The diagnostic differential suggested an infectious, para-infectious, or a paraneoplastic syndrome. Additional diagnostic studies included a paraneoplastic panel, CT chest/abdomen, CA-125, and obstetrics/gynecology consult. CT identified an ovarian mass, and CA-125 was significantly elevated at 3,703 μ/mL. Parallel to the diagnostic effort, she began 1 g IV methylprednisolone daily, followed by five sequential, daily plasma exchange (PLEX) treatments. Subsequently, she underwent complete surgical excision of the identified ovarian mass, which yielded a diagnosis of ovarian carcinoma. In 10 days, the paraneoplastic panel result was positive for PCA-1 antibodies.

After surgery, treatment with carboplatin partially resulted in improvement and resolution of her AVS within 2 weeks despite persistent DBN; however, visual acuity was not significantly impaired. Gait remained unstable, unable to ambulate beyond a few steps independently, and continued to depend on a wheelchair for mobility. Follow-up CA-125 decreased to 111 U/mL after initial treatment. She remained neurologically stable for about 2 years. Unfortunately, due to later tumor recurrence with systemic metastases including supratentorial brain lesions, she elected to withdraw life-prolonging treatments and transitioned to hospice cares. At her last visit with neurology, she did not have neurologic deficits outside her known cerebellar abnormalities.

The autopsy was significant for extensive cerebellar folia atrophy and loss of PCs in the midline and lateral cerebellar hemispheres (Figure 2). In addition, she had cerebral hemisphere metastases of ovarian origin. Of note, there was no evidence of active inflammation.

TABLE 1 AVS characteristics preceding ataxia in anti-yo antibody syndrome.

Age/gender	Duration of acute vertigo, nausea and vomiting	Straight ahead nystagmus SPV	Lateral gaze nystagmus	Head impulse test	Other^
Female 67	15 days	DBN * 2 deg/sec	R: h/RBN + DBN L: h/LBN + DBN	Normal**	Wide base stance. Could not do tandem gait by history
Male 68	1 week	DBN 3 deg/sec	R: h RBN/DBN L: h LBN/DBN	RL: 0.57 ± 0.05 LL: 0.89 ± 0.05 LA: 0.95 ± 0.11 RP: 0.57 ± 0.08 LP: 0.69 ± 0.13 RA: 1.44 ± 0.13	Could not sit up without support Skew. R hypotropia
Female 80	1 week	DBN 3 deg/sec	R: h RBN/DBN L: h LBN/DBN	Normal**	Wide base stance. Could not do tandem gait

DBN, Downbeat nystagmus; h-RBN, Right beat nystagmus; h-LBN, Left beat nystagmus; SPV, slow phase velocity.
*Subtle nystagmus on straight gaze visible with ophthalmoscopy or magnification from Frenzel or Video goggles.
**Clinical head impulse.
^Wide base stance rapidly evolved to inability to sit in patients 1 and 2, patient 3 had a slower transition according to records, when first examined she could not sit without support.

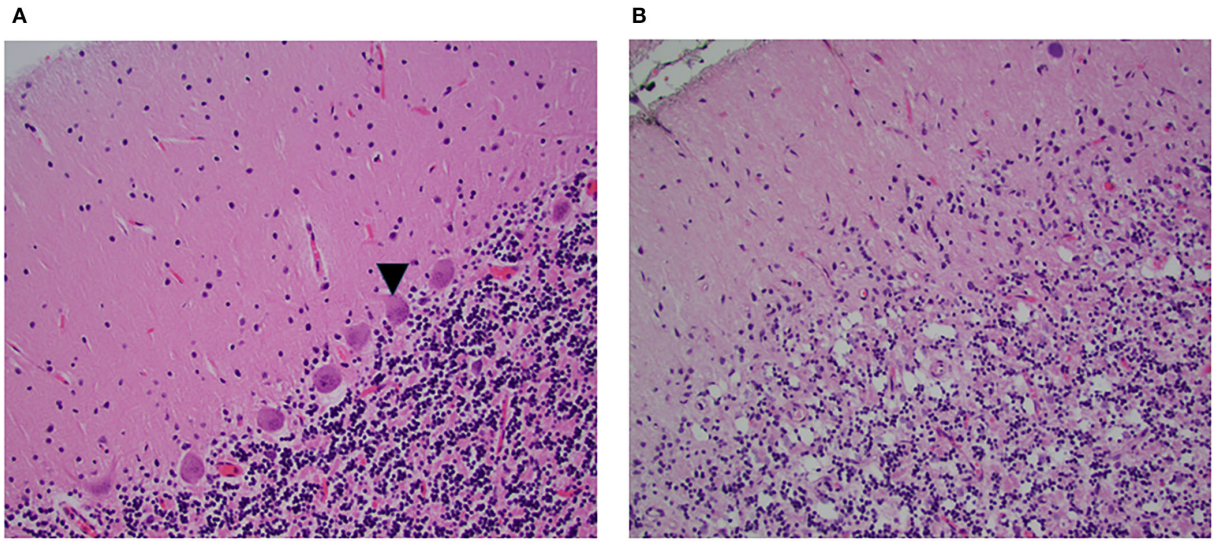

FIGURE 2
Microscopic examination of the hemispheric cerebellar cortex. H&E x20. **(A)** Normal cerebellar cortex, the arrow points to morphologically intact Purkinje cells. **(B)** Similar section inpatient 1 shows absent Purkinje cells, note absent of acute inflammation. In this patient, the deep nuclei were normal.

Patient 2

A 68-year-old man presented as a transfer from an outside hospital with acute continuous vertigo, nausea, vomiting, oscillopsia, and ataxia with worsening ability to stand over the week prior to admission. Examination on arrival was notable for subtle DBN when looking straight ahead, more prominent in lateral gaze, and mixed with a direction-changing horizontal component in lateral gaze (Table 1, patient 2). We found DBN superimposed on the horizontal and downward pursuit and poor VFX of rotational nystagmus, and he had decreased VOR gain and overt corrective saccades in response to a left head impulse test (Figure 3). He could not sit without support and had bilateral upper and lower extremity ataxia. The nausea and vomiting subsided with medication; however, DBN increased in intensity. There were no signs of elevated intracranial pressure or meningeal irritation. A head MRI was normal making the likelihood of PRION unlikely.

The patient underwent evaluation for infectious, para-infectious, and paraneoplastic etiologies. CSF studies revealed

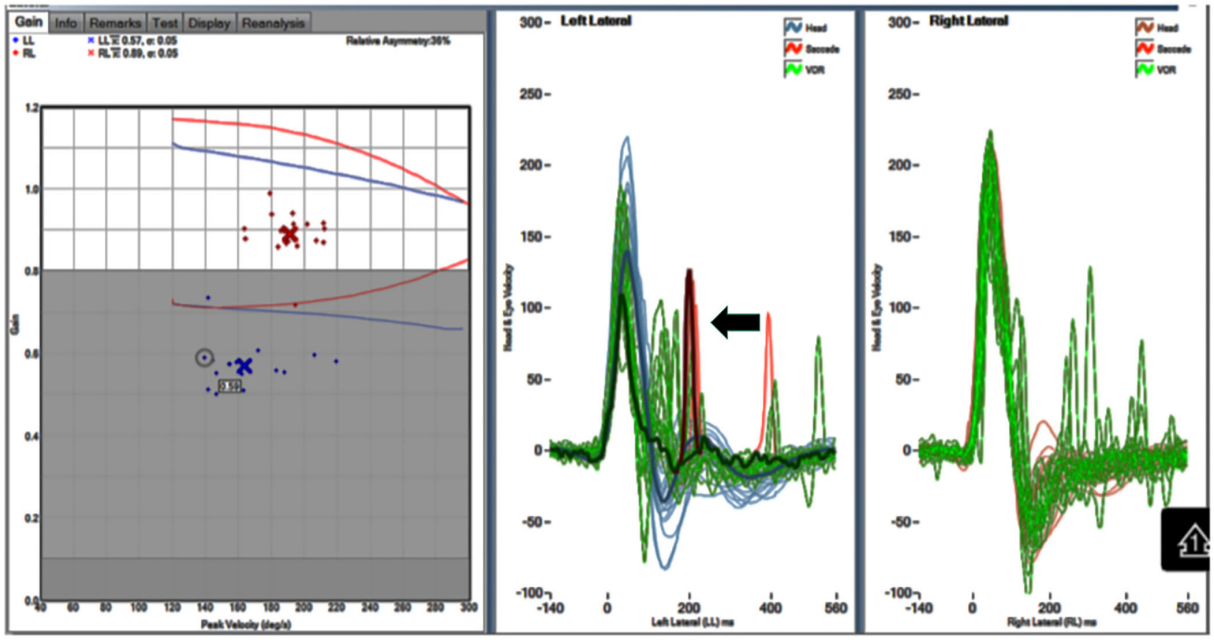

FIGURE 3
Video head impulse test (vHIT) of the horizontal VOR. Gain: 0.57 right and 0.89 left. Note catch-up saccade. There is a catch-up saccade 100 m sec after the end of the left head impulse (arrow).

lymphocytic pleocytosis (50 cells/1 mm^3, 100% lymphocytes), and protein mildly elevated 54.5 mg/dL (Table 1, patient 2). Treatment with high-dose steroids and PLEX began. Oncologic workup was significant for a distal esophageal mass, and biopsy showed poorly differentiated adenocarcinoma of the distal esophagus. A paraneoplastic panel was positive anti-PCA-1 antibodies. In the rehabilitation unit 2 weeks later, the patient continued to deteriorate rapidly with progressive confusion, diaphragm, and generalized truncal tremor/myorhythmia syndrome. He elected no further treatment and later transitioned hospice care.

Patient 3

An 80-year-old previously healthy Caucasian female presented as a transfer from an outside hospital for a one-month history of new rapidly progressive dysarthria and ataxia. Of note, we did not see her during the initial phase of her illness. Past medical history was significant for ulcerative colitis and hysterectomy with unilateral oophorectomy for reported symptomatic fibroids during her adolescent years. Initial symptoms were sudden onset unprovoked continuous vertigo, generalized weakness, and nausea with vomiting. According to her description and chart records within days of symptom onset, while her nausea, vomiting, and vertigo improved, her speech function rapidly deteriorated with slow and slurred speech, along with continued deterioration of her ability to ambulate due to ataxia.

Notable exam findings included delayed vertical saccades and subtle fixation DBN, more prominent on left and down gazes, mixed with a horizontal direction-changing nystagmus, as well as dysarthria best described as a monotonous scanning speech, with slow articulation and variable pitch and loudness. Generalized and non-lateralizing weakness developed with age-appropriate deep tendon reflexes and sensory examination. In addition, the patient had moderate ataxia of all extremities but more prominent on her left side.

Serial MRI brain with gadolinium studies performed on initial symptom onset, 1-week post-onset, and 2-week post-onset was unremarkable with no interval findings to correlate with symptom progression. CSF analysis 1-week post-symptom onset was significant for elevated protein (118 mg/dL) and lymphocytic pleocytosis (31 WBC/mm^3, 95% lymphocytes, and 4/mm^3 RBC). CSF glucose was 43 mg/dL. Incidental finding of St. Louis Encephalitis IgG with titer 1:4 (negative IgM), however, PCA Ab type-1 was positive with significant titer of 1:6,1440 (normal <1:240).

Preceding her transfer from the referring hospital, attempts to treat for suspected paraneoplastic rhombencephalitis with

a 5-day course of high-dose solumedrol alternating with IV immunoglobulin treatment days, with inconsistent neurologic improvement and an overall continued steady decline of independent mobility, speech, and function.

Oncologic workup done prior to transfer included transvaginal pelvic ultrasound as well as CT chest, abdomen, and pelvis with contrast all of which were unremarkable for suspicious masses or fluid collection. Serum CA-125 marker was elevated at 183.6 U/mL, with borderline CEA elevation at 3.1 ng/mL.

During her hospitalization, we treated her with a 5-day course of PLEX every other day alternating with a second course of high-dose methylprednisolone. However, there was minimal recovery and functional improvement on this treatment, the patient stabilized with no further functional decline and progression in symptoms after initiating plasmapheresis. PET scan was performed while inpatient and demonstrated multiple hypermetabolic, non-enlarged peri-esophageal, gastro-hepatic, and periaortic lymph nodes. Initial lymph node biopsy was notable for non-small cell carcinoma of unknown primary. CA-125 repeat level was 234 U/mL. Fine-needle aspiration of lymph node showed non-specific malignant neoplasm pathology (possibly pancreatic–biliary or upper GI tract origin), though colonoscopy and MRI abdomen were all non-diagnostic. After completing plasmapheresis treatment, the patient started on initial maintenance rituximab infusion; however, we discontinued life-prolonging treatments following patient and family's directive to transition to hospice due to severity of her persistent disability.

Discussion

The most common cause of an AVS is an acute vestibular neuritis (or acute vestibulopathy) (10), whereas the most common central cause is stroke. We hope that introducing awareness of additional central causes, albeit uncommon, increases the diagnostic accuracy of clinician evaluating acute vertiginous patients. Here, the otoneurologic examination was sensitive to central localization and provided compelling evidence to proceed investigating a specific non-vascular etiology. For organization purposes, we will discuss the initial AVS characteristics in these patients, followed by comments on their subsequent progressive ataxia syndrome.

AVS: An initial manifestation of anti-Yo antibody syndrome

Continuous vertigo associated with nausea, vomiting, and head movement intolerance lasting for a prolonged period (longer than 72 h) is most frequently associated with an acute vestibular neuritis (acute unilateral vestibulopathy). The cause for an AVS is peripheral in most patients, and about 5–15% of cases have unilateral central lesions. The symptoms cannot provide a peripheral vs. central localization diagnosis, and the physical examination identifying "central signs" provides the localization/lateralization information (6, 7). In two of our patients, subtle DBN in straight gaze was initially detected using ophthalmoscopy and goggles, increasing in lateral gaze and mixed with a horizontal direction-changing nystagmus, suggesting central localization in either the cerebellum or brainstem (7). None of our patients had a metabolic abnormalities, infectious cerebellitis, or medication effects to cause DBN; thus, the nystagmus direction here was the only initial overt and unequivocal central localization abnormality, particularly with normal brain MRI. In addition, patients 1 and 3 had a normal HIT, indicating preserved horizontal VOR gain (Table 1). Patient 2 had unilaterally decreased VOR gain (Table 1, Figure 3), while this combination points to combined peripheral/central etiology. In this context, it is probably secondary to vestibular nuclear or a floccular abnormality (11, 12).

Unlike peripheral cases of AVS, as nausea/vomiting and vertigo subsided, our patients worsened with increasing DBN and truncal ataxia as well as new signs of developing generalized cerebellar dysfunction.

All patients underwent a second MRI to exclude a stroke before formal audiology evaluation was done. Because of the subacute progressive ataxia, despite resolution of the AVS symptoms, we considered the possibility of rhombencephalitis, either viral, autoimmune, or paraneoplastic. Our patients did not have initial upbeat nystagmus (UBN) switching to DBN, as seen frequently in Wernicke's encephalopathy (13) or magnesium depletion (14). The obvious next step was an examination of the CSF and serum paraneoplastic/autoimmune investigation. Normal MRI of the brain in sequence excluded demyelinating diseases such as neuromyelitis optica spectrum disorders (15) and infectious etiologies. Finally, prion disorders with some frequency begin with rapidly progressive ataxia (7) and rarely with an AVS as well (16).

Subacute progressive ataxia syndrome

Once the AVS resolved, unexpectedly, the truncal ataxia increased, the nystagmus did not resolve, and additional signs of cerebellar dysfunction such as dysarthria and limb ataxia developed, by this time the CSF showed a lymphocytic pleocytosis, without evidence of an infectious process. The CT scan of chest/abdomen revealed abnormal mass lesions in all three patients, with biopsy confirmation of cancer and a positive paraneoplastic panel with anti-PCA-1 (Anti-Yo) antibodies detected by Western blot. Our patients fit the diagnostic criteria for paraneoplastic neurologic syndromes as described in 2004 (17).

The clinical manifestations of the anti-Yo antibody syndrome are consistent particularly because of the dysimmune response targeting specific neurons in the cerebellum, thus manifesting a central AVS associated with DBN, followed by an acute or a subacute progressive cerebellitis, typically in women with normal neuroimaging, inflammatory CSF findings, and increased CA-125 levels. In retrospect, initial dysfunction of the flocculus explains the DBN, in addition to the worsening gaze holding failure, abnormal pursuit, and impaired VFX (12) noted in our three patients. On occasion, the HIT may be abnormal as well, as noted in patient 2, rarely a finding in lesions of the flocculus (11). Anti-Yo antibody syndrome is extremely uncommon in men (18), most associated with cancer of the ovary or other gynecologic malignancies (5). The differential diagnosis includes infectious or post-infectious cerebellitis, other paraneoplastic syndromes, and prion diseases (5). Obviously, lymphocytic pleocytosis excludes the latter.

Nausea and vomiting are common in AVS, most attributed to asymmetric firing of vestibular nuclei neurons in the medial vestibular nucleus leading to motion sickness due to activation of the nucleus solitarius, the reticular formation, and the parabrachial nucleus (19). In patient 2, this was the likely mechanism, as the h-VOR gain was asymmetric. In anti-Yo, an alternative mechanism of nausea and vomiting could be secondary to involvement of the area postrema, which is specifically demonstrated in neuromyelitis optica (20). Asymmetric disinhibition of vestibular nuclei is a possibility (6, 7). In general, nausea and vomiting in our patients lasted longer than the average duration associated with vestibular neuritis (6). In the Peterson series, vomiting was infrequent (5).

Anti-Yo antibody syndrome is infrequent in men and raises concern for a false-positive result (17, 18). Our patients #2 and #3 were tested with Western blot and reported by the Immunology Laboratory of the Mayo Clinic, Rochester, MN, and correlated with a clinically consistent AVS. Importantly, there are a handful of preceding reports identifying this antibody in men, at least two patients with GI adenocarcinoma, one in the stomach with post-mortem identification of the anti-Yo antibody in the neoplasm, and a second report the same year in association with a neoplasm of the esophagus (3, 21). Moreover, our patients had a neurologic syndrome preceding the diagnosis of cancer, initially associated with an AVS, followed by ataxia. At minimum, this presentation is clinically consistent with the current diagnostic criteria for a paraneoplastic syndrome (17) and is consistent with serologic anti-Yo antibody positivity in the absence of alternate causes excluded by comprehensive evaluation. In addition, the rhythmic movement of the abdominal wall is potentially related to inferior olivary nucleus deafferentation from dentate nucleus involvement. Confusion develops frequently in anti-Yo syndrome patients (5).

The neuropathology of this syndrome relates to loss of PCs and other cerebellar neurons in the granular layers of the cerebellum (5). In patient 1, the autopsy showed loss of PCs, with demyelination of the dentate nuclei (Figure 2). The anti-PCA-1 antibody binds to a CDR2 protein involved in transcription (3). Eventually, there is a severe and disabling ataxia with an inability to sit without support. The particularly aggressive course in patient 2 may possibly relate to the uncommon gender and cancer association (18). The fact that the antibodies bind to nuclear rather than cell surface or synaptic antigens (22) may possibly explain a decreased therapeutic response to available treatment. Rarely, rapid tumor extraction, oncotherapy, and immunosuppression lead to improvement of symptoms (5).

One of our cases, who consistently demonstrated a therapeutic response, suggests a more favorable neurologic prognosis with earlier treatment following onset of AVS, the reported mechanism of PCA-1 causing irreversible injury to PCs theoretically slows down with timely intervention. The profound degeneration of the cerebellum associated with PCA-1, noted in the pathologic examination in patient 1, explains the poor neurologic prognosis. Thus, our series highlights the importance of prompt treatment in aborting the disease process and attempting to treat the underlying cancer. Definitive oncotherapy remains insufficient. Tumor recurrence led patient 1 to discontinue treatment; at autopsy, she had severe cerebellar degeneration and diffuse ovarian cancer metastases.

Both our experience and the literature in PCA-1 aim to improve awareness of paraneoplastic disorders. As current data shows greater and longer quality of survival, relating to early treatment, in an otherwise devastating condition, with has unchanged prognosis for the last three decades (5). Recent development in the treatment of cancer with checkpoint inhibitors has not shown effectiveness yet in epithelial ovarian carcinoma (23). It is possible that in the near future, an expeditious diagnosis will be critical. Checkpoint inhibitors theoretically may worsen neurologic abnormalities, which may warrant development of specific protocols to preserve the anti-neoplastic response while modulating the co-existent neurologic syndrome.

As previously mentioned, our best survival outcome possibly relates to expeditious treatment. In patient 1, slow neurologic deterioration for at least 18 months post-symptom onset enabled her to regain independent function abilities. Currently available maintenance options include rituximab, cyclophosphamide, and corticosteroid treatment; formal guideline is not yet established. Obviously, these measures were implemented in concert with surgical tumor resection and proper oncotherapy.

The main limitation in this paper is the small number of patients. In addition, the fact that patient 2 is a male with a paraneoplastic syndrome raises the possibility of an alternative antibody. However, the association between anti-Yo paraneoplastic syndrome and esophageal cancer was previously reported (21). Finally, we examined patient 3 with formal audiology evaluation after the illness initial phase had resolved. This limitation was countered by the patient providing reliable

history along with detailed extensive neurologic documentation on record and collateral history provided by family.

The second most common paraneoplastic antibody associated with ataxia is probably anti- ANNA-1 (Anti-Hu) (24), and the anti Kelch-11 protein antibody is associated with small cell cancer of the lung and testicular seminoma, germinomas, or teratoma (25). The latter is associated frequently with sensorineural hearing loss and episodic vertigo, DBN, and progressive ataxia.

In conclusion, the PCA-1 (anti-Yo) immunophenotype is very characteristic, and the pathogenesis of the syndrome remains unclear; therefore, a promising disease-modifying treatment is not yet available, except at best to cure the cancer and stop neurologic deterioration. Future approaches should consider the clinical characteristics.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

ES: direct patient evaluation, hospital care and article review, and edits. SB: processed autopsy samples to create original pathology slides. CG: video frenzel goggle testing and nystagmography. JK: direct manuscript editor, performed examination in all three subjects, and analyzed their eye movement recordings. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.960584/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Recording of eye movements with the use of Frenzel glasses to block fixation. The patient has low-amplitude, slow velocity DBN that increases in lateral gaze in amplitude and velocity.

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The pharmacological treatment of acute vestibular syndrome

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Acute vestibular syndrome (AVS) represents a clinical picture that involves urgent management due to the important procession of symptoms accompanying the event, which can be positively or negatively influenced by therapeutic choices and intervention timing. This forces a differential diagnosis and therapeutic choices to be made in conditions that are not always favorable and often not in the specialist field. In this work, we will examine in detail the pharmacological therapeutic possibilities, correlating them to the differential and, as far as possible, to the etiological diagnosis. In particular, the pharmacological possibilities for the two main conditions we can face will be investigated, namely, vestibular neuritis and posterior circulation stroke.

KEYWORDS

acute vestibular syndrome, vestibular neuritis, posterior circulation stroke, vertigo, pharmacologic treatment

Introduction

Vertigo and/or dizziness are frequently reported in patients admitted to the emergency department (ED), accounting for nearly 4% of admissions (1). There is a wide spectrum of causes including cardiovascular, neurological, vestibular, and systemic disorders (2). It has been observed that 10–20% of the patients admitted to ED due to persistent vertigo and dizziness have an acute vestibular syndrome (AVS) (3). AVS is defined as the sudden onset of acute, "continuous" vertigo (lasting longer than 24 h), associated with nausea, vomiting and head motion intolerance, gait instability, and nystagmus (ny). It results from a unilateral vestibular lesion that causes a sudden asymmetry of the neuronal nuclei firing rate and is largely associated with severe anxiety and vasovagal responses (2). The main causes of AVS are vestibular neuritis (VN), which nearly counts for 70% of cases, and posterior circulation stroke (PCS), accounting for 25% of diagnoses (1, 4). Discrimination between these pathologies is necessary for correct patient management, but despite a large investment of resources, PCS still too often escapes diagnosis and is sometimes missed (5). Approximately 10–20% of spontaneous AVS are due to stroke in the brainstem or cerebellum, nevertheless fewer than 20% present with focal neurological signs (6, 7). VN is the third most common, peripheral

vestibular disorder, after benign positional paroxysmal vertigo (BPPV) and Meniere's disease (MD). The leading hypothesis involves reactivation of a latent neurotropic virus, for example, herpes simplex virus (HSV) types 1 and 2, and herpes zoster virus (HZV). VN has recently been related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, but this association is still uncertain and definitive evidence is lacking (8–10). Other supposed etiologies include vascular, immunologic, and inflammatory (11, 12). Stroke affects the brain circle, resulting in the death of neurons, according to oxygen and nutrients deprivation (13). Ischemic stroke is more likely to determine AVS, compared to hemorrhagic stroke. The stroke involves more frequently posterior inferior cerebellar artery (PICA) than anterior inferior cerebellar artery (AICA) (14). Some patients with AVS can show focal lesions in the nodulus of the cerebellum, in the cerebellar peduncles, in the dorsolateral pons, in the lateral medulla, in the root of the eighth cranial nerve at the pontomedullary junction, or in the vestibular nuclei (15–19). Other possible causes of AVS are MD, multiple sclerosis, thiamine deficiency, BPPV, and vestibular migraine. Multiple sclerosis is an uncommon and infrequent cause of acute vertigo (4%). Demyelinating plaques can be located in and around the eighth nerve fascicle or vestibular nuclei but also in the brainstem and cerebellar peduncles. Considering that demyelinating lesions during an acute attack may not be evident on MRI, clinical examination in AVS is essential. In these patients, more evident oculomotor signs are often present (limitation of ocular motility or vertical nystagmus) (20).

Thiamine deficiency underlying Wernicke encephalopathy (WE) should be considered in patients with nutritional deprivation and unexplained acute or subacute vestibular symptoms, even absent encephalopathy. The complete WE triad includes ophthalmoplegia, ataxia, and encephalopathy. In about 90% of cases, there is altered mental status and nystagmus with central features. Nystagmus was the only ocular feature in 65% of cases. The most common human vestibular finding in WE is bilateral vestibular hypofunction, occurring in about 90% of cases. In the pre-encephalopathy phase, thiamine-deficient patients presenting with predominantly vestibular symptoms and signs can mimic vestibular neuritis or stroke with acute, persistent, vertigo, severe vomiting, and gait ataxia for 48 h. MRI of the brain in the pre-encephalopathy phase may be normal. Subsequently, it can present alterations consistent with WE such as areas of increased fluid-attenuated inversion recovery/T2 signal in the midline thalami, upper midbrain, and pons. Vestibulopathy in WE disease is due to direct bilateral damage of brainstem most likely in the dorsal medulla and pons in the region of the medial vestibular nuclei and nucleus prepositus hypoglossi in the medulla. The therapy involves the administration of vitamin B1 which in most cases determines an improvement in the patient's condition (21, 22). However, these clinical entities are less frequent than VN and stroke in AVS-like presentation and should be held in account when other causes are not identified (5).

Differential diagnosis

Correctly distinguishing between VN and PCS is essential although it is not always easy, due to the possible similar clinical presentation. Hemiparesis, headache, diplopia, dysarthria, and ataxia are neurological deficits that may be signs of PCS; however, they are not present in all patients (2, 23). In stroke suspicion, anamnesis has a key role. Smoke, diabetes mellitus, hypertension, hypercholesterolemia, diet, physical activity, and cardiovascular disease are important clues (24). VN ny is generally horizontal, maintains the same direction after changing gaze side, and is attenuated by visual fixation. Conversely, ny of central origin is multidirectional, and its intensity is less affected by visual fixation. Although horizontal mixed torsional ny is possible in both central and peripheral pathologies, vertical or pure torsional ny is suggestive of a central origin. Negative clinical head impulse test (HIT), direction changing ny, and skew deviation (HINTS) are suggestive of central origin. HINTS test is highly sensitive and specific in detecting vestibular strokes, and it outperforms acute magnetic resonance imaging (MRI) within 48 h from symptoms onset (6, 25). MRI diagnosis of smaller strokes (<1 cm) indeed can fail up to 50% of the cases within the first 24 h (26). ABCD2 score is also useful to quantify the risk of stroke, evaluating age, blood pressure, clinical features, duration, and diabetes in subjects (27). In the acute setting, computed tomography (CT) is more useful to evaluate a patient with suspected stroke, because it is quicker and easily available. MRI is more sensible in detecting early signs of ischemia. Brain imaging is essential in patients with suspected PCS and who may need thrombolysis or thrombectomy. These choices should be made based on risk factors, signs, and symptoms (2, 23). MRI has been shown to be effective in detecting signs of recent PCS onset, and it, therefore, allows patients to be referred for thrombolysis within the time interval suggested by the guidelines (28, 29). The symptoms and signs in patients with an AVS associated with a stroke commonly evolve over hours and often require frequent monitoring. In patients with the AVS, the finding of ocular lateral deviation (OLD), although infrequent (8.4%), usually reflects lateral medullary syndrome (LMS), particularly when associated with hypometric corrective saccades on opening the eyes. OLD is a conjugate, ipsilesional, horizontal ocular deviation associated with brief (3–5 s) closing of the eyes that is highly specific for a central disturbance. OLD is easily tested at the bedside and can be a quick confirmatory sign when patients have a HINTS pattern of eye movements suggesting a central cause, particularly when initial imaging is negative. To maintain specificity, a complete horizontal deviation must be present after a brief period (3–5 s) of simply closing the eyes. Clinicians

should look for OLD with brief, gentle eyelid closure and for a series of hypometric, corrective saccades back to straight ahead on opening the eyes. Both findings point to a central lesion that usually is in the lateral medulla on the same side as the OLD (30).

Also, the "STANDING" appears to show high sensitivity and specificity to detect central vestibulopathy, with good reliability in the emergency setting, and seems to be associated with a reduction of neuroimaging burden and hospital admission rates. STANDING is an acronym for the four-step clinical algorithm based on ny observation, and diagnostic maneuvers (Dix-Hallpike and Pagnini-McClure positionings) include the discrimination between SponTAneous and positional nystagmus, the evaluation of the Nystagmus Direction, the head Impulse test, and the evaluation of equilibrium (staNdinG) (31).

Larger cerebellar strokes (usually PICA, or less commonly SCA territory) with only vestibular and ocular motor signs need close monitoring in the intensive care unit for the development of malignant ischemic edema, which may be delayed at times for several days. Treatment may require hypertonic saline or different surgical interventions (external ventricular drain) or resection of necrotic tissue with good post outcome. Videonystagmography, electronystagmography, and/or vestibular evoked myogenic potentials (VEMPs) are useful to better qualify and quantify vestibular deficit (26).

Pharmacological treatment

Vestibular neuritis

The VN pharmacological management is aimed to reduce symptoms and inflammation in the acute phase. In fact, most people undergo complete resolution, but imbalance may last for weeks (11, 32, 33). Vestibular suppressants and antiemetics are useful for short intervals of time. If their administration is prolonged, they may obstacle VC (11, 26). In the acute setting, intravenous dimenhydrinate showed a major efficacy compared to intravenous lorazepam, in a randomized clinical trial by Marill and colleagues, in 74 patients (34). Antihistamines, benzodiazepines, anticholinergics, and dopamine receptor antagonists are possible therapeutic options in the first 2–3 days (33, 35). Corticosteroids use in VN is a controversial topic (36). Fishman et al. showed the absence of a long-term effect on symptoms. These compounds had a significant effect only on 1-month-performed caloric test (37). Other authors confirmed these results (38, 39). However, their use is a matter of fact and may provide symptoms relief in patients in the first 72 h (11, 26). Goudakos et al. experimental results sustain an earlier corticosteroids efficacy. However, the study was single blinded and had limitations (39). Vestibular rehabilitation has an important role in patient with long-term symptoms and seems to be comparable to corticosteroids in the main early outcomes (11, 33, 39). Nutraceuticals, including *Ginkgo biloba*, *Salvia officinalis*, *Melissa officinalis*, and *Zingiber officinalis*, may improve patient's conditions with a low amount of side effects (12). We previously treated these drugs' mechanism of actions, interactions, and side effects in a narrative review (35). Further details are summarized in Tables 1–3.

Posterior circulation stroke

Tissue plasminogen activators

Alteplase and tenecteplase are tissue plasminogen activators. Their main activity consists in the conversion of plasminogen to plasmin: this action is responsible for fibrinolysis (96, 97). Alteplase IV administration (in patients $\geq$ 18 years: 0.9 mg/kg, maximum dose 90 mg over 60 min; in the beginning, 10% of dose must be given as a bolus over 1 min) is recommended until 4.5 h after stroke onset. Treatment should be started as soon as possible. In severe stroke, after 3–4.5 h from symptoms onset, some categories of patients must be excluded (or have a lower evidence indication) for the high risk of hemorrhage: patients >80 years; combined history of diabetes–stroke; warfarin assumption, without considering international normalized ratio (INR); and very severe stroke with National Institutes of Health Stroke Scale (NIHSS) > 25 (29, 98). Alteplase is recommended for patients with mild stroke and mild disabling symptoms (NIHSS 0–4/5) until 3 h, and may be a therapeutic option in the same category, in a 3–4.5 h interval. A weaker indication is present (3–4.5 h interval) for patients > 80 years, with severe stroke (NIHSS > 25) and diabetes–stroke history. However, the use in these categories may be effective (29).

Important contraindications are represented by severe hemorrhages/risk of bleeding (e.g., intracerebral hemorrhage; head trauma; coagulopathy; use of anticoagulants or antiaggregant medications; and low platelets count), glycemia <50 or >400 mg/dl, systolic blood pressure > 185 mmHg, or diastolic blood pressure >110 mmHg. Nevertheless, the concomitant administration of anticoagulant or antiaggregant drugs may not be contraindicated if patients take it for solid clinical reasons (29, 96). Besides, its possible interaction with drugs acting on coagulation/aggregation (e.g., direct oral anticoagulants, aspirin, and coumarols), angiotensin-converting enzyme (ACE) inhibitors, may increase the risk of hypersensitivity generated by alteplase (96). Angioedema is a possible, but less common, alteplase side effect. It is probably related to the increase of bradykinin by plasmin activation. Therefore, the coadministration of ACE inhibitors may result in a worsening of macroglossia and angioedema (99). Tenecteplase is a modified alteplase analog. It has a longer half-life, a more specific action on fibrin, and a minor susceptibility to inhibitors (100). In EXTEND-IA TNK trial, tenecteplase (0.25 mg/kg, higher total dose 25 mg) was associated with a better reperfusion, compared to alteplase, in stroke patients until

TABLE 1 Mechanism of action and dosage of vestibular neuritis drugs.

	Mechanism(s) of action	Dosage suggested	Route of administration
Betahistine	Strong antagonist of histamine H3 receptors and a weak agonist of H1 receptors (40, 41)	24/48 mg daily (40)	OS (40)
Benzodiazepines			
Diazepam	Allosteric modulation of $GABA_A$ receptor (42, 43)	4–60 mg/daily (OS) 10–60 mg/daily (IV, IM) (44)	OS, IV, IM, rectal (43)
Lorazepam	Allosteric modulation of $GABA_A$ receptor (42, 43)	2–10 mg/daily (45, 46)	OS, IM, IV (43)
Anticholinergics			
Atropine	Non-selective muscarinic blocker (47)	0, 3–4 mg (depending on clinical indication) (47, 48)	IV, IM, SC (47, 48)
Glycopyrrolate	Non-selective muscarinic blocker (49)	2 mg in clinical trial (50), but may vary depending on clinical indication 1–8 mg (OS) (51) Various (parenteral) (49, 52)	IV, OS, IM (49, 51, 53)
Scopolamine	Non-selective muscarinic blocker (54)	0, 25–1 mg daily (IM,IV) (54) 0, 5 mg (TD) in clinical trial (55)	IM, IV, TD (54, 55)
Antihistamines			
Dimenhydrinate + cinnarizine	D: antagonist of H1 receptor (56) C: It blocks voltage-gated calcium channels, preventing calcium translocations across the vestibular air cells and, thus, regulating hair cell afferent vestibular transmission, anti-vasoconstrictor activity, reduction in the blood viscosity of the inner ear's circulatory system (56)	Dimenhydrinate: 25–200 mg (OS) (57) Basis of 50 mg (IV-IM), but may vary (58) Cinnarizine: 15–225 mg (OS) (59, 60) Recommended clinical dose (vestibular disorders): varies between 25 mg thrice-daily and 75 mg once-daily, up to a maximum of 225 mg (60) Dimenhydrinate/cinnarizine (co-formulation): 20/40 mg thrice a day (61)	IV, IM, OS (d) (57, 58) OS (c) (59) OS (co-formulation) (62)
Diphenhydramine	Antagonist of H1 receptor (62, 63)	25 mg-50 mg (62, 64, 65)	OS (62, 64)
Meclizine	Antagonist of H1 receptor (66)	12, 5–25 mg (67, 68)	OS (67)
Promethazine	Antagonist of H1 receptor (68, 69)	25–100 mg (OS) 25–50 mg; max:100 mg (IM,IV) (69) May vary (70)	OS, IM, IV (69)
Other antiemetics			
Metoclopramide	It acts on 5HT4 (agonist), 5HT3 (antagonist) and dopamine D_2 (antagonist) receptors (43, 70, 71)	10–30 mg or max 0, 5 mg/kg (IV-IM-OS) (71, 72)	OS, IM, IV, rectal (71, 72)
Ondansetron	5HT3 antagonist (73, 74)	4–8 mg capsules (OS), multiple administration also 8 mg (IV-IM) 16 mg (rectal) (74)	OS, IM IV, rectal (74)

GABA, gamma aminobutyric acid; IM, intramuscular; IV, intravenous; OS, oral; SC, subcutaneous; TD, transdermal.

4.5 h (100). However, tenecteplase (0.4 mg/kg, higher total dose 40 mg) failed to demonstrate superiority with a similar safety profile in a mild stroke prevalent court (101). These results induce guidelines for a lower strength (and maybe temporary) recommendation (IIb) for patients eligible for mechanical thrombectomy and as an alternative in mild stroke (no severe deficits or occlusions). However, in a mild stroke court, Tenecteplase showed to be equal to alteplase (and then it can be used as an alternative). In a tougher clinical context (occlusion of MCA, basilar, carotid), tenecteplase has shown superiority, and these findings will be the object of further studies to maintain or change the indication (29, 100, 101). Tenecteplase has similar adverse events and contraindications compared to alteplase (97). No other tissue plasminogen activators are approved by guidelines (29) (see Tables 4, 5 for details). In patients with an uncertain time of onset, performing a diffusion-weighted MRI (DW-MRI) and fluid-attenuated inversion recovery (FLAIR) sequences is useful: no signal in

TABLE 2 Pharmacokinetics of drugs used in peripheral vestibular vertigo (part I).

	Oral Bioavailability	Time to Peak Concentration	Serum Half-life (t1/2)	Protein Binding	Transporter proteins	Metabolism	Metabolites
BHS	NA	1 h	3.5 h	5%	-	Monoamine oxidases (MAO) A/B	2-pyridylacetic acid (2-PAA)
BDZ							
CLZ	90%	1.2 h	23 ± 5 h	82–86%	-	Liver (glucuronidation), CYP3A4	7-aminoclonazepam and 7-acetamido-clonazepam
DZP	90–100%	0.5–1.5 h	24–48 h	96–98%	-	Liver (glucuronidatio), CYP3A4, CYP2C19	Desmethyldiazepam, oxazepam, temazepam
LOR	90%	2–3 h	12–16h	85–90%	-	Liver (glucuronidatio)	3-O-phenolic glucuronide
ACDs							
ATP	-	10 min (IM)	4 h	-	-	50% liver 50% unmodified	NA
GLY	3% (children) NA, but higher (adults)	NA	0.83 ± 0.27 h (IV) 75 min (IM) 2.5–4 h (OS, solution)	-	-	NA	NA
SCO	NA	2 min (IM) 24h (TD)	8 h	-	-	Hepatic	NA
AHs (H1 antagonists)							
DIM + CNZ	43–72% (d)	1–4h (d); 2–4h (c)	6–7h (d); 4–5h (c)	80–85% (d)		Hepatic (d, *see the section below*). CYP2D6 and CYP2B6, but other CYP may be involved (c)	D: diphenhydramine, DMDP; C: conjugated with glucuronic acid
DPH	43–72%	1–4h	3–9.3 h	80–85%	-	Hepatic first-pass metabolism CYP2D6, and to a minor extent CYP1A2, CYP2C9 and CYP2C19	DMDP
MEC	NA	1.5–6h	5.21 ± 0.80 h	NA	-	Hepatic CYP2D6	Norchlorcyclizine (rats), 10 different metabolites in human urines. Human metabolites have not been identified, but meclizine undergoes aromatic hydroxylation or benzylic oxidation.
PMZ	25%	2–3h	4–6h (OS) 9–16 (IV) 6-13 (IM)	-	-	Hepatic first-pass metabolism	Promethazine sulfoxide (PMZSO), N-demethylpromethazine
Other antiemetics							
MCP	35–100%	0.5–2h (OS); 3 h (IM)	5–6h	13–40%	-	Hepatic: CYP2D6 isoform, and possibly CYP1A2 and CYP3A; conjugation.	Argikar et al. identified 10 metabolites of metoclopramide (M1-M10) in the urine after oral administration. Of those (M1, M2, M6, M7, and M8) were conjugated to either glucuronide or sulfate. Mono-de-ethyl-metoclopramide and N-4 sulfate conjugated are two important products.
OND	56% (OS); 60% (rectal)	1.5 h (OS); 6 h (rectal)	3–6 h	70–76%	P-gp substrate	Hepatic first-pass metabolism, CYP1A2, CYP2D6, CYP3A4	Hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

ACDs, anticholinergic drugs; AHs, antihistamines; ATP, atropine; BDZ, benzodiazepines; BHS, betahistine; CLZ, clonazepam; CNZ, cinnarizine; CYP, cytochromes P450; DIM, dimenhydrinate; DMDP, monodesmethyldiphenhydramine; DPH, diphenhydramine; DZP, diazepam; GLY, glycopyrrolate; IM, intramuscular; IV, intravenous; LOR, lorazepam; MAO, monoamine oxidase; MCP, metoclopramide; MEC, meclizine; NA, not available; OND, ondansetron; OS, oral; P-gp, p-glycoprotein; PMZ, promethazine; SCO, scopolamine; TD, transdermal.

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TABLE 3 Pharmacokinetics of drugs used in peripheral vestibular vertigo (part II).

	Enzymes Inductor/Inhibitor	Elimination	Dose Changes in Hepatic Disease	Dose Changes in Renal Disease	References
BHS	-	85% urine Low levels in bile	No dosage adjustment seems to be needed	No dosage adjustment seems to be needed	(40, 75)
BDZs					
CLZ	-	50–70 % in urine 10–30 % feces	Protein binding may be changed by cirrhosis, increasing the free fraction. Caution needed. Contraindicated in severe hepatic impairment.	Caution needed	(43, 45, 76)
DZP	-	100% urine	Contraindicated in severe hepatic impairment. Caution needed in other mild and moderate hepatic impairment	Caution needed	(43–45, 77)
LOR	-	88 ± 4% urine 7± 2% feces.	Caution needed. Contraindicated in severe hepatic impairment	Caution needed in severe hepatic impairment	(45, 46, 78, 79)
ACDs					
ATP	-	50% liver 50% urine	Caution needed	Caution needed	(47, 48, 80)
GLY	-	Urine, only 5% bile	Further studies needed. Since kidney elimination has a major role, hepatic impairment seems not to be relevant, despite a certain negative effect of anticholinergic drugs on hepatic damage.	Dose reduction by 30% in patients with mild to moderate renal impairment. Contraindicated in severe renal impairment.	(49, 52, 81)
SCO	-	Urine	Caution needed for the risk of CNS reactions	Caution needed for the risk of CNS reactions	(54, 80, 82)
AHs (H1-antagonists)					
DIM + CNZ	Inhibition of CYP2D6 (d)	Mainly in urine (d)	Caution needed (d)	Caution needed (d)	(57, 61, 62, 83, 84)
		40–60% feces and minor quote in urines (c)	Coadministration contraindicated in patients with severe hepatic impairment	Coadministration contraindicated in patients with eGFR< 25 ml/min	
(DPH	It inhibits CYP2D6	Mainly in urine	Caution needed	Caution needed	(62, 70, 85–87)
MEC	Meclizine seems to reduce the expression of CYP2B10, 3A11, 1A2 in experimental models	Urine, feces	Caution needed (need further evaluation)	Caution needed (need further evaluation)	(66, 88, 89)
PMZ	-	Urine	Caution needed (need further evaluation)	Caution needed (need further evaluation)	(69, 70, 90, 91)
Other antiemetics					
MCP	-	86% urine, minor quote in bile	Caution needed	Caution needed In patients with last stage renal impairment (eGFR ≤ 15 ml/min): dose reduction of 75%. Severe/moderate renal impairment (eGFR 15-60 ml/min): dose reduction of 50%.	(70–72, 92, 93)
OND	-	Majority hepatic, 5% urine	Caution needed, especially in severe hepatic impairment	Caution needed, although studies on moderate renal impairment did not show significant changes	(43, 73, 74, 94, 95)

ACDs, anticholinergic drugs; AHs, antihistamines; ALT, alanine aminotransferase; ATP, atropine; BDZ, benzodiazepines; BHS, betahistine; BUN, blood urea nitrogen; CLZ, clonazepam; CNS, central nervous system; CNZ, cinnarizine; CYP, cytochromes P450; DIM, dimenhydrinate; DPH, diphenhydramine; DZP, diazepam; eGFR, estimated glomerular filtration rate; GLY, glycopyrrolate; LOR, lorazepam; MCP, metoclopramide; MEC, meclizine; NIH, National Institutes of Health; NA, not available; OND, ondansetron; P-gp, P-glycoprotein; SCO, scopolamine; PMZ, promethazine.

FLAIR and DW-MRI lesion minor than one-third of middle cerebral artery (MCA) is eligible for fibrinolysis.

Antiplatelet treatment

Acetylsalicylic acid

Acetylsalicylic acid (ASA; also aspirin) exerts its antiplatelet activity by inhibiting cyclooxygenase 1 (COX-1) and depressing thromboxane synthesis (102–104). Aspirin is recommended in stroke patients 24–48 h after onset. In the case of alteplase administration, aspirin is delayed 24 h unless there are other clinical indications or benefits: in this case, it might be useful (29). Hemorrhagic risk should be evaluated carefully, especially in patients who consume multiple medications (29, 104). A systematic review by Sandercock et al. assessed that aspirin 160–300 mg OD (oral) significantly decreased death and complications (except hemorrhage, whose risk was low compared to benefits) (105). Combination therapy of clopidogrel and aspirin shows effectiveness in patients with non-cardioembolic ischemic stroke and NIHSS $\leq$3, not receiving alteplase (beginning in 24 h and continuing for 21 days) (29). The dosage was different in the two main trials. POINT trial randomized patients to a clopidogrel loading dose of 600 mg, followed by clopidogrel 75 mg/day, plus aspirin 50–325 mg/day, for 90 days, compared to aspirin alone. The results showed real effectiveness, but an increase in hemorrhagic risk. There was no benefit in stroke reduction risk after 30 days of treatment, whereas bleeding probability was enhanced after 7 days of treatment (101). A different dose (clopidogrel loading dose 300 mg, and then 75 mg/day, for 90 days, and aspirin 75 mg/day, for the first 21 days) was administered in the CHANCE trial, in comparison with aspirin. This therapeutic scheme generated similar percentages of hemorrhage (0.3%) in the two groups, increasing efficacy. Maybe these results are related to a smaller loading dose or limited duration of dual therapy (106, 107). Furthermore, CYP2C19 Asian polymorphisms may have a role in the development of adverse events, since clopidogrel may be variously transformed in its active metabolite, depending on ultrarapid/slow metabolism (106, 108). In a study by Khatri et al., alteplase was compared to aspirin in people with ischemic stroke, but minor disabling deficits (NIHSS 0-5). Aspirin was superior, despite some study limitations, according to guidelines recommendation. However, the results were not conclusive according to the trial brief duration (109). ASA may be used also in primary (risk factor management) and secondary prevention (50–325 mg daily) (29, 110, 111). ASA is not relevantly metabolized by cytochrome 450 (CYP450) enzymes, and it is not a substrate of transporters. It may compete with other non-steroidal anti-inflammatory drugs (NSAIDs) that also act on COX-1, lowering the ASA effect (112).

Interaction with selective serotonin reuptake inhibitors (SSRI) is also important. These antidepressant drugs reduce the platelet reuptake of serotonin, inhibiting aggregation. Therefore, increased hemorrhagic risk may result from coadministration (104, 112, 113). Another important interaction in this clinical setting involves antihypertensive drugs. In fact, NSAID may suppress renin activity, increase sodium retention, impair the activity of kidney prostaglandins (114), increase the risk of kidney injury, and impair diuretics activity (115). However, other authors suggest that low-dose aspirin does not have an important interaction with kidney and antihypertensive drugs. In fact, COX-2 is principally involved in the production of kidney prostaglandins 2, and aspirin acts on COX-1 (112) (see Tables 4, 5 for details).

Clopidogrel

Clopidogrel is an antiplatelet agent, which acts as a prodrug. The active compound is generated by CYP450 metabolism, and then, it blocks $P2Y_{12}$ platelet receptor. Through this pharmacodynamic action, it prevents the binding of adenosine diphosphate (ADP) to the same target (116, 117). Activation of $P2Y_{12}$ in physiological conditions leads to the activation of a pathway that determines the release of granules, a stronger platelet aggregation, and the activation of the glycoprotein IIb/IIIa receptor (GP IIb/IIIa) (118). Clopidogrel (75 mg) may be used in non-cardioembolic stroke or transient ischemic stroke (TIA) as secondary prevention for patients with risk factors. Antiplatelet treatment is strongly recommended by guidelines (10, 29). In this setting, aspirin (50–325 mg) alone, clopidogrel (75 mg) alone, and aspirin (25 mg) + dipyridamole (200 mg) are the main options. In non-cardioembolic stroke patients with NIHSS $\leq$3 or high-risk TIA ($ABCD^2$ score $\geq$4), double antiplatelet therapy (DAPT) with aspirin plus clopidogrel in 12–24 h from clinical insurgence is the right option (if alteplase has not been administered). This therapy should be maintained up to 21–90 days, then switching to single antiplatelet therapy: a longer treatment period would result in increased bleeding risk without benefit (29, 111). Clopidogrel is mainly transformed by CYP2C19 that produces its active metabolite (R-130964), a thiol derivative. CYP1A2, 2B6, and 3A4 have a certain role in this process (116). Therefore, inhibition (e.g., some proton pump inhibitors [PPI], some SSRI, and some antifungal medication resulting in reduction of active metabolite production) or induction (rifampicin) of CYP2C19 may alter therapeutic action (116, 118). Bleeding or side effects related to reduced platelet action are the most common side effects (116, 119) (see Tables 4, 5 for details).

Antiplatelet combination therapy and other options

The ASA was tested in clinical trials in coadministration with dipyridamole. Dipyridamole has both, vasodilator and antiplatelet effects. This drug inhibits adenosine reuptake from red blood cell precursors and inhibits cyclic-3'5'-adenosine monophosphate (cAMP) phosphodiesterase. Therefore, cAMP accumulates and exerts an antiaggregant activity. Vasodilator effect is generated by cyclic-3'5'-guanosine monophosphate

TABLE 4 Antiaggregant or fibrinolytic drugs (part I).

	Bioavailability	Half-life	Metabolism	Protein binding
Antiaggregant				
Aspirin	50% (88)	2–3 h	Hepatic (conjugation)	99%
Clopidogrel	50% minimum	6 h	Hepatic, CYP2C19	98%
Dipyridamole	60%	2.2–15 h	Hepatic (conjugation)	97–99%
Fibrinolytic				
Alteplase	-	40 min	Hepatic	-
Tenecteplase	-	90–130 min	Hepatic	-

If not, differently specified information can be found in SmPC.

TABLE 5 Antiaggregant or fibrinolytic drugs (part II).

	Dosage	Elimination	Dose adjustment kidney impairment	Dose adjustment hepatic disease
Antiaggregant				
Aspirin	Various trial dosages 25–600 mg in monotherapy or combination (*see text)*	Mainly renal	Use with caution. Contraindicated in severe impairment	Use with caution. Contraindicated in severe impairment
Clopidogrel	75 mg	50% urine; 46% feces	Few data available	Few data available
Dipyridamole	200 mg (in combination)	95% feces; 5% urine	No expected pharmacokinetics variations	Use with caution
Fibrinolytic				
Alteplase	0.9 mg/kg, maximum dose 90 mg over 60 min	Liver/plasma	Use carefully in hemostatic defects including those secondary to severe hepatic or renal disease	Use carefully in hemostatic defects including those secondary to severe hepatic or renal disease
Tenecteplase	0.25 mg/kg, higher total dose 25 mg	Liver/plasma	Use carefully in hemostatic defects including those secondary to severe hepatic or renal disease	Use carefully in hemostatic defects including those secondary to severe hepatic or renal disease

If not, differently specified information can be found in SmPC.

(cGMP) phosphodiesterase inhibition by dipyridamole. It results in an increase of cGMP and of its action on blood vessels (120). Some trials observed a better efficacy of aspirin plus dipyridamole compared to ASA alone in stroke secondary prevention (121). Clopidogrel plus ASA showed a better efficacy compared to ASA plus dipyridamole as antiaggregant therapy (122). However, ASA + clopidogrel DAPT has very specific indications, and dipyridamole + ASA is considered a good therapeutic option (111). Triple therapy (ASA + clopidogrel + dipyridamole) has been revealed to be dangerous, without any benefit, and it is contraindicated by guidelines (29, 122). An important statement is that, in case of cardiac disease/embolic origin of stroke, anticoagulants (direct anticoagulants or warfarin, varying in different indications) have a major role in secondary prevention (especially in atrial fibrillation). Nevertheless, antiplatelet agents may be used alone or in combination with anticoagulants, depending on etiology (111).

Glycoprotein IIb/IIIa inhibitors are not useful in this pathology. Tirofiban and eptifibatide efficacy have not been observed, and abciximab administration may even be dangerous, especially when associated with alteplase (29). A systematic review by Ciccone et al. showed an increase of hemorrhagic risk without benefit in terms of clinical effectiveness. However, the majority of the studies included regarded abciximab. Although its dosage and specific indications have not been described, tirofiban showed an interesting potential in stroke (123, 124). Nevertheless, other authors denied eptifibatide and tirofiban safety and effectiveness. Guidelines used a IIb recommendation on tirofiban and eptifibatide, assessing the need of further trials and analysis (29, 125). Ticagrelor, a $P2Y_{12}$ antagonist, has an uncertain role in stroke secondary prevention. Guidelines talk about a IIb recommendation, according to THALES trial. In fact, ticagrelor plus aspirin showed a better outcome of death stroke, compared to aspirin alone. The study included patients with a

mild to moderate pathology assessment (NIHSS ≤5) or TIA. The risk of hemorrhage was increased with ticagrelor (111, 126). Ticagrelor alone was inferior to aspirin in SOCRATES trial in the management of minor acute stroke, with comparable safety outcomes (127) (see Tables 4, 5 for details).

Discussion

The AVS represents a dramatic clinical situation causing an important feeling of fear in the patients who experience this event. A rapid and correct diagnosis must be the main goal when evaluating a patient with AVS. In fact, a wrong or delayed diagnosis does not allow to formulate an effective treatment plan and may cause devastating consequences for the patient's health. The initial phase of AVS is mainly managed by general practitioner and emergency room doctors. Patient's complained symptoms show a wide variability, including vertigo, vomiting/nausea, dizziness, headache, confusion, hearing alteration, and neurological deficits. This makes difficult to achieve a correct diagnosis with a basic clinical evaluation, making it necessary to perform specialistic instrumental evaluation and/or imaging investigation. As mentioned above, CT and MRI represent two fundamental radiological aids that allow to detect the eventual signs of ischemia or hemorrhage. According to recent studies, VN occurs more frequently in people over the age of 70 years (128, 129). Its exact etiology still remains unclear. Regarding viral infection of the vestibular nerve, it is considered that viruses causing infections of the upper respiratory tract, such as influenza virus, adenovirus, HSV, cytomegalovirus, Epstein-Barr virus, parainfluenza virus, and, recently, SARS-CoV-2, could be VN related, because associations with preceding or concurrent viral infection in the upper respiratory tract occur in 43% to 46% (130). Among them, HSV type 1 is the most common cause of viral infection of the vestibular nerve and ganglion. Recently, *in vivo* work demonstrated that HSV infection can induce VN and sudden deafness in a mouse model (131). Immunological mechanisms have also been suggested as possible causes of VN. A pathological CD4/CD8 quotient, which appears in 48% of NV cases, further supports a causal immunological origin (11). The characteristic clinical features of VN are abrupt true-whirling vertigo, lasting for more than 24 h, with nausea and vomiting, in middle age without cochlear symptoms and other neurological symptoms and signs. Prodromal dizziness lasting few minutes, in the few days just before the full onset of symptoms, may precede prolonged spontaneous vertigo in about 25% of patients (132). Unlike BPPV and MD, the clinical features of VN can make this pathological entity resemble PCS. In fact, during BPPV the vertigo is caused by head movement, and exacerbations of MD typically present specific audiological symptoms associated with vertigo (133–135). For these reasons, VN must be considered as the main pathological condition that may mimic a CNS ischemic stroke. Various treatments have been reported for VN, which can be largely divided into symptomatic therapy, specific drug therapy, and vestibular rehabilitation. Vestibular suppressants are widely used because they are effective against dizziness, nausea, and vomiting. During the acute stage of VN, an intramuscular or intravenous route for vestibular suppressants and antiemetics is usually preferable because of severe nausea and decreased gastric motility. However, most vestibular suppressants can have sedative effects, so they should not be used when patients are engaged in activities that require a high level of alertness, such as driving, operating machinery, or participating in athletic activities. Regarding specific drug therapy, steroid therapy has been reported to relieve dizziness and promote VC in VN. Methylprednisolone is much more effective than placebo in reducing vertiginous symptoms in patients with acute vestibular vertigo, and early treatment of acute VN with high doses of glucocorticoids accelerates and improves the recovery of vestibular function (136). Nevertheless, a recent meta-analysis by Leong et al. concluded that corticosteroids appear to have short-term benefits in canal paresis but no long-term benefits in canal paresis and symptomatic recovery (137). Concerning VN long-term treatment, the gold standard for therapy is represented by vestibular rehabilitation. Its targets are to improve vertigo, gaze stability, postural stability, and daily living activities through VC and central neuroplasticity. Vestibular rehabilitation consists of a dynamic compensation of vestibular reflexes that are activated by movement, and it is composed of adaptation, habituation, and substitution. Vestibular rehabilitation exercises are safe, highly therapeutic, highly cost-effective, and significantly hasten vestibulospinal compensation in patients with VN (138–140). Balance and gait exercises significantly reduce the time required for vestibulospinal compensation. Voluntary eye movements, active head movements, goal-directed movements, and walking should be encouraged to restore postural control and balance as soon as possible. Patients with VN should exercise for at least 30 min, 3 times a day (132). An interesting therapeutic opportunity is also offered by nutraceuticals, especially in the intercritical phases of the disease or in the recovery of residual imbalance in some subjects. These are safe and effective compounds that can be administered without associated drugs or in combination to decrease their dosage (12, 141). The prognosis in patients with VN is generally good, but residual dizziness may remain in some patients after the acute phase, similar to persistent disabling imbalance after successful repositioning maneuvers for BPPV. This can be due to many factors, including inadequate central compensation, incomplete peripheral recovery, and psychophysiological and psychological characteristics. The decreasing postural control can affect the quality of life, contributing to falls and psychological problems (142). In contrast, approximately 20% of ischemic events involve tissue supplied by the posterior circulation territory,

such as the cerebellum and brainstem. The incidence of cerebellar infarction in larger series of patients with stroke is approximately 1.5 %, with an average patient age of about 60 years (143). Tissue plasminogen activators and antiplatelet treatment represent the two principal categories of drugs for the prompt treatment of cerebral ischemic stroke. Regarding AVS, the main clinical goal is to obtain a fast and correct differential diagnosis between VN and cerebellar stroke. Indeed, the best therapeutic effects can be greatly reduced when stroke treatment is administered late. For this reason, when evaluating a patient with AVS, the crucial question is to clarify the correct etiology of the symptoms. Dizziness/vertigo is a common symptom in patients with isolated strokes of the cerebellum, usually with other neurological symptoms and signs. However, the diagnosis of isolated vertigo from brainstem and cerebellar stroke has increased markedly with recent developments in clinical neurotology and neuroimaging. Patients with infarction in the AICA territory may have isolated recurrent vertigo, acute hearing loss, and/or tinnitus as the initial symptoms (144). This particular clinical entity is also well defined as "labyrinthine infarction." The acute hearing loss is usually caused by the thrombotic narrowing of the AICA or the basilar artery at the orifice of the AICA. Through this mechanism, decreased blood flow in the affected AICA might cause either a transient episode of selective ischemia to the inner ear, resulting in isolated prodromal vertigo, or permanent damage to the widespread areas involving the middle cerebellar peduncle, lateral pons, and anterior cerebellum, resulting in acute hearing loss and prolonged vertigo in addition to other central symptoms and signs (145). The apical region of the cochlea is particularly vulnerable to vascular damage and, therefore, low-frequency hearing loss is common in inner ear ischemia (146). To date, at least eight subgroups of AICA infarction have been identified, according to the pattern of neurotological presentations, among which the most common pattern of audiovestibular dysfunction is the combined loss of auditory and vestibular functions (147). Ischemia of the PICA usually produces no auditory symptoms, because it does not perfuse the auditory tract, generally. However, PICA infarction may rarely be associated with acute hearing loss as the internal auditory artery sometimes originates from the PICA or directly from the basilar artery (148). For a proper management, in all cases of AVS, it is very important to know when a patient needs an urgent brain scan, and what role does neuroimaging play in diagnosis. Because central signs, such as spontaneous vertical ny, direction-changing gaze-evoked ny, perverted head shaking ny, or severe postural instability with falling, are known to have high specificity, but low sensitivity, for detecting a central cause of vertigo, isolated acute vertigo due to cerebellar infarction at the bedside remains a diagnostic challenge. The cerebellum plays an important role in maintaining body posture, regulating the muscle tension associated with postural movements, and coordinating voluntary movements (149). The vermis is involved in the coordination of eye and body movements, provides visual and auditory input related to balance, and is involved in vestibular system regulation and in maintaining the position of the head (150). Unfortunately, pharmacotherapy and conventional rehabilitation treatments, including core strength exercises, visual feedback training, neurodevelopmental therapy, and proprioceptive neuromuscular facilitation, performed unsatisfactory results on balance recovery among stroke patients (151).

Conclusion

The therapeutic approach to AVS conditioned by the ability to make a correct differential diagnosis and as certain as possible from an etiological point of view. While we have sufficient tools to identify the location and mechanism of the damage, it is not always possible to have immediate evidence of the etiology. This can affect the accuracy of the therapeutic choice by forcing less specific therapies from a causal point of view. Furthermore, the correct pharmacological action lays the foundations for obtaining an effective VC. At the same time, another determining element, directly linked to the therapeutic choice, is the time factor. In fact, the precocity of intervention can guarantee, in general, better outcomes and, in some specific cases, can avoid the evolution toward much more critical clinical pictures and, in a significant percentage, toward non-compensation or transformations into persistent dizziness (152).

Author contributions

PV, FG, and GM: conceptualization, methodology, investigation, data analysis, visualization, and writing—original draft. AA, DP, and AS: investigation and data analysis. AC, EB, and VR: investigation, data analysis, and project administration. MR and GC: investigation, visualization, and software. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Head-shaking-induced nystagmus reflects dynamic vestibular compensation: A 2-year follow-up study

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Purpose: We aimed to assess the ability of a head-shaking test (HST) to reflect vestibular compensation in patients after unilateral peripheral vestibular loss and to provide missing evidence and new insights into the features of head-shaking-induced nystagmus (HSN) over a 2-year follow-up.

Background: HSN may occur after a prolonged sinusoidal oscillation of the head. HSN is frequently observed in subjects with vestibular function asymmetry; it usually beats toward the functionally intact or "stronger" ear and can be followed by a reversal of its direction.

Study design: A prospective observational case-control study.

Settings: A tertiary academic referral center.

Methods: A total of 38 patients after acute unilateral vestibular loss (22 patients with vestibular neuronitis and 16 patients after vestibular neurectomy) and 28 healthy controls were followed for four consecutive visits over a 2-year period. A complex vestibular assessment was performed on all participants, which included spontaneous nystagmus (SPN), the caloric test, the head-shaking test (HST), the video head impulse test (vHIT), the Timed Up and Go (TUG) test, and the Dizziness Handicap Inventory (DHI) questionnaire. We established the criteria for the poorly compensated group to assess different compensatory behaviors and results.

Results: We found a time-related decrease in HSN ($\rho < -0.84$, $p < 0.001$) after unilateral vestibular loss. After 2 years of follow-up, HSN intensity in compensated patients reached the level of the control group; TUG and DHI also improved to normal; however, the caloric and vHIT tests remained abnormal throughout all follow-ups, indicating a chronic vestibular deficit. Besides, poorly compensated patients had a well-detectable HSN

throughout all follow-ups; TUG remained abnormal, and DHI showed at least a moderate deficit.

Conclusions: Our study showed that, after a unilateral peripheral vestibular loss, the intensity of HSN decreased exponentially over time, reflecting an improvement in dynamic ability and self-perceived deficit. HSN tended to decline to the value of the control group once vestibular compensation was satisfactory and sufficient for a patient's everyday life. In contrast, well-detectable HSN in poorly compensated patients with insufficient clinical recovery confirmed the potential of HSN to reflect and distinguish between adequate and insufficient dynamic compensation. HSN could serve as an objective indicator of stable unilateral vestibular loss.

KEYWORDS

head-shaking nystagmus, head-shaking test, head-shaking-induced nystagmus, vestibular compensation, follow-up study, velocity storage

Introduction

Head-shaking-induced nystagmus (HSN) was first described by Bárány (1); the first formal description was given by Vogel (2) and the test was standardized by Kamei et al. (3). HSN is a jerk nystagmus that may occur after a prolonged sinusoidal oscillation of the head and lasts at least a few seconds (4). HSN in the horizontal or vertical plane is abnormal. In subjects with vestibular function asymmetry, HSN is frequently observed, usually beating toward the functionally intact or "stronger" ear, and may be followed by a reversal of its direction (5, 6). The head-shaking test (HST) is an easy-to-perform test and can be performed as a low-cost bedside test with minimal equipment (Frenzel goggles) or can be assisted with video oculography (VOG) for precise evaluation of the slow phase of nystagmus.

Head-shaking-induced nystagmus was described in the literature corresponding to vestibular function asymmetry (7–9) and might be associated with the degree of functional deficit (10). In contrast, other studies found varying degrees of sensitivity and specificity in identifying such an asymmetry (11, 12). The discrepancy between the conclusions raises the question of whether HSN may reflect dynamic compensation rather than vestibular asymmetry.

Our study aimed to provide long-term missing evidence and new insights into the features of HSN in patients with unilateral vestibular loss (UVL) over a 2-year follow-up period. We tested the feasibility of HST to reflect dynamic vestibular compensation in UVL. To date, we have not found any literature on the long-term properties of HSN that evaluates HSN as a possible indicator of individual dynamic compensation.

Abbreviations: aSPV, average slow phase velocity; HST, head-shaking test; hVOR, horizontal vestibuloocular reflex; L-SCC, lateral semi-circular canal; SPN, spontaneous nystagmus; UW, unilateral weakness; VOR, vestibuloocular reflex; VOG, videooculography; VHIT, video head impulse test; DHI, dizziness handicap inventory; Questionnaire.

Methods

Participants

We used data from 66 participants: 28 healthy volunteers and 38 patients (22 patients with vestibular neuronitis and 16 patients after vestibular neurectomy). Subsequently, we divided participants into four groups according to their different vestibular behaviors, results, and complaints.

Vestibular neuronitis, surgery, and control groups

The inclusion criteria for the vestibular neuronitis group included a history of the first vertigo attack and a confirmed acute UVL without any neurological or cochlear deficit. According to the HINTS plus protocol (13–15) and normal magnetic resonance imaging (MRI) results, peripheral vestibular deficit was proven. For the surgery group, subjects with MRI-confirmed vestibular schwannomas [Koos classifications 1–2 (13)] with normal or near-normal vestibular function before the surgery were included. The inclusion criteria for the control group included no evidence of any balance problems currently or in the past, no history of vestibular disease, and normal hearing thresholds. We examined participants from January 2018 to February 2022.

Poorly compensated group

To assess the features of HSN during vestibular compensation, we defined the criteria for poorly compensated patients as those who had a unilateral vestibular deficit [>26% unilateral weakness (UW) by a bithermal caloric test] and who had at least three of the following criteria: complaints of blurred vision (subjectively often described as slow or lazy eyes) during daily life head turns (e.g., turning the head to the left and right before crossing the street) or dizziness, defined as a total score higher than 16 on the Dizziness Handicap Inventory (DHI) (14), having a gait disturbance defined as a timed up and go (TUG) test score more than 10 s (or in need of assistance), or having spontaneous nystagmus (SPN). According to our criteria, we planned to establish a poorly compensated group after V4 was completed because there is no test to confirm sufficient and finished dynamic compensation. Six patients fulfilled the criteria during all follow-ups, and *post-hoc* formed the poorly-compensated group.

Post-hoc, we established four groups for comparison: the neuronitis and surgery groups (compensated patients), the poorly compensated group, and the control group. We analyzed 20 subjects with vestibular neuronitis (neuronitis group, five women, 15 men, mean age 45 years), 12 patients with vestibular schwannoma after unilateral vestibular neurectomy (surgery group, two women, 10 men, mean age 51), and six subjects who were poorly compensated from both groups (poorly compensated group, two from neuronitis and four from the surgery group, five women and one man, mean age 49 years). The control group consisted of 28 volunteers (15 women, 13 men, mean age 48 years).

Settings

We examined all subjects at a tertiary referral center, University Hospital.

Measurements

We measured average slow phase velocity (aSPV) [°/s] of spontaneous nystagmus (SPN) and head-shaking-induced nystagmus (HSN), unilateral weakness (UW) during the caloric test, and video head impulse test (vHIT) gains.

Devices used for a study

VOG VisualEyes^{TM} 525 (Interacoustics, Denmark) and VHIT EyeSeeCam (Interacoustics, Denmark) were used to perform a complex vestibular examination on all participants.

SPN recording method

The patient was asked to sit upright, and visual fixation was denied. The tracing was recorded for 40 s (sitting position, head still, and goggle closure). If any nystagmus occurred, the VOG software measured its slow phase component.

VOG-assisted bithermal air caloric test procedure

The patient was asked to lie in a caloric position, and each ear was irrigated with warm (50°C) and cold (24°C) air for 60 s and nystagmic response was recorded for 120 s.

HST procedure

The patient was asked to sit upright, and visual fixation was denied. Eye movements were observed for 10 s to obtain a baseline. The examiner moved the patient's head (pitched forward 30°) briskly to the left and the right, aiming for a frequency of ∼2 Hz and a head displacement of roughly 40–60°, 20 cycles (duration of 10 s), and then stopped abruptly. VOG was recorded for 120 s; induced nystagmus was evaluated. If there were more than two repetitive nystagmus beats after a headshake, they were analyzed.

VHIT procedure

The patient was asked to sit upright, with visual fixation of a spot at a distance of approximately 1 m, unpredictable and passive head turns, a peak head velocity of between 150° and 250°/s, and the amplitude of a head turn being 10–20°.

Questionnaires

The subjective functional status of participants was assessed using the DHI questionnaire, which represents the functional, emotional, and physical aspects of subjectively reported disability (14).

Timed up and go test

The Timed Up and Go test measures functional mobility to estimate the risk of falling and the ability to maintain balance while walking. The patient was asked to sit in a chair; after the examiner said "go," the timer started, and the patient got up from the chair, walked a distance of 3 m, turned and walked back to the chair, and sat down again and the timer stopped.

We also evaluated the need for assistance. One limitation of the TUG test was the subjective connotation of the "normal walking speed." Some could interpret this as a brisk walk, while others interpreted it as a leisurely pace.

Scheduled follow-ups

We scheduled four examinations: the first (V1) within the 1st week after unilateral vestibular loss (UVL), the second (V2) after 4–6 months, the third (V3) after 12 months, and the final (V4) after 24 months.

Variables, bias, study size

Our study used continuous quantitative variables (aSPV of SPN and HST in degrees/s, caloric weakness in %, vHIT gains). To evaluate the potential of HSN to reflect vestibular compensation after UVL, we had to exclude potential sources of bias. First, compensation for previous vestibular loss, which could be present in the schwannoma group before the surgery, was possibly and might have already started or even completed. A longer compensation period could give false results during the scheduled 2-year period. Second, normalization of vestibular function (functional recovery) at follow-up in the neuronitis group would not assess a compensation process. Finally, differences in behavior exist in the poorly compensated group.

To minimize bias, we first established two study groups in which normal or near-normal vestibular function was expected before unilateral vestibular loss (measured in the surgery group and expected in neuronitis without a history of imbalance). We excluded patients who had abnormal vHIT gains and significant caloric weakness present before surgery (the surgery group consisted of small Koos 1 or 2 tumors).

Second, we *post-hoc* excluded neuronitis patients with normalized vestibular function (normalized caloric test) and performed a *post-hoc* analysis of patients with significant vestibular loss (caloric weakness >26%) during all scheduled follow-ups.

Finally, we *post-hoc* established a poorly compensated group according to the defined criteria to reflect differences in behavior between poorly and well-compensated patients after UVL.

Statistical analysis

As part of the descriptive statistics, we evaluated the normality of the data distribution using the Anderson–Darling test for the average velocities of the slow phase of SPN, HSN, caloric weakness, and gains from the vHIT regression analysis in all groups. Because some continuous variables did not show a normal distribution, we reported medians and lower and upper quartiles for all continuous variables. To compare patient data to control group values, we used an unpaired two-tailed *t*-test in case of confirming the normality of the data distribution. Otherwise, a non-parametric two-tailed Wilcoxon rank-sum test was used.

We used linear regression analysis to statistically evaluate the evolution of examination results over time. Because the exploratory analysis showed exponential dependencies, we log-transformed time. We then calculated the slope of the regression line, hereafter referred to as the trend, for each patient. We tested the set of individual trends using the one-sample *t*-test or the Wilcoxon test for significant differences from 0.

The relationship between the examination methods was assessed using the correlation analysis of individual trends. The individual trend was calculated using linear regression, and, as the data showed an exponential dependency, time was logarithmized. The relationship between the methods was calculated using Pearson's test in the case of a normal distribution and Spearman's test in the absence of a normal distribution. A significant positive correlation between the methods indicates that faster improvement in one method leads to a faster improvement in the other.

To compare the sensitivity between the examinations, we contrasted the measured values with the cutoffs as follows. The abnormal cutoffs for HSN (2.03°/s) and SPN (1.70°/s) were determined as 97.5% of our control group, 26% UW for the caloric test, and a gain of 0.78 for vHIT (15). We assessed sensitivity separately for each visit (V1–V4). Individual tests were not corrected for multiple comparisons because this would increase the likelihood of false negative results. R-project software was used for statistical processing (R Development Core Team 2022) (10).

Standard protocol approvals, registrations, and patient consents

Before including a subject in this study, we received written informed consent signed by a volunteer/patient.

Results

We attached the results of each group during all visits and reported the test trends during the follow-ups and the significance of the intergroup difference (between the results of each group and the control group) in Table 1. To visualize the trend of each test during a 2-year follow-up, we depicted the median values of the vestibular neuronitis group on an Estimated Vestibulogram (EVEST) (16) in Figure 1.

For comparison, the results of the control group were: HST 0.5 (0; 1.05), SPN 0 (0; 0.625), vHIT 0.9 (0.858; 0.935) and 0.89

TABLE 1 Groups results: For the vestibular tests the medians and lower and upper quartiles are shown (HST, head-shaking test; SPN, spontaneous nystagmus; vHITfe(af), video head impulse test on affected (fellow) side; CT, caloric test; TUG, timed up and go test; DHI, dizziness handicap inventory).

		Visit 1	Visit 2	Visit 3	Visit 4	Trend [ln(months)]	*p*
Neuronitis group ($n = 20$)	HST [°/s]	15* (9.75; 19.25)	5* (3; 6.5)	1* (1; 2)	0.25 (0; 1.925)	−4.848 (−5.65; −2.76)	9.19e-09
	SPN [°/s]	9.5* (6.75; 13.5)	1.6* (0; 2.5)	0 (0; 1)	0 (0; 0)	−3.25 (−4.38; −2.15)	4.86e-07
	vHITfe [–]	0.85 (0.78; 0.91)	0.90 (0.82; 0.98)	0.87 (0.8; 0.94)	0.90 (0.86; 1.02)	0.022 (−0.007; 0.055)	0.035
	vHITaf [–]	0.36* (0.298; 0.42)	0.5* (0.38; 0.67)	0.53* (0.45; 0.70)	0.6* (0.56; 0.69)	0.077 (0.043; 0.11)	5.41e-6
	CT [%]	100* (100; 100)	100* (89; 100)	100* (57; 100)	100* (56; 100)	0.0 (−13.7; 0.0)	0.003
	TUG [s]	20* (18; 23)	8.0 (8.0; 9.0)	8.0 (8.0; 9.0)	8.0 (7.0; 8.75)	−3.82 (−4.7; −3.7)	1.42e-08
	DHI [–]	86* (80; 90)	44* (38; 48)	10* (8; 12)	8* (6; 8)	−26.28 (−27.4; −24.7)	2.91e-20
Surgery group ($n = 12$)	HST [°/s]	12.5* (11.5; 15.5)	7* (5.25; 8.75)	2* (1; 6)	0.25 (0; 2)	−3.55 (−4.58; −2.5)	6.39e-06
	SPN [°/s]	12.5* (7.5; 14.75)	2 (1; 2.75)	0 (0; 1)	0 (0; 0.125)	−4.07 (−5.34; −2.28)	2.09e-05
	vHITfe [–]	0.79 (0.73; 0.95)	0.865 (0.815; 0.937)	0.83 (0.79; 0.9)	0.835 (0.8; 1)	0.014 (−0.033; 0.049)	0.334
	vHITaf [–]	0.35* (0.23; 0.39)	0.36 (0.26; 0.46)	0.37 (0.24; 0.455)	0.435 (0.32; 0.49)	0.017 (−0.006; 0.062)	0.118
	CT [%]	100* (100; 100)	100 (100; 100)	100 (100; 100)	100 (100; 100)	0.0 (0.0; 0.0)	0.02
	TUG [s]	20* (14; 20.25)	10* (10; 10.75)	9* (8.75; 9)	9* (9)	−3.4 (−4.58; −1.69)	0.0004
	DHI [–]	88* (80; 90)	40* (36; 47)	14* (11.5; 16)	8 (6.5; 10)	−25.68 (−27.9; −24.1)	3.14e-12
Poorly-compensated ($n = 6$)	HST [°/s]	15* (12; 16.5)	6.5* (4.5; 8.5)	6* (2; 7)	3.5* (2; 5)	−3.002 (−3.98; −2.83)	0.031
	SPN [°/s]	11.5* (9.25; 14.5)	3* (2; 3)	2* (1.75; 2.25)	1* (1)	−3.191 (−4.14; −2.58)	0.031
	vHITfe [–]	0.79 (0.74; 0.94)	0.82 (0.78; 0.92)	0.8 (0.79; 0.9)	0.83 (0.78; 0.86)	−0.004 (−0.025; 0.004)	0.843
	vHITaf [–]	0.37* (0.34; 0.39)	0.38* (0.35; 0.42)	0.4* (0.38; 0.48)	0.41* (0.38; 0.57)	0.018 (0.011; 0.031)	0.031
	CT [%]	100* (100; 100)	100* (100; 100)	100* (100; 100)	100* (100; 100)	0 (0; 0)	1.000
	TUG [s]	22* (20; 23)	11* (11)	12* (11.75; 15.5)	11.5* (11; 12.75)	−3.17 (−3.65; −1.54)	0.0935
	DHI [–]	85* (80; 90)	54* (50; 60)	24* (20; 30)	17* (14.5; 34.5)	−17.68 (−22.49; −8.97)	0.031

Descriptive characteristics are listed for each visit (visits 1–4). The trend column shows an estimate of the linear evolution of the tests over time. Because the data showed an exponential pattern in time, it was logarithmized. Trend values are shown with 95% confidence intervals. The column labeled p indicates the statistical significance of the hypothesis that the trend is different from zero. The significant difference between the group results and the control group was assigned with a (*).

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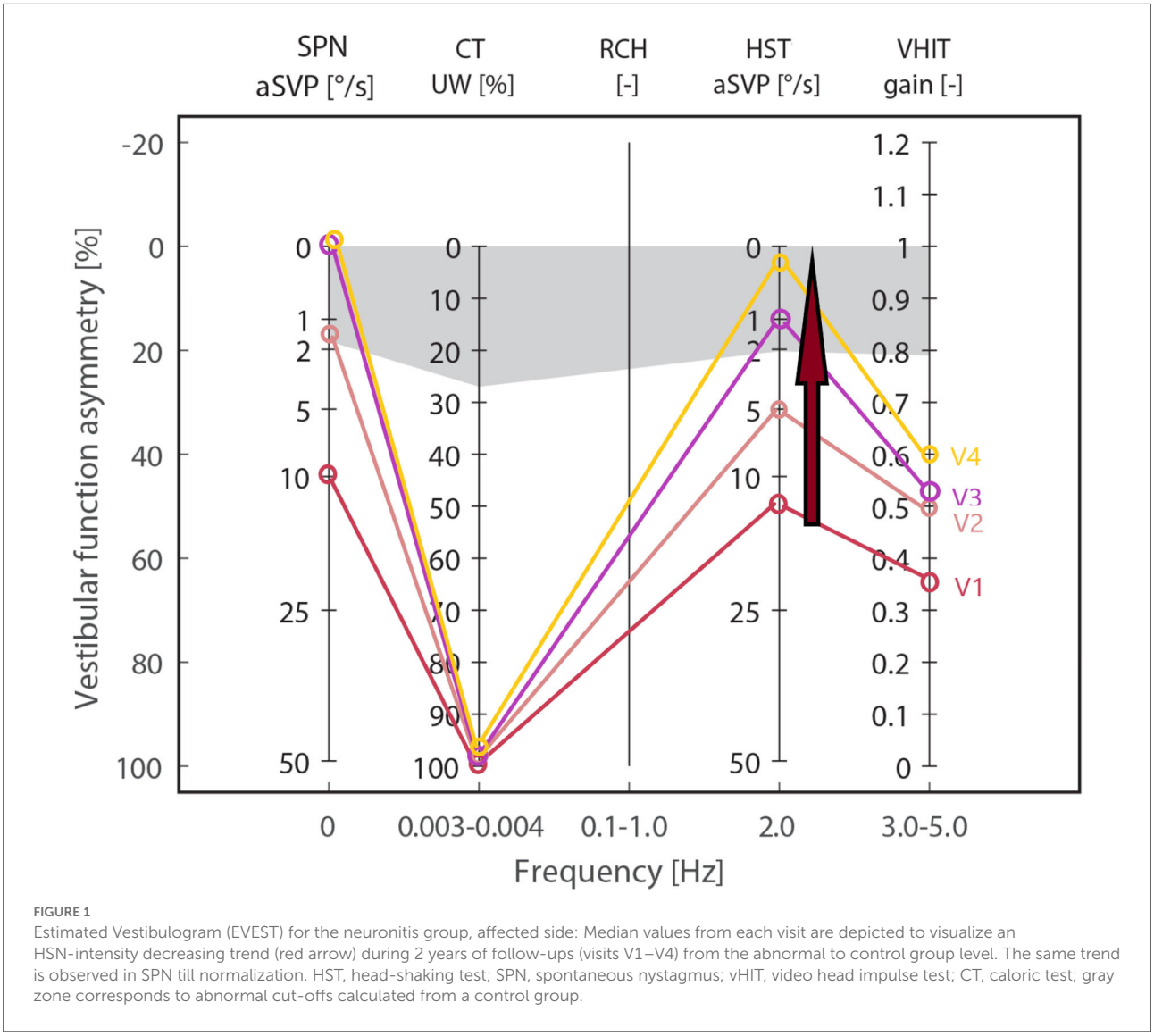

FIGURE 1
Estimated Vestibulogram (EVEST) for the neuronitis group, affected side: Median values from each visit are depicted to visualize an HSN-intensity decreasing trend (red arrow) during 2 years of follow-ups (visits V1–V4) from the abnormal to control group level. The same trend is observed in SPN till normalization. HST, head-shaking test; SPN, spontaneous nystagmus; vHIT, video head impulse test; CT, caloric test; gray zone corresponds to abnormal cut-offs calculated from a control group.

(0.815; 0.927), caloric weakness 12 (8.5; 15.5), TUG 8 (7; 9), and DHI 0 (0; 0).

Comparison between groups and controls

SPN

When SPN in both the neuronitis and surgery groups was compared to the control group, there were significant differences in V1 and V2, and there were no intergroup differences in V3 and V4 between the groups. In contrast, there was a significant difference between the poorly compensated and control groups in all examinations (for statistical significance, see Table 1). The results showed a reduction of SPN to normal within the 1st year in the neuronitis and surgery groups, reflecting a finished static VOR compensation after UVL in contrast to the poorly compensated group who showed detectable SPN even 2 years after UVL.

HSN

When HSN in both the neuronitis and surgery groups was compared to the control group, there were significant differences at V1–V3, while there were no intergroup differences at V4. In contrast, there was a significant difference during all visits in the poorly compensated group. The results showed a decreasing trend of HSN intensity in the neuronitis and surgery groups in contrast to the poorly compensated individuals who showed a well-detectable HSN in all follow-ups.

Caloric test

When caloric weakness in all groups was compared to the control group, there were significant differences in visits V1–V4, indicating a vestibular deficit at all follow-ups.

VHIT affected

When the vHIT-affected side in all groups was compared to the control group, there were significant differences in visits V1–V4, showing a detectable vestibular deficit at all follow-ups.

TUG

There was a significant difference between the neuronitis and control groups in V1, but no intergroup difference in the remaining follow-ups, reflecting sufficient gait control. There was a significant difference between the surgery and control groups at each visit. However, the surgery patients had TUG at V2–V4 below the abnormal cutoff (10 s), indicating sufficient gait control. There was a significant difference between poorly compensated and control groups in all examinations, while the poorly compensated group showed TUG above the abnormal cutoff in all visits.

DHI

When DHI in all groups was compared to the control group, there were significant differences between the groups in all examinations. In contrast to the poorly compensated group, the DHI score median in the neuronitis and surgery groups was within a normal range (below 16 points) at V3 and V4. The poorly compensated group reported a mild self-perceived handicap (16–34 points) even at V3 and V4.

Summary

The results showed that SPN decreased to a control group level after 1 year, while HSN decreased after 2 years in the majority of compensated patients. HSN was more intense or similar in intensity to SPN at V1 and was significantly more intense at V2 (in all groups). In contrast to the poorly compensated group (median 2), SPN disappeared at V3 in compensated groups (median 0). HSN was still present at V3 (median 1 in the neuronitis group and 2 in the surgery group, 6 in the poorly compensated group). After 2 years (V4), HSN intensity in the compensated groups also reached the control group's result (median 0.25 in the neuronitis group and 0.3 in the surgery group) in contrast to the poorly compensated group (median 3.5).

In contrast, despite a slight improvement in the neuronitis group, the caloric and vHIT tests remained abnormal during the followed period, indicating a chronic vestibular deficit.

We used a TUG (the ability to maintain balance while walking) and the DHI questionnaire (measures the self-perceived handicap) to assess, to assess the dynamic vestibular function and the impact of dizziness on daily life, respectively. TUG and DHI improved to normal in the compensated neuronitis and surgery groups at follow-ups but not in the poorly compensated group. The poorly compensated group showed significant SPN and HSN intensities, abnormal TUG, and higher DHI scores during/ at all follow-ups.

Trend analysis

The result trends from all vestibular tests are presented in Table 1 and visualized in Figures 1, 2 for the neuronitis group and the neuronitis and surgery groups, respectively.

Correlation analysis

Time correlated to each test

We did a correlation analysis between time and each test for the neuronitis and surgery groups (as only a few results were within the poorly compensated group). We found strong and highly significant negative correlations between time and HSN intensity (Spearman's $\rho < -0.84$, $p < 0.001$), time and SPN ($\rho < -0.80$, $p < 0.001$), time and TUG ($\rho < -0.67$, $p < 0.001$), and time and DHI ($\rho < -0.94$, $p < 0.001$) in both the groups. The results confirmed the time-related improvement of these tests.

We found a weak relation between time and the caloric test in the neuronitis ($\rho = -0.34$, $p = 0.005$) and surgery groups ($\rho = -0.27$, $p < 0.047$), as well as a weak positive relation between time and vHIT-affected side in the neuronitis ($\rho = 0.52$, $p < 0.001$) and surgery groups ($\rho = 0.28$, $p = 0.040$). Both the groups showed no significant relationship between time and vHIT on the fellow side ($\rho < 0.26$, $p > 0.137$). The correlation analysis reflected an almost stable caloric weakness (indicating the presence of vestibular loss/asymmetry) or just a slight improvement in vHIT (but still abnormal) during follow-up.

HSN correlations to the remaining tests

To assess the similar or different trends for improvement, we performed a correlation analysis between HSN and the remaining tests for the neuronitis and surgery groups. We did not perform a correlation analysis for the poorly compensated group according to a small group size.

Head-shaking-induced nystagmus vs. SPN ($r = 0.877$; $p < 0.001$) were significantly correlated with each other. A significant positive correlation indicates a simultaneous individual change in the results of each examination over time, and a faster improvement in one method leads to a faster improvement in the other method.

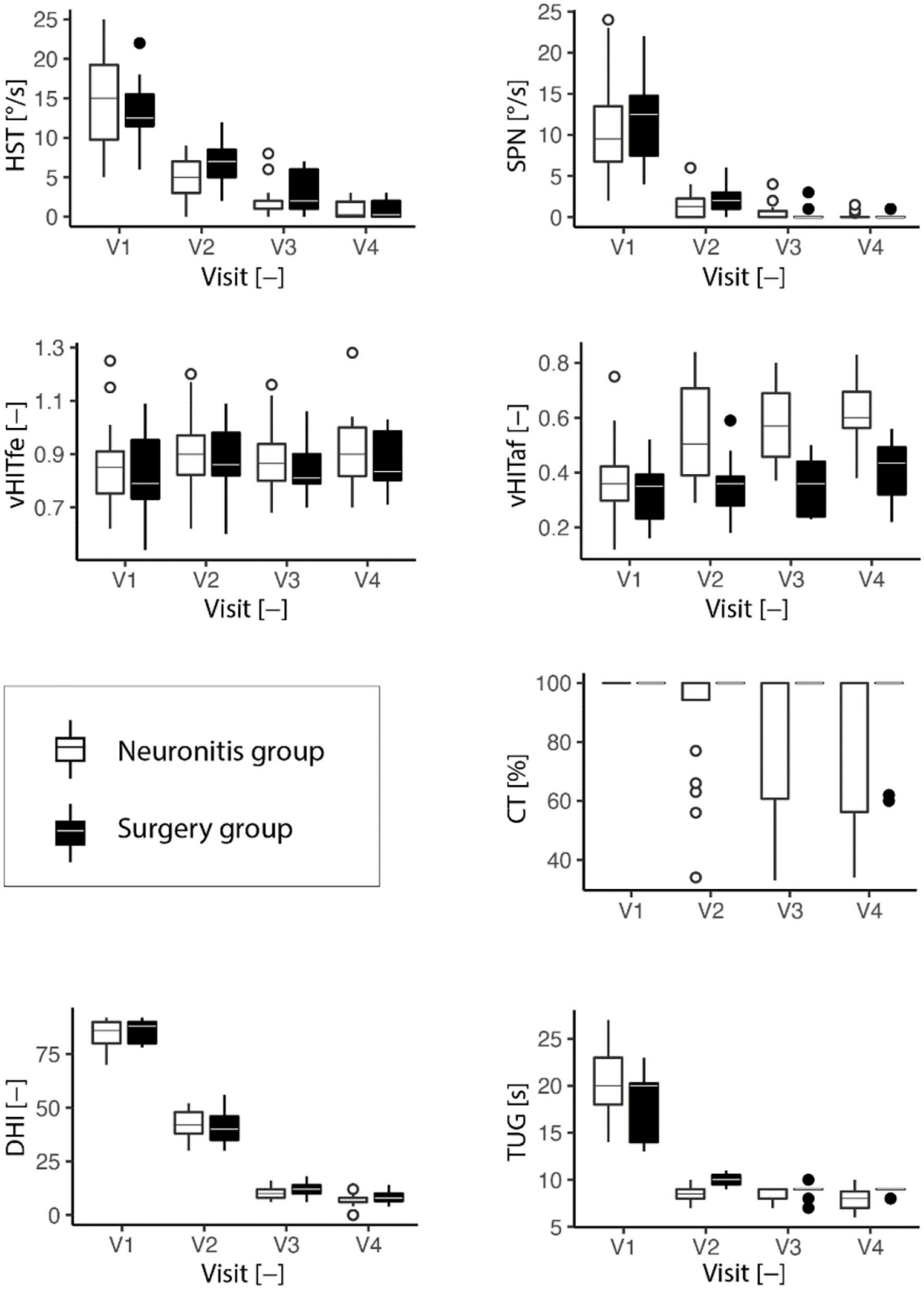

FIGURE 2
Development of the vestibular tests (HST, head-shaking test; SPN, spontaneous nystagmus; vHITfe(af), video head impulse test on the affected (fellow) side; CT, caloric test; TUG, timed up and go test; DHI, dizziness handicap inventory) over four visits (the last visit). Descriptive characteristics are listed for each visit (2 years). The box plots are depicted. In the boxplots, the bottom line of the box represents the first quartile, second (middle of the box) median, third (top of the box) quartile, and the whiskers extend to the most extreme data point, but no more than one and half of the interquartile range.

Head-shaking-induced nystagmus vs. vHIT affected side ($r = -0.14$; $p = 0.44$) as well as HSN vs. caloric weakness ($\rho = -0.07$; $p = 0.67$) were not correlated because HSN had a decreasing trend, whereas vHIT and caloric test had stable trends.

Interestingly, HST vs. DHI ($r = 0.192$; $p = 0.28$) and TUG ($r = 0.055$; $p = 0.82$) were not correlated despite the decreasing (improving) trends. The explanation could be a rapid improvement in TUG from V1 to V2, followed by almost stable results, similar to the improvement of V3–V4 in DHI. In contrast, the intensity of HSN decreased across all visits.

Specificity and sensitivity

We contrasted the measured values to the following cutoffs to compare the sensitivity and specificity (to identify vestibular loss) between the different vestibular tests. Abnormal cutoffs for HSN (2.03°/s) and SPN (1.70°/s) were determined to be 97.5% of our control group (as continuous variables did not show a normal distribution); the abnormal cutoff for the caloric test was used as 26% of UW and for vHIT was a gain of 0.78 (15).

The specificity for identifying controls was 94% for HST, 93% for SPN, 94% for caloric weakness, and 75% for vHIT.

To assess a trend to identify a vestibular loss (vestibular asymmetry), we calculated the sensitivity for each visit (V1–V4) separately. In the neuronitis group, the sensitivity of HST was 100% at V1, 79% at V2, 24% at V3, and 6% at V4. The sensitivity of SPN was 100% at V1, 47% at V2, 12% at V3, and 0% at V4. The sensitivity of vHIT was 100% at V1, 84% at V2, 94% at V3, and 83% at V4. The caloric test sensitivity was 100% on each session.

In the surgery group, the sensitivity of HST was 100% at V1, 93% at V2, 42% at V3, and 20% at V4. The sensitivity of SPN was 100% at V1, 57% at V2, 17% at V3, and 0% at V4. The sensitivity of vHIT and caloric weakness was 100% at all sessions.

In the poorly compensated group, the sensitivity of HST was 100% at V1 and V2, 66% at V3, and 50% at V4. The SPN was 100% at V1 and V2, 83% at V3, and 17% at V4 (a weak SPN of at least one aSPV was present in all poorly compensated groups).

To summarize, the caloric test and vHIT showed almost stable sensitivity to detect vestibular loss, whereas SPN and HST demonstrated a strongly decreasing ability to detect asymmetry, particularly in compensated patients.

Discussion

Theoretical explanation of HST

Several mechanisms have been proposed to explain HSN (5, 9). The etiology of HSN is thought to be related to both Ewald's second law and an asymmetry in the central velocity storage mechanism (17). In healthy subjects, each head turn is immediately opposed by a contralateral head turn during a head shake, resulting in a balanced ratio of excitation/inhibition from both sides.

In vestibular loss, there is a need to reestablish tonic and phasic vestibular function. Evidence suggests that second-order vestibular neurons tend to modulate their neuronal resting discharge and reach prelesion levels (16, 18–20), placing the site of neural rearrangement in commissural pathways (21), leading to clinical improvement and static compensation. Due to inhibitory saturation, the centrally restored pacemaker discharge is insufficient to restore the whole ipsilesional dynamic range (22). Therefore, during HST, head turn toward the healthy side is opposed during ipsilesional head turn only by inhibitory cutoff from the healthy side. Excitation is more effective than inhibition as a vestibular stimulus. During 20 cycles of HST, non-linearity arises and may charge the velocity storage mechanism in an asymmetric manner. When the head abruptly stops, HSN will result from the discharge of the asymmetrically charged velocity storage mechanism.

Studies suggest that, when lower frequency sinusoidal stimuli are used, the performance of the VOR often recovers over time, and asymmetries are only noted at higher rotational velocities with increasing head velocity (23) as a result of linear and nonlinear VOR pathways (24, 25).

Clinical utility of HST

Head-shaking test was extensively tested for its sensitivity and specificity in identifying different vestibular diagnoses and in patients with peripheral and central vestibular lesions (3, 4). The presence of HSN in peripheral vestibular lesions varies between 34% (26), 40% (27), 90% (28), and 100% (17) and was also reported in benign positional paroxysmal vertigo (29, 30), in central disorders of 23% and was found to be present in 10–14% of healthy controls (3, 26), in 74% of dizzy patients (3), and 15% dizzy but normal patients with electronystagmography (31). The well-established literature review by Burgio (32) reported that HST is neither sensitive nor specific enough to be used as a screening test for vestibular loss. Another study found a closer connection between HSN and poorly compensated UVL than functional asymmetry (33).

To conclude, research results appear to be inconsistent. Some studies used active head movements, while others used passive head movements; some used scleral search coil, ENG, or VNG, while others used only Frenzel goggles. The study size, patient inclusion criteria, and the HST method also differed. We found different HST amplitudes (half a distance) in the literature, varying from 15 to 45° (6, 8, 10, 17, 34), resulting in different velocities (120–360°/s).

The authors attempted to explain discrepancies between the studies and suggest that some may arise from partial UVL, which may not have sufficient asymmetry, to elicit HSN, or that the

central velocity storage may be reduced or lost after UVL. Others point out that HST evaluates a wider frequency range than the standard caloric or rotary chair stimulation (31).

We support the suggestion that HSN should always be interpreted in relation to other tests, such as SPN, VHIT, and a side of caloric weakness (35).

As the evidence appears inconclusive, the role of HST in clinical practice is still unclear.

Our results

To summarize our results, HSN was not related to vestibular asymmetry (loss) at all follow-ups, but it did show a strong time-related intensity decrease, reflecting an improvement in dynamic ability and a decrease in self-perceived handicap. The decreasing trend in HSN sensitivity to identify vestibular loss also supports the ability of HSN to reflect dynamic vestibular compensation after UVL. Similar results were revealed by Angeli et al. (33), suggesting that HSN had a stronger correlation with poorly compensated unilateral peripheral loss than functional asymmetry.

According to evidence, ∼20% of patients with chronic stable UVL continued to experience chronic postural imbalance (the syndrome of chronic vestibular insufficiency) (36). We had a similar report of 15% poorly compensated patients, showing a well-detectable HSN and SPN as well as a higher TUG and DHI score at all follow-ups.

We provide the first long-term evidence of the features of HSN, showing the ability of HSN to reflect dynamic vestibular compensation and decreasing sensitivity to identify chronic and stable vestibular asymmetry. We found no theoretical explanation for the decreasing trend in the sensitivity of an HST to identify vestibular loss (high sensitivity in the 1st year after UVL and low sensitivity in 2 years). We found no literature based on animal electrophysiological experiments on chronic adaptive changes of the VOR explaining long-term (years) characteristics in velocity storage and on long-term dynamic changes of the VOR more than a few months after UVL. We hypothesize that the sensitivity of HST to identify vestibular asymmetry could be decreased by individual adaptive changes in velocity storage, including the use of non-linear/linear pathways to compensate for dynamic asymmetry during a long-term compensation process.

Strength of this study

Despite the small sample size (due to strict inclusion/exclusion criteria such as "no-allowed-recovery" and "no-allowed-prior-deficit"), the power size of the main message (time-related decrease in HST intensity) was strong (for the neuronitis group: Spearman's $\rho = -0.8436362$; $p =$ 3.228042e-19, two-tailed test: effect size and confidence limits, $d = -3.14$ [−4.04 −2.24]), (for schwannoma group $\rho = -0.8912293$; $p =$ 3.819181e−19, two-tailed test: effect size and confidence limits, $d = -3.93$ [−5.13 −2.73]) and the power of the study with aforementioned effect was = 1.

Conclusions

Our study showed that, after UVL, HSN intensity decreases exponentially with time, reflecting an improvement in dynamic ability and self-perceived deficit in most patients. Once vestibular compensation was satisfactory and sufficient for a patient's daily life, HSN tended to decline to a control group's value. In contrast, poorly compensated patients with insufficient clinical recovery showed a well-detectable and more intense HSN during all follow-ups. HSN could serve as an objective vestibular indicator of individual dynamic compensation. However, these findings should always be interpreted with respect to other results, such as SPN and a side of caloric or vHIT deficit.

Data availability statement

The anonymized data supporting the conclusions of this article will be shared by request to any qualified investigator.

Ethics statement

The study was performed according to the ethical standards of the Declaration of Helsinki and following procedure approval of the Ethics Committee of the University Hospital Hradec Kralove (Reference number 202012 P03).

Author contributions

MS and JK conducted the study. MS and KT did measurements. MS wrote the manuscript and JK provided statistical analysis. All other authors provided critical revisions to the draft, read, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Posterior semicircular canal ossification following acute vestibular loss mimicking inferior vestibular neuritis: A case report

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Vestibular neuritis (VN) mostly involves the superior vestibular nerve. Isolated inferior vestibular neuritis (IVN) has been more rarely described. The diagnosis of IVN is based on an abnormal head impulse test (HIT) for the posterior semicircular canal (PSC), pathological cervical vestibular-evoked myogenic potentials (C-VEMPs), and spontaneous downbeat nystagmus consistent with acute functional loss of inner ear sensors lying within the inferior part of the labyrinth. HIT for both lateral and superior semicircular canals is normal, as are ocular VEMPs and bithermal caloric irrigations. The etiology of IVN is debated since peripheral acute vestibular loss with a similar lesion pattern can often be associated with ipsilesional sudden hearing loss (HL). Viral inflammation of vestibular nerves is considered the most likely cause, although reports suggest that VN usually spares the inferior division. On the other hand, an ischemic lesion involving the terminal branches of the common cochlear artery has been hypothesized in cases with concurrent HL. Debated is also the lesion site in the case of IVN without HL since different instrumental patterns have been documented. Either isolated posterior ampullary nerve involvement presenting with selective PSC functional loss on video-HIT, or only saccular lesion with isolated ipsilesional C-VEMPs impairment, or inferior vestibular nerve damage (including both saccular and posterior ampullary afferents) exhibiting an impairment of both C-VEMPs and PSC-HIT. We report an interesting case of a patient with an acute vestibular loss consistent with IVN without HL who developed a PSC ossification on follow-up, questioning the viral origin of the lesion and rather orienting toward an occlusion of the posterior vestibular artery. To the best of our knowledge, this is the first report of PSC ossification after a clinical picture consistent with IVN.

KEYWORDS

acute vestibular loss, labyrinthine ossification, video head impulse test, labyrinthine ischemia, case report, inferior vestibular neuritits

Introduction

Vestibular neuritis (VN) represents the most common cause of peripheral acute vestibular loss (AVL) (1) and usually involves either the superior vestibular nerve or both superior and inferior divisions (2–4). In rare cases, an isolated inferior vestibular neuritis (IVN) may occur (3, 5–8), while bilateral involvement has been only anecdotally reported (9, 10). The diagnosis of IVN is based on an abnormal head impulse test (HIT) for the posterior semicircular canal (PSC), pathological cervical-vestibular evoked myogenic potentials (C-VEMPs), and spontaneous downbeat nystagmus (DBN) with variable torsional components aligning with the plane of the affected PSC, consistent with an acute functional loss of labyrinthine sensors lying within the inferior part of the inner ear (5, 8). Since the receptors innervated by the superior vestibular branch are spared, HIT for the horizontal (HSC) and superior semicircular canals (SSC) is normal, as well as ocular-VEMPs (O-VEMPs) and bithermal caloric stimulation. The etiology of VN is still debated. A viral inflammation involving either the whole vestibular nerve or one of its divisions is the most likely cause (1, 2, 4, 11), even though selective ischemia of the terminal branches of the internal auditory artery has been demonstrated to result in similar clinical pictures and instrumental patterns (12–14). However, it has also been reported that VN often spares the inferior vestibular branch and that AVL exhibiting a clinical picture consistent with IVN can be non-rarely associated with sudden hearing loss (HL), indicating a vascular origin of the lesion rather than neural damage (15–18). Moreover, various degrees of involvement of the end-organs innervated by the inferior vestibular nerve (i.e., PSC and saccule) have been described in the case of IVN without HL. It has been reported that either an isolated acute PSC failure with pathological HIT for the affected PSC and normal C-VEMPs, or a selective saccular lesion presenting with impaired C-VEMPs and normal vestibulo-ocular reflex (VOR) gain for the PSC, or eventually a sudden hypofunction of both saccular and posterior ampullary afferents presenting with simultaneous C-VEMPs and PSC VOR-gain impairment (5, 8, 17–20). Only the latter combination properly refers to IVN, as the other aforementioned lesion patterns could be attributed to other selective intralabyrinthine lesions. Conversely, in the case where AVL involving both saccular and PSC afferents is associated with sudden HL, a vascular occlusion of the common cochlear artery (CCA) or one of its branches should always be considered as the most likely underlying pathomechanism (14–18), as the lack of cochlear symptoms should be needed to fulfill VN diagnostic criteria (4). We herein report an interesting case of AVL without HL consistent with IVN, presenting with spontaneous DBN, PSC hypoactivity on video-HIT, and absent C-VEMPs on the affected side, that developed ipsilesional PSC ossification after a brief follow-up questioning the viral origin of the lesion and rather orienting toward an occlusion of the posterior vestibular artery (PVA). To the best of our knowledge, this is the first case of labyrinthine ossification following an AVL mimicking IVN.

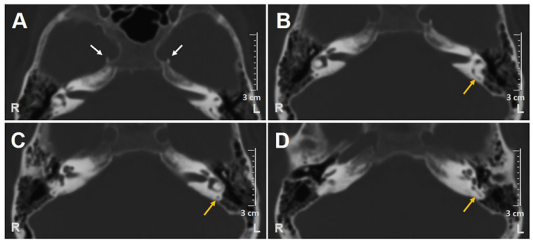

FIGURE 1
Axial scans of brain CT show **(A)** bilateral carotid siphon calcifications (white arrows) and **(B–D)** patent left PSC (yellow arrows). CT, computed tomography; L, left; PSC, posterior semicircular canal; R, right.

Case description

A 62-year-old male with acute vertigo, unsteadiness, nausea, and vomiting was admitted to the emergency department. He denied recurrent headaches and significant auditory symptoms. His clinical history was consistent with hypercholesterolemia and acid reflux. Six years earlier, he had presented with a sudden flat right-sided sensorineural HL that recovered fully on oral steroids. On admission, neurological evaluation and bedside oculomotor testing (including saccades, smooth pursuit, and test of skew) excluded signs of central nervous system (CNS) involvement. Both blood pressure and pulse rate were within normality ranges, and electrocardiography was unremarkable. Only slight signs of bilateral carotid siphon calcifications were noted on a standard brain CT scan (Figure 1A), whereas serology for SARS-CoV-2 was negative. Otoneurological examination with monocular video-Frenzel goggles detected spontaneous vertical DBN inhibited by visual fixation while slightly enhanced by 100 Hz-mastoid vibrations and head shaking. In addition, horizontal right beating components could be detected in a supine position, whereas neither bilateral gaze nor hyperventilation tests changed spontaneous oculomotor patterns (Supplementary Video 1). No

Abbreviations: AVL, acute vestibular loss; CCA, common cochlear artery; CNS, the central nervous system; CT, computed tomography; DBN, downbeat nystagmus; HIT, head impulse test; HL, hearing loss; HSC, horizontal semicircular canal; HSV, Herpes Simplex Virus; IVN, inferior vestibular neuritis; LO, labyrinthitis ossificans; MRI, magnetic resonance imaging; PSC, posterior semicircular canal; PVA, posterior vestibular artery; SSC, superior semicircular canal; VEMPs, vestibular-evoked myogenic potentials; VN, vestibular neuritis; VOR, vestibulo-ocular reflex.

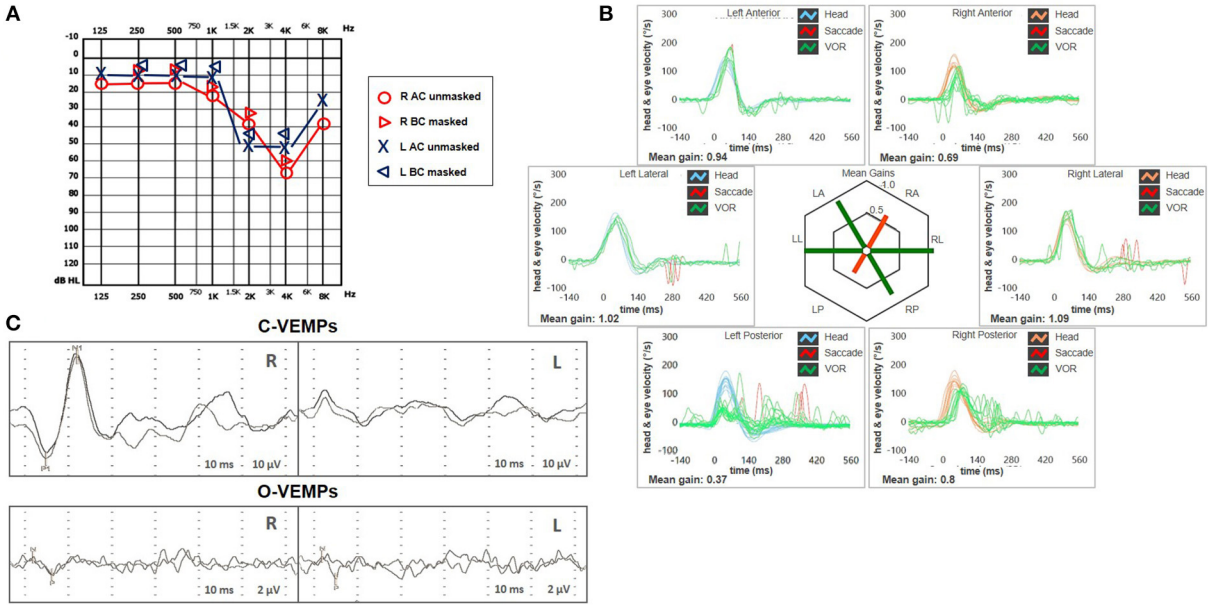

FIGURE 2
Presenting scenario including **(A)** Pure-tone audiometry exhibiting bilateral high-frequency sensorineural hearing impairment, slightly greater on the right side. **(B)** Video-HIT was performed using a portable high-frame-rate video-oculography device (ICS Impulse, Natus Medical Inc, Denmark). Blue lines represent head impulses exciting left canals, orange lines correspond to impulses for right canals, green lines represent eye movements induced by the activation of VOR following each impulse, and red lines correspond to corrective saccades. The mean value of VOR-gain (eye velocity/head velocity) is reported for each canal. The hexagonal plot in the center of the figure summarizes the mean VOR gains for each canal; normal gains are shown in green, and deficient gains are in red. Gains are considered normal if> 0.8 for lateral canals and> 0.7 for vertical canals. A severe VOR-gain impairment for the left PSC (0.37) with mainly overt saccades can be observed, and a slight reduction of contralateral ASC VOR-gain (0.69). **(C)** C-VEMPs (above) and O-VEMPs (below) for air-conducted sounds recorded with a 2-channel evoked potential acquisition system (Viking, Nicolet EDX, CareFusion, Germany). Potentials were measured by delivering tone bursts (intensity: 100 dB nHL, frequency: 500 Hz, duration: 8 ms, stimulation rate 5 Hz) *via* headphones. The recording system used an EMG-based biofeedback monitoring method to minimize variations in muscle contractions and VEMPs amplitudes. Each stimulus was retested to assess the reproducibility of responses. For C-VEMPs, right and left lines correspond to myogenic responses (p1–n1) recorded on the right and left SCM muscle (i.e., right and left saccular responses), respectively. For O-VEMPs, being crossed responses, right and left lines representing potentials (n–p) are recorded under the left and right eye (i.e., right and left utricular responses), respectively. VEMP testing revealed normal responses on the right side (105.5 µV) and absent potentials on the left, whereas symmetrical amplitudes for ocular VEMPs (R: 4.4 µV and L: 5.7 µV) could be detected. AC, air-conduction; ASC, anterior semicircular canal; BC, bone-conduction; C, cervical; HIT, head impulse test; L, left; LA, left anterior; LL, left lateral; LP, left posterior; O, ocular; PSC, posterior semicircular canal; R, right; RA, right anterior; RL, right lateral; RP, right posterior; SCM, sternocleidomastoid; VEMPs, vestibular evoked myogenic potentials; VOR, vestibulo-ocular reflex.

corrective saccades could be detected on the horizontal bedside HIT, and moderate-to-severe ataxia was found in the Romberg test. Therefore, the patient was scheduled for an additional CT scan 48 hours later to rule out a posterior fossa stroke. New imaging still excluded abnormal findings in the brainstem and the cerebellum. Despite low-resolution scans and thick slices, normal patency and morphology of the inner ear structures could be verified in temporal bone scans (Figures 1B–D). The patient was then submitted to an extensive instrumental assessment. On micro-otoscopy, tympanic membranes were unremarkable, impedance audiometry was normal, while pure tone audiometry detected bilateral sensorineural high-frequency HL, with noise-induced components slightly greater in the right ear, comparable to the previous audiogram (Figure 2A). Video-HIT documented a severe impairment for the left PSC VOR-gain (0.37) with mainly overt saccades (Figure 2B), whereas bithermal caloric irrigations were within normality ranges. While O-VEMPs were symmetrical, C-VEMPs revealed no responses on the left side, consistent with saccular impairment (Figure 2C). A gadolinium-enhanced brain MRI performed the following week only showed signs of periventricular leukoaraiosis, with normal findings in the posterior fossa. Therefore, left-sided IVN was diagnosed according to clinical and instrumental findings. Despite a first therapeutic approach including steroids, vestibular suppressants, and antiemetic drugs followed by a 3-month pharmacological treatment enhancing vestibular compensation (Betahistine 24 mg twice a day and Citicoline 1 g a day), the patient kept complaining of continuous unsteadiness and oscillopsia, particularly walking down the stairs. He was then sent to a tertiary referral center for vestibular dysfunction. The persistence of slight spontaneous DBN inhibited by visual fixation was ascertained

on video-Frenzel examination. Skull vibration greatly enhanced spontaneous nystagmus and a new video-HIT confirmed the left PSC hypoactivity, despite a slight VOR-gain improvement (0.54) (Figure 3A). A cone-beam CT scan of the temporal bones was scheduled to exclude possible semicircular canal dehiscences. Surprisingly, a sub-total left PSC ossification was found (Figure 3B), consistent with ischemic damage in the labyrinthine territory supplied by the PVA. Prophylactic treatment with acetylsalicylic acid was then suggested, and the patient was advised to undergo vestibular rehabilitation therapy. Written informed consent was obtained from the patient to publish this case report, including all data and images.

Discussion

The vestibular nerve is composed of two branches, i.e., the superior and the inferior vestibular nerve. While the former is composed of the lateral and anterior ampullary nerves and the utricular nerve, the inferior vestibular nerve is composed of the singular nerve (or posterior ampullary nerve) and the saccular nerve (21) (Figure 4A). IVN is considered a rare entity, with a possible prevalence of 1.3–18% among overall VN cases, depending on different inclusion criteria and available instrumental battery (3, 7, 8, 22–25). Diagnosis is often challenging due to spontaneous vertical nystagmus and lack of corrective saccades on horizontal HIT, which is supposed to guide toward an acute CNS disorder (5, 26). Before the widespread availability of modern tools for vestibular testing enabling a rapid assessment of both otolith and ampullary receptors, the correct diagnosis of IVN could only rely on the identification of the plane aligning with spontaneous DBN and reduced VOR-gain measures for the PSC using a scleral search coil, in association with normal findings on caloric irrigations (3, 5). Only in recent years has the combined use of the video-HIT and VEMPs enabled clinicians to measure the high-frequency response of all labyrinthine receptors, even in an acute setting, allowing reliable detection of isolated dysfunctions and lesion patterns peculiar to specific pathomechanisms (8, 16–18, 24, 25).

The clinical presentation of IVN, fairly atypical for AVL and rather addressing a CNS lesion, at first sight, might account per se for a possible underestimation of the actual incidence of the disorder (3, 5, 22, 26). Moreover, the rare involvement of the inferior vestibular nerve in VN has been mostly explained by anatomic differences rendering the superior division more vulnerable to entrapment during inflammatory swelling and ischemia than the singular and inferior vestibular nerves. They include the greater length of the superior vestibular division, the narrower canal lumen, and the larger percentage of bony spicules occupying the channel where the superior nerve and its vascular supply run (27, 28). Moreover, in human temporal bone specimens, anastomoses between the facial nerve (representing an additional pathway for viral spread) and the superior vestibular nerve have been more commonly found than the inferior branch (29).

In the reported case, the presenting clinical scenario perfectly overlapped an AVL involving the inferior vestibular nerve. In fact, spontaneous DBN associated with a selective loss of left PSC and ipsilaterally absent cVEMPs with no auditory impairment could likely be due to a left IVN. Moreover, both the enhancement of DBN after head shaking and skull vibration and the paretic horizontal components elicited in the supine position have also been described in other reports of IVN (7, 8, 18, 22).

Despite the association of spontaneous DBN with a selective loss of PSC on vHIT has been reported in other conditions, such as a canalith jam involving the posterior canal (30, 31) or Meniere's disease in the ictal stage (32, 33), neither a sign of benign paroxysmal positional vertigo nor fluctuating HL have been documented before and after our evaluation; therefore, other inner ear disorders than IVN were excluded. Nevertheless, hyperventilation did not affect spontaneous nystagmus in our case. This finding seemed not to be perfectly in line with the typical directional and amplitude changes of spontaneous nystagmus described in the acute stage of VN, where ionic alterations due to a reduction of $paCO_2$ should result in a transient improvement of the neuronal excitability of the affected side (34).

The great debate is, therefore, focused on the etiology, particularly the pathomechanisms underlying IVN. Generally, it seems well accepted that VN is caused by a viral infection or viral reactivation, although a previous upper respiratory tract infection is mostly lacking in the patient's history. Furthermore, the pattern of clinical recovery from IVN seems somehow different from superior or total VN, exhibiting some controversial issues. In fact, it has been documented how the time course of IVN is shorter than other VN, with a faster recovery for afferents running in the inferior branch (22), while, in contrast, the PSC seems to recover more slowly than other semicircular canals in VN according to other descriptions (23). On the other hand, it has been well documented how clinical and instrumental patterns consistent with AVL could be due to selective ischemia of the terminal branches of the internal auditory artery (12–14). In particular, presenting scenarios overlapping IVN associated with cochlear symptoms has oriented the aetiologic hypothesis toward a possible occlusion of the CCA (15–18).

Our finding of an early ossification of the PSC after a clinical picture consistent with IVN without HL increases the aetiologic dilemma. Herpes Simplex Virus (HSV) represents one of the most commonly associated viral agents accounting for VN (11, 35). Nevertheless, histopathologic examination of the temporal bones in patients with previous VN revealed neural atrophy and variable degeneration of the labyrinthine neuroepithelium but no signs of ossification (1, 21, 36). Similarly, in experimental HSV labyrinthitis, Nomura et al. (37) described an involvement of both the cochlea and the posterior labyrinth when the virus

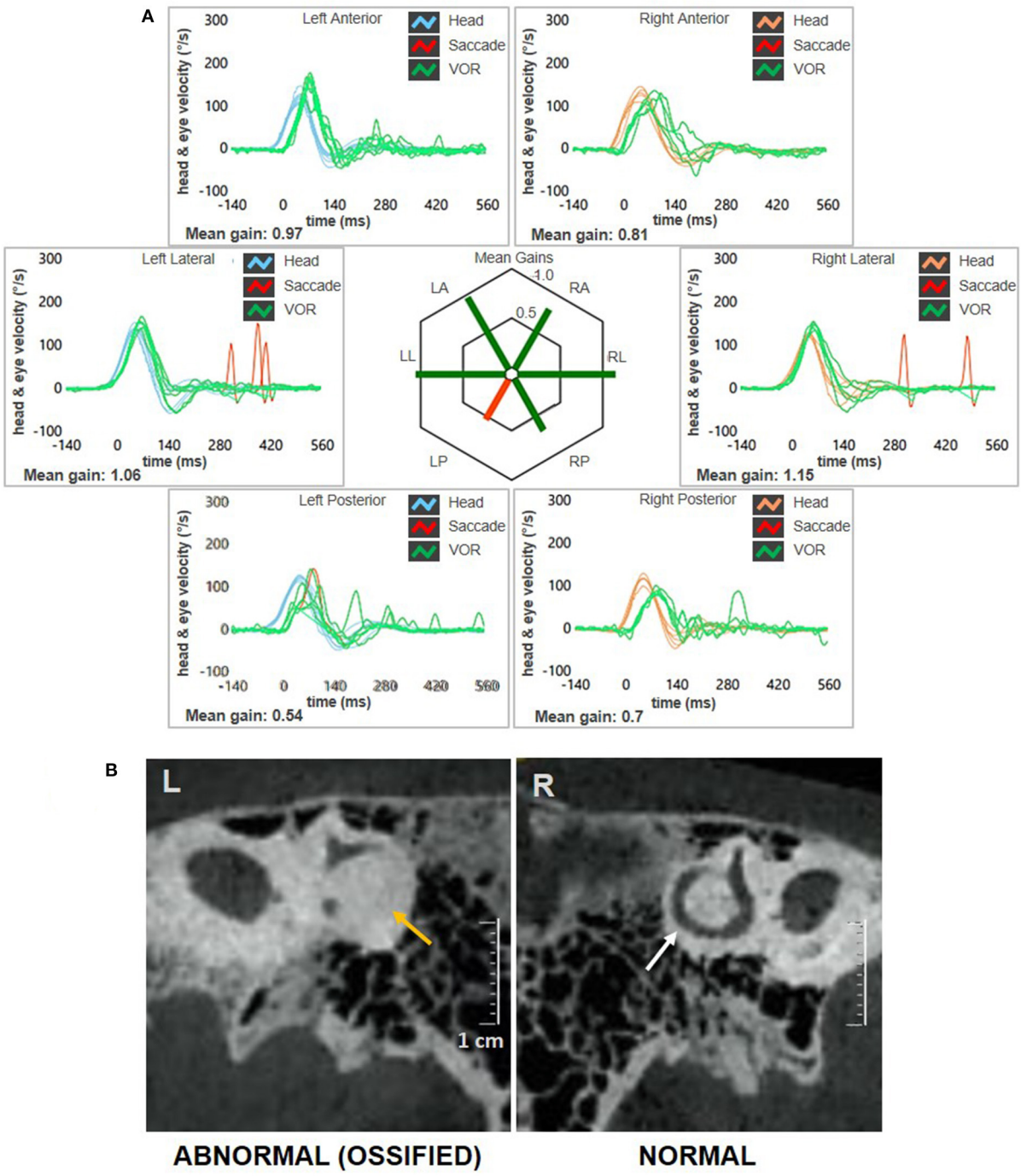

FIGURE 3
Instrumental picture observed at 3-months follow-up. **(A)** Video-HIT exhibited persistent selective loss for the left PSC VOR-gain (0.54) with only covert saccades. The affected canal VOR-gain is slightly increased compared to presenting values. **(B)** Cone-beam CT scans of the temporal bones with parasagittal reconstructed images along the Stenver plane detecting normally patent right-sided PSC (white arrow) and a near-complete PSC ossification on the left side (yellow arrows). CT, computed tomography; HIT, head impulse test; L, left; LA, left anterior; LL, left lateral; LP, left posterior; PSC, posterior semicircular canal; R, right; RA, right anterior; RL, right lateral; RP, right posterior; VOR, vestibulo-ocular reflex.

was inoculated *via* the middle ear, while ossification of the semicircular canals was not described. Moreover, Himmelein et al. (29), studying the presence of HSV in the vestibular nerves and ganglion, rarely found the virus itself in the IVN, and a complete absence of latent mRNA of HSV in the IVN was ascertained.

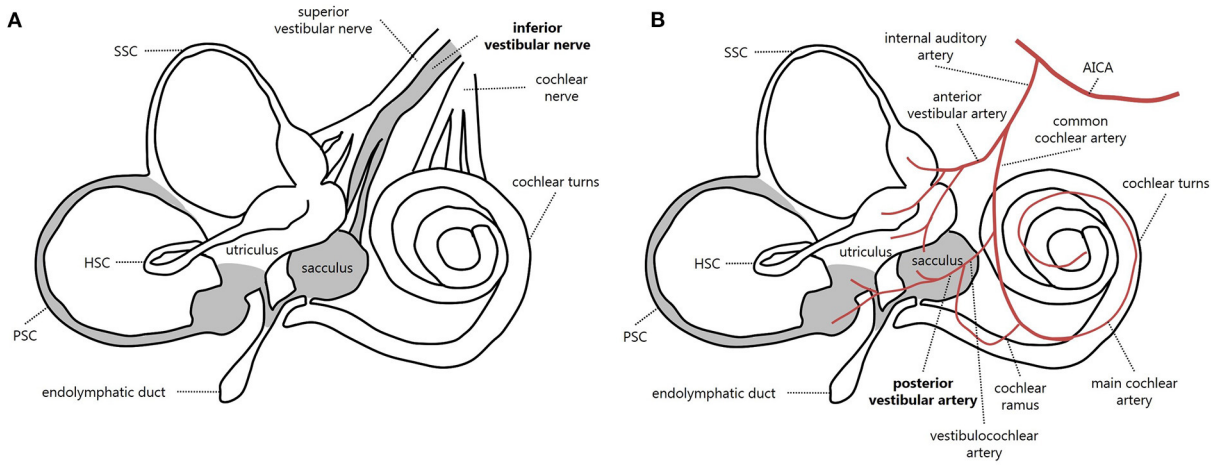

FIGURE 4
Schematic representation of inner ear innervation **(A)** and vascular supply **(B)** showing possible pathomechanisms accounting for an acute loss of PSC and saccular function [modified from (21)]. Labyrinthine receptors innervated by the inferior vestibular nerve and mainly supplied by the posterior vestibular artery are gray. AICA, anterior-inferior cerebellar artery; HSC, horizontal semicircular canal; PSC, posterior semicircular canal; SSC, superior semicircular canal.

Labyrinthitis ossificans (LO) is a pathologic process resulting from the progressive new bone formation (i.e., ossification) within the membranous labyrinth, leading to sensorineural HL in the majority of cases. Suppurative infection of the middle/inner ear, otosclerosis, head trauma, surgery of the temporal bone, malignant infiltration of the inner ear, autoimmune processes, meningitis, sickle cell disease, and other genetic disorders such as Fabry's disease represent the most common causes (21). Selective ossification of a single semicircular canal is very rare. Castellucci et al. (38) were recently able to demonstrate a filling defect in the PSC on MRI, consistent with early fibrosis of the canal, in a patient with a sudden cochleovestibular loss likely due to CCA ischemia. A labyrinthine ossification was clearly demonstrated two months after vascular inner ear occlusion in guinea pigs by Kimura and Perlman (39, 40). Therefore, ischemia also represents a possible etiologic factor resulting in LO.

The inner ear is supplied by the internal auditory artery, which branches from the anterior-inferior cerebellar artery and divides into two main terminal branches: the anterior vestibular artery and the CCA. Whereas the first mostly supplies the utricle and both HSC and SSC, the latter mainly serves the cochlea, saccule, and PSC. In turn, the CCA divides into the vestibulocochlear artery, which serves the PSC, saccule, and cochlear basal turn. The main cochlear artery supplies the rest of the cochlear neuroepithelium. Finally, the PVA is generated from the vestibulocochlear artery and provides blood supply to both the PSC and saccule (21, 39–41) (Figure 4B). Therefore, the clinical and instrumental effects of PVA occlusion perfectly overlap with IVN. While in the case described by Castellucci et al. (38), an occlusion of CCA was suggested to explain the involvement of the lower labyrinthine structures and PSC fibrosis, a possible PVA terminal occlusion seems to represent the possible site of vascular lesion in our case, resulting in acute PSC and saccular impairment without auditory symptoms. Since our patient denied previous infections, trauma, surgery, and middle/inner ear dysfunctions other than previous contralateral sudden sensorineural HL, most conditions accounting for LO could be reasonably excluded, while inner ear ischemia seems to represent the most likely pathomechanism. Kimura and Pearlman (40) found that the PSC ampulla was more often involved in ischemia than HSC and SSC ampullae because the particular vessel coagulated. Fibrosis was noted after two weeks and ossification after two months, and in our case, the ossification was similarly detected after a few months.

To the best of our knowledge, this is the first report showing LO involving an inner ear structure based on CT findings before and after an AVL mimicking IVN. Since it is well known how vascular lesions of the inner ear may precede a major stroke involving CNS (42, 43), otoneurologists should be aware of the possibility of labyrinthine ischemia and treat patients accordingly. Therefore, we encourage clinicians to routinely exclude ischemic damage to the inner ear with proper investigations, including imaging, even when clinical presentation and instrumental pattern indicate a VN, particularly when symptoms do not improve over time as expected.

Besides detecting PSC ossification, cone-beam CT scans also allowed us to rule out canal dehiscence. In fact, it has been well documented how vertical canal dehiscence might

account for vertical/torsional nystagmus after skull vibrations and reduced VOR-gain value for the affected canal on video-HIT (44–46). Nevertheless, in the case of dehiscence, both C-VEMPs and O-VEMPs should have exhibited enhanced potentials and reduced thresholds on the affected side, besides ipsilesional low-frequency conductive HL, unlike the case herein described.

Another interesting finding in our case is that the VOR-gain value for the affected left-sided PSC was not zero on video-HIT but rather improved from 0.37 to 0.54 in a few months despite a complete ossification of the canal. Similarly, VOR-gain values for the contralesional SSC were slightly impaired at presentation despite the right ear not being affected. These findings confirm that canal VOR-gain values, as measured by the video-HIT gain, reflect the loss of function of the ampullary receptor and are related to the function of the paired semicircular canal aligning with the stimulation plane (47). The reason is that the excitatory and inhibitory responses from the right and left paired canals work in a push-pull manner to generate compensatory eye movements, and video-HIT measurements are probably influenced by additional compensatory mechanisms that still need to be fully understood. The lack of frequent saccades for the affected PSC-HIT likely reflects poor visual compensation enhancing the patient's unsteadiness. On the other hand, low-amplitude refixation saccades detected after the head impulses for the contralesional PSC could be either related to a previous subclinical vestibular involvement, likely concomitant with the right-sided sudden sensorineural HL, or ascribed to an age-related physiological impairment (48).

Conclusions

In conclusion, the case herein described represents the first observation of PSC ossification after a clinical picture consistent with IVN. Owing to an extensive assessment, including instrumental tests measuring labyrinthine function and imaging, it could be possible to identify the labyrinth as the site of the lesion, highlighting the possible role of PVA occlusion. In the case of AVL without HL consistent with IVN, a vascular pathomechanism should always be considered in the differential diagnosis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the patient to publish this case report, including all data and images.

Author contributions

FC: conceptualization, investigation, data acquisition and interpretation, and original draft preparation. AC: investigation, data acquisition, interpretation, images and artwork, and manuscript review. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1015555/full#supplementary-material

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VOR gain of lateral semicircular canal using video head impulse test in acute unilateral vestibular hypofunction: A systematic review

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Introduction: Acute unilateral vestibular hypofunction is characterized by sudden onset of vertigo or dizziness, vomiting/nausea, gait instability, and nystagmus. This is commonly described as an acute vestibular syndrome and usually attributed to vestibular neuritis; however, up to 25% of acute vestibular syndrome is caused by a stroke of posterior circulations. The video head impulse test is a recent tool in the vestibular test battery that assesses the vestibule-ocular reflex by measuring the VOR gain and recording overt and covert saccades, these findings have been found to be helpful in the diagnosis of various vestibular disorders.

Method: A literature search was conducted in databases, including PubMed Central, PubMed, and Web of Science. All the articles that define video head impulse test (vHIT), acute vestibular hypofunction, and vestibular neuritis were considered for the preliminary search. No limits were placed on the date of publication. The searches were limited to studies with full-text availability, published in English, and including human subjects. Search words such as "head impulse test," "video head impulse test," "vestibular ocular reflex," "acute vestibular syndrome," "acute vestibular hypofunction," "vestibular neuritis," and "vHIT in central vestibular disorders" were entered into different databases in different combinations using boolean operators such as AND, OR, and NOT.

Results: Searches across different databases, including Web of Science, PubMed Central, and PubMed, resulted in a total of 1,790 articles. Title screening was done for all the articles. Out of the 1,790 articles, we found that 245 articles were related to vestibular hypofunction i.e., 1,545 articles were removed at this stage. A further 56 duplicate articles were removed. This led to a final screening of 189 articles. The exclusion criteria included unavailability of full text, studies reported in languages other than English, case reports, reviews, and articles including participants having other comorbid conditions. This final screening led to 133 articles being excluded, which led to the full-text screening of 56 articles. After screening the full-text articles as per the eligibility criteria, 21 articles were found to be eligible for the systematic review. Among the remaining studies, six articles were excluded due to different specific reasons. A total of 15 articles were included in this systematic review.

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The mean VOR gain for the patients with vestibular neuritis was 0.48 ± 0.14 for the ipsilesional ear, whereas the mean VOR gain was > 0.80 in the contralesional ear for all the patients with acute vestibular neuritis. In patients with PICA lesions, the VOR gain for the ipsilesional ear was 0.90 (range 0.87–0.94) and for the contralesional ear was 0.88 (range 0.84–0.93). In patients with AICA lesions, the mean VOR gain was variable. Based on the above mean VOR gain findings, the authors propose the following adjective description scale of VOR of the lateral canal using vHIT: normal VOR gain above 0.80, mild VOR gain loss for 0.70–0.79, moderate loss for 0.69–0.4, severe loss for 0.39–0.2, and profound loss for < 0.2.

KEYWORDS

VOR gain, vestibular hypofunction, vHIT, AICA, PICA

Introduction

Every year, approximately 15 to 20% of adults suffer from dizziness, wherein about a quarter is accounted for due to vestibular dysfunction, which has an annual incidence and prevalence of 1.4 and 5%, respectively (1). One of the major reasons for prolonged vertigo which patients encounter is acute unilateral vestibular hypofunction and its mimics. Acute unilateral vestibular hypofunction typically presents as a sudden or acute onset of vertigo or dizziness, nausea/vomiting, gait instability, and nystagmus, a constellation of manifestations called acute vestibular syndrome. The condition is usually attributed to vestibular neuritis; however, up to 25% of acute vestibular syndrome cases are caused by posterior fossa stroke (2–4).

Vestibular neuritis is the most common cause of acute vestibular syndrome (2, 5). It selectively affects the function of the vestibular system and usually, the hearing is preserved. In the acute stage of the disease, is quite challenging to differentiate vestibular neuritis from posterior circulation stroke; clinical signs such as (a) direction of the fast phase of spontaneous nystagmus, (b) ocular torsion, (c) skew deviation, and (d) postural instability can help clinicians differentiate between the two conditions (6).

Anterior inferior cerebellar artery (AICA) territory infarcts comprising 1% of ischemic cerebellar strokes are less common than posterior inferior cerebellar artery (PICA) infarcts (7, 8). Around 10% of patients with cerebellar infarction do not show clinical neurological manifestations apart from vertigo or dizziness (9). Sometimes, isolated central acute vestibular syndrome is referred to as *pseudoneuritis* since it closely mimics the signs of vestibular neuritis (10).

Abbreviations: AICA, Anterior Inferior Cerebellar Artery; PICA, Posterior Inferior Cerebellar Artery; SCC, Semicircular Canal; vHIT, Video Head Impulse Test; VOR, Vestibuloocular Reflex.

One of the recent vestibular function assessment tools is the video head impulse test (vHIT). vHIT is used to assess vestibular functions by comparing head velocity to eye velocity where brief, unpredictable head impulses are given. vHIT measures the functions of all six semicircular canals individually and their corresponding nerves (superior and inferior vestibular nerves) when the head impulses are provided in horizontal, RALP (right anterior and left posterior), and LARP (left anterior and right posterior) planes. It assesses the vestibulo-ocular reflex (VOR) and records the presence of overt and covert saccades, thus aiding in the differential diagnosis of various vestibular disorders. VOR is the physiological mechanism of the vestibular system that generates equal and opposite eye movements when there is a head turn, which helps us to have clear vision during head movements.

The main measures in vHIT are the VOR gain, VOR gain asymmetry, and the presence or absence of compensatory saccades. The VOR gain assesses the function of the semicircular canals and their corresponding nerves on both sides. A clinical head impulse test and, afterward, a vHIT are beneficial in the early detection of isolated central acute vestibular syndrome, where traditional neurological signs are absent. vHIT has specific patterns in some neurological disorders such as Thiamine deficiency (Wernicke's encephalopathy) and multiple sclerosis with subclinical internuclear ophthalmoplegia. Generally, vHIT is a promising tool in differentiating the central and peripheral causes of acute vestibular syndrome (1, 11–16).

The acute stage is defined in this manuscript as within 1 week after the onset of symptoms. The acute phase of unilateral vestibular hypofunction points to the first few days, especially the first 3 days after the onset of symptoms (6). A 1-week cut-off permits the inclusion of more relevant studies to the review and, at the same time, avoids the inclusion of cases where recovery or vestibular compensation might significantly change the results of VOR gain. Patients with unilateral vestibular neuritis show significantly reduced VOR gain values on the ipsilesional side with normal VOR gain in the opposite ear.

Patients with PICA infarcts demonstrate normal or near-normal VOR gain on both sides, whereas patients with AICA infarcts have a heterogeneous pattern of VOR gain values (17). There are also studies reporting bilaterally reduced VOR gain values in cases of vestibular neuritis (18).

Thus, using vHIT, we can differentiate between vestibular neuritis and a PICA infarct. However, in the case of an AICA infarct, we need to seek other clinical tests such as (a) gaze-evoked nystagmus, (b) a test of skew deviation, (c) head-shaking test, and (d) a test of hearing sensitivity. We cannot rely on vHIT findings alone to avoid misdiagnosis (2, 19–24). One study reported that the horizontal head impulse test in the HINTS test battery has a higher sensitivity (∼91%) and specificity (∼100%) when compared to MRI-DWI in the diagnosis of acute vestibular syndrome due to posterior circulation stroke in the first 48 h (22).

The main aim of this research is to systematically review various patterns of VOR gain values in acute unilateral vestibular hypofunction and its mimics using vHIT across research studies. This study aims to address the possibility of differentiating vestibular neuritis from PICA and AICA infarcts based on ipsi- and contralesional VOR gain values. Such a categorization of peripheral and central causes of acute vestibular Syndrome using VOR gain values obtained through vHIT would be important for clinicians, especially those attending acute vertigo. Another aim of this study is to present a grading scale for VOR gain values to facilitate interdisciplinary communication and to be used in clinical practice to help in the differentiation between vestibular neuritis and posterior circulation infarct and in the diagnosis of other vestibular disorders (10). The descriptive categorization of VOR gain proposed in this research is similar to Goodman's scale for hearing impairment (25). Adjective descriptors of hearing loss levels are still the preferred classification among clinicians, and possibly the proposed adjective description of vestibular VOR gain loss will be perceived similarly by clinicians (26).

Methods

Searches

A literature search was conducted in databases, including PubMed, PubMed Central, and Web of Science. The review was conducted in accordance with preferred reporting items for systematic reviews and meta-analysis (PRISMA). All the articles that defined vHIT and acute unilateral vestibular hypofunction were considered for the preliminary search. No limits were placed on the date of publication. The searches were limited to studies with full-text availability, that were published in English, and had human subjects. Search words such as "video head impulse test and acute vestibular syndrome," "acute vestibular Hypofunction and video head impulse test," "vHIT in central vestibular disorders," "vHIT and vestibular neuritis," "vHIT and vestibular Hypofunction," "vHIT and AICA stroke," and "vHIT and PICA stroke" were entered into different databases in different combinations using boolean operators AND, OR, and NOT. Study designs such as retrospective and prospective observational studies, cross-sectional studies, longitudinal studies, and randomized clinical trials were included. Studies that do not report direct or indirect observations or original data, case studies, letters to editors, expert opinions, animal studies, conference abstracts, and reviews were excluded from the present study.

Condition or domain being studied

1. Evaluation of lateral semi-circular canal function in cases with acute unilateral vestibular hypofunction and its mimics.
2. Ipsilesional and contralesional VOR gain value of the lateral canal in cases with acute unilateral vestibular hypofunction and its mimics.

Participants/population

Inclusion: Individuals of any age presenting with signs and symptoms of acute unilateral vestibular hypofunction were considered for the study. Studies also included normal individuals without acute vestibular hypofunction as control groups.

Analysis

Data extraction (selection and coding)

The titles and abstracts of all the obtained articles from different databases were screened by two authors (AM, SKS) independently. Only the articles fulfilling the inclusion criteria were included. The reference list of the included studies was further reviewed to obtain additional relevant articles. Any discrepancies or disagreements regarding the methodology of the article were resolved through discussions between the two authors. A full-text screening of the included studies was done in the second stage of analysis through the same process. The reasons for exclusion were documented and reported at this phase following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (27). The risk of bias was calculated, and the two reviewers carried out the assessment for the same independently. Abnormal or normal VOR gain, ipsilesional and contralesional VOR gain value of the lateral canal, and the presence or absence of compensatory saccades were taken as the data elements of interest.

Risk of bias analysis

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), an evidence-based quality assessment tool, was used to assess the risk of bias in the included studies by the two independent authors. QUADAS-2 has been specifically developed to be used in systematic reviews of diagnostic accuracy studies, with four critical domains, including patient selection, index test(s), reference standard, flow, and timing. After obtaining the rating for each question, the percentage of "yes" was calculated for each study by finding the total number of "yes" out of 11 questions. Any disagreements regarding the quality assessment of the article were resolved through discussions between the two authors.

Strategy for data synthesis

The data synthesis was carried out by analyzing the homogeneity of the data, and different analysis parameters such as VOR gain (ipsilateral and contralateral).

Results

Searches across different databases, including Web of Science, Pubmed Central, and PubMed, resulted in a total of 1,790 articles. Title screening was done for all the articles. Out of the 1,790 articles, we found 245 articles that were related to vestibular hypofunction meeting the objectives of the study i.e., 1,545 articles were removed at this stage. Again, 56 duplicate articles were removed. This led to a final screening of 189 articles. Using the exclusion criteria, which included the unavailability of full text, studies reported in languages other than English, case reports, reviews, and participants with other comorbid conditions, 133 articles were excluded, which led to the full-text screening of 56 articles. After screening for full text, as per the eligibility criteria, 21 articles were found to be eligible for the systematic review. Among the remaining 21 studies, six articles were excluded due to the following reasons. One article was excluded as the article describes a case of a mixture of AICA-PICA syndrome and did not describe the AICA and PICA syndromes separately. One article described the vHIT results as right and left ear and not ipsilesional and contralesional. One article described the vascular risk factor for stroke and not an actual stroke. One article described the prognosis of the cases and does not describe the VOR in the acute phase. One article was excluded as it was a review paper, and the last article was excluded as it was not clear which day the testing was done (28–33). In total, 15 articles were included in this systematic review. The screening process and the reasons for exclusion are depicted in the PRISMA flow (Figure 1).

Characteristics of selected studies

All the records included in this study analyzed VOR gain in cases of acute unilateral vestibular hypofunction and its mimics. The number of participants with acute unilateral vestibular hypofunction cases varied between 1 and 63 in the included 15 studies. VOR gain and saccades were analyzed in all the studies. The characteristics of the studies including participants and the findings of vHIT described in acute unilateral vestibular hypofunction cases and its mimics are given in Table 1.

Risk of bias analysis

The risk of bias analysis of all the studies showed a low risk of bias. Hence, all the studies were included in the final analysis and review.

Analysis parameters

The most studied video head impulse test parameter is the VOR gain, calculated by instantly comparing the eye movement to the head movement, which normally should be the same amount of movement but in opposite direction. The exact method of calculating the VOR gain is different from one system to another. The ratio of the area under the eye velocity curve to the area under the head velocity curve is used in the ICS GN Otometrics system and SLMED system, but instantaneous gain is used in the Eyeseecam Interacoustics system (11, 34, 35). Both the ICS GN Otometrics and Interacoustics systems were validated against a magnetic search coil (11, 47). The SLMED system was validated against special calibration system using an artificial eye (Personal communication).

All the studies included in this systematic review process evaluated the VOR gain but the cut-off criteria between normal and abnormal VOR gain varied from study to study.

Vestibulo-ocular reflex gain in acute vestibular neuritis

Nam et al. (34) described the VOR gain values of the horizontal, posterior, and anterior semi-circular canals using the video head impulse test in 17 patients with vestibular neuritis. All the participants suffered acute prolonged vertigo, nausea or vomiting, and gait disturbance. The subjects were tested with vHIT in the first week after symptom onset. The diagnosis of vestibular neuritis was made based on a history of acute onset vertigo with the presence of unidirectional spontaneous nystagmus, abnormal clinical HIT and canal paresis, and the absence of central signs. The VOR gain was abnormal in all 17 participants for the horizontal canal. The mean ipsilesional VOR gain varied between 0.44 and 0.61 for all the participants.

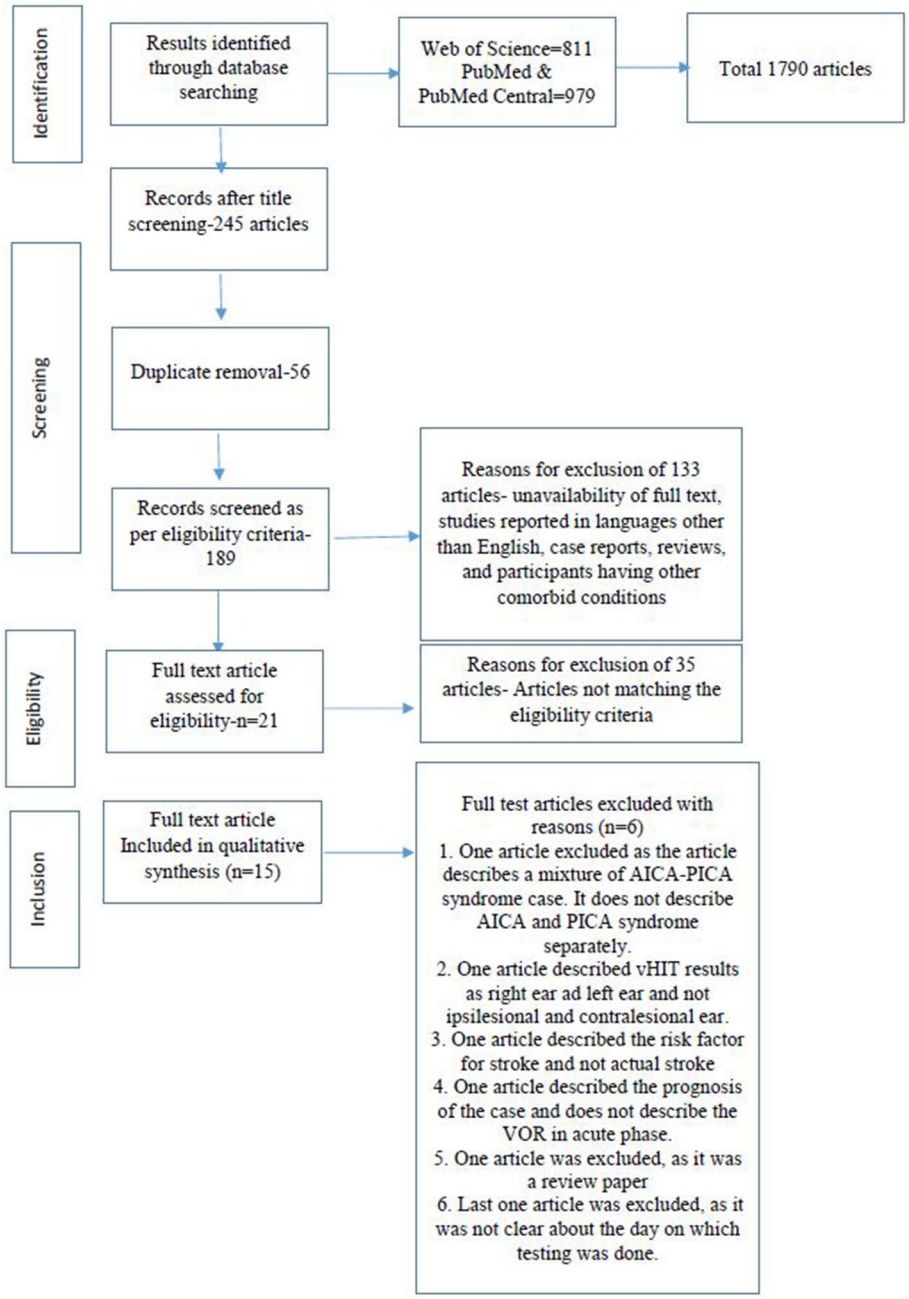

FIGURE 1
PRISMA chart for systematic reviews and meta-analysis.

Blodow et al. (35) evaluated VOR gain using the vHIT in 52 patients with unilateral vestibular neuritis. The diagnosis of vestibular neuritis was based upon the presence of rotatory vertigo, horizontal-rotatory spontaneous nystagmus, gait imbalance and falling, vomiting, nausea, and a pathological side difference (>25%) at bithermal caloric irrigation. The normal VOR gain threshold was set to 0.79. The presence of abnormal VOR gain was recorded in 94.2% of the patients with vestibular neuritis. The mean ipsilesional VOR gain value for patients with vestibular neuritis was 0.43 ± 0.20.

Yang et al. (37) recorded vHIT in 63 patients with acute unilateral vestibular neuritis. All the patients were tested within 1 week of the onset of vestibular neuritis. The diagnosis of VN was made based on a history of acute onset of severe prolonged

TABLE 1 Characteristics of studies included in the review.

S. No	Study	Equipment used	Number of patients	VOR gain of ipsilesional lateral canal	VOR gain of contralesional lateral canal
1.	Nam et al. (34)	SLMED, Seoul, Korea)	17 patients with PICA 17 patients with VN	Mean VOR gain = 0.87 ± 0.13 Mean VOR gain = 0.56 ± 0.16	Mean VOR gain = 0.84 ± 0.13 Mean VOR gain = 0.91 ± 0.04
2.	Blödow et al. (35)	Interacosutics.Middelfart, Denmark	52 patients with VN	Mean VOR gain = 0.43 ± 0.20	
3.	Halmagyi and Curthoys (36)	GN Otometrics, Taastrup, Copenhagen, Denmark	1 patient with VN	Mean VOR gain = 0.32 ± 0.09	Mean VOR gain = 0.86 ± 0.04
4.	Yang et al. (37)	GN Otometrics, Taastrup, Copenhagen, Denmark	63 patients with VN	Mean VOR gain = 0.49 ± 0.03	Mean VOR gain = 0.95 ± 0.12
5.	Manzari et al. (6)	GN Otometrics, Taastrup, Copenhagen, Denmark	28 patients with VN	Mean VOR gain = 0.39 ± 0.17	Mean VOR gain = 0.91 ± 0.11
6.	McGarvie et al. (38)	GN Otometrics, Taastrup, Copenhagen, Denmark	1 patient with VN	Mean VOR gain = 0.33 ± 0.05	Mean VOR gain = 0.64 ± 0.3
7.	Lee et al. (39)	(SLMED, Seoul, Korea)	13 patients with VN	Mean VOR gain = 0.58 ± 0.21	
8.	Mantokoudis et al. (17)	GN Otometrics, Taastrup, Copenhagen, Denmark	16 patients with VN 7 patients with PICA 3 patients with AICA	Mean VOR gain = 0.52 ± 0.04 Mean VOR gain = 0.94 ± 0.04 Mean VOR gain = 0.84 ± 0.10	Mean VOR gain = 0.87 ± 0.04 Mean VOR gain = 0.93 ± 0.04 MeanVOR gain = 0.74 ± 0.10
9.	Yoo et al. (40)	SLMED, Seoul, Korea)	23 patients with VN	Mean VOR gain = 0.55 ± 0.29	Mean VOR gain = 1.00 ± 0.17
10.	Kim et al. (41)	GN Otometrics, Taastrup, Copenhagen, Denmark	30 patients with VN	High velocity Mean VOR gain = 0.50 ± 0.26 Low velocity Mean VOR gain = 0.62 ± 0.25	
11.	Walther and Blödow (42)	Interacosutics, Middelfart, Denmark	20 patients with VN	Mean VOR gain = 0.41 ± 0.17	Mean VOR gain = 0.93 ± 0.08
12.	Redondo-Martínez et al. (43)	Otometrics, Taastrup, Copenhagen, Denmark	20 patients with VN	Mean VOR gain = 0.50	Mean VOR gain = 0.89
13.	Skorić et al. (44)	Interacosutics,Middelfart, Denmark	31 patients with VN	R Mean VOR gain = 0.61 ± 0.30 L Mean VOR gain = 0.63 ± 0.34	
14.	Chang and Schubert (45)	GN Otometrics, Taastrup, Copenhagen, Denmark	4 patients with VN	Mean VOR gain- = 0.57	
15.	Roh et al. (46)	GN Otometrics, Taastrup, Copenhagen, Denmark	21 patients with VN	Mean VOR gain = 0.52 ± 0.17	Mean VOR gain = 1.00 ± 0.13

VN, Vestibular neuritis; AICA, Anterior inferior cerebellar artery; PICA, Posterior inferior cerebellar artery; SD, standard deviation; V-OR, Vestibulo-Ocular reflex gain.

vertigo lasting 24 h, the presence of spontaneous horizontal unidirectional nystagmus without hearing loss or middle ear pathology on clinical examination, and abnormal caloric test results. The VOR gain was affected in 87% of the patients with vestibular neuritis. The VOR gain of the lesioned side in patients with vestibular neuritis varied between 0.15 and 1.18 (mean ipsilesional VOR gain = 0.49 ± 0.03. The VOR gain for the contralateral side ranged between 0.70 and 1.28.

Manzari et al. (6) recorded vHIT in 28 patients with vestibular neuritis. All the participants in the study were tested within 6 weeks of the onset of vestibular neuritis. The diagnosis of vestibular neuritis was made based on a history of acute

onset of severe, prolonged rotatory vertigo, nausea, postural imbalance, presence of horizontal nystagmus, and abnormal VEMP test results. Manzari et al. (6) further subdivided the patients with vestibular neuritis into two groups. The first group included the patients assessed within the first 72 h after the onset of symptoms and the second group included patients tested after 72 h. The mean ipsilesional VOR gain for 15 patients who were tested within 72 h was 0.39 ± 0.17. Lee et al. (32) reported a VOR gain in 13 patients with acute vestibular neuritis. The mean VOR gain for patients with acute vestibular neuritis was 0.58 ± 0.21.

Yoo et al. (40) reported a VOR gain in 23 patients with vestibular neuritis who were tested within one week after the onset of vertigo. The mean ipsilesional VOR gain was 0.55 ± 0.29 for patients with vestibular neuritis. Kim et al. (41) reported a VOR gain in 30 patients with vestibular neuritis. The VOR gain was measured at two different peak head velocities. The VOR gain in patients with vestibular neuritis was 0.50 ± 0.26 for high head velocity and 0.62 ± 0.25 for low head velocity. Walther et al. (42) reported a VOR gain in twenty patients with acute vestibular neuritis and the VOR gain was 0.41 ± 0.17 on the affected side and 0.93 ± 0.08 on the healthy side. Redondo-Martinez et al. (43) reported the VOR gain to be 0.50 in the lesioned ear of the participants with vestibular neuritis. Halmagyi and Curthoys (30) reported the VOR gain to be 0.32 ± 0.09 in the ipsilesional ear of one patient with vestibular neuritis. McGarvie et al. (38) reported the VOR gain to be 0.33 ± 0.05 in a single patient with vestibular neuritis.

To summarize, the VOR gain is significantly reduced in patients with acute unilateral vestibular hypofunction due to vestibular neuritis, when they are tested within 7 days of the onset of symptoms.

VOR gain in AICA and PICA lesions

Nam et al. (34) characterized VOR gain using vHIT in 17 patients with a PICA stroke. The study participants were included based on the presence of acute continuous vertigo, nausea or vomiting, and gait disturbance, seen within 7 days after the onset of symptoms. Patients with a previous history of stroke or vestibular disorders were excluded from the study. The diagnosis of a PICA stroke was confirmed with an MRI scan. The VOR gain for the horizontal canal in the PICA group was 0.87 ± 0.13 (range = 0.80 to 0.93). However, in 9 out of 17 participants the VOR gain was slightly reduced on both sides. The authors suggested that a VOR gain higher than 0.71 ipsilesional in acute vestibular syndrome can predict a PICA stroke, yet they recommended that this value should be validated in clinical practice.

Mantokoudis et al. (17) described the VOR gain in 7 patients with PICA and 3 patients with AICA stroke. The patients presented with acute vestibular syndrome. Patients with known prior vestibular oculomotor diseases, acute drug/alcohol intoxication, or new head trauma were excluded from the study.

TABLE 2 VOR gain loss grading scale.

VOR gain	Grade
≥ 0.8	Normal VOR gain
0.79–0.70	Mild VOR gain loss
0.69–0.4	Moderate VOR gain loss
0.39–0.2	Severe VOR gain loss
<0.2	Profound VOR gain loss

The VOR gain for individuals with PICA stroke was normal on both sides without VOR asymmetry. There was also no difference between the ipsilesional and contralesional VOR gain values. The VOR gain for the ipsilesional side was 0.94 ± 0.04 and the contralesional side was 0.93 ± 0.04. Three patients with AICA stroke had variable VOR gain values. The mean VOR gain value for individuals with AICA stroke was 0.84. Also, the mean VOR gain values on the contralesional side for the individuals with AICA stroke (0.74) were less compared to the ipsilateral side (0.84). Based on these findings, they concluded that if the normal VOR gain criterion was kept at 0.7 or more for suspected stroke, it could lead to the diagnostic accuracy of 90% for individuals with PICA stroke.

Mean VOR gain in vestibular neuritis & AICA and PICA lesion

The VOR gain for the patients with vestibular neuritis varied between 0.15 and 0.89 for the ipsilesional ear, whereas the VOR gain was < 0.80 in the contralesional ear for all the patients with acute vestibular neuritis. The mean VOR gain was calculated for the mean gain values reported in all the studies. The mean ipsilesional lateral canal VOR gain of all the studies is 0.48. In the contralesional ear of patients with vestibular neuritis, the mean VOR gain is 0.85 (range 0.50 to 1.00). In patients with PICA lesions, the VOR gain for the ipsilesional ear is 0.90 (range 0.87–0.94) and for the contralesional ear is 0.88 (range 0.84–0.93). In patients with AICA lesions, the mean VOR gain is 0.84 for the ipsilesional ear and 0.74 for the contralesional ear. Based on the above mean VOR gain findings, we propose the following scale for VOR gain calculations (Table 2).

The proposed grading scale of the severity of VOR gain loss in acute unilateral vestibular hypofunction might help in understanding the etiology, predicting the outcome, and providing easier inter-professional and clinician-patient communication.

Discussion

Different synonyms such as vestibular neuritis, vestibular neuronitis, acute unilateral vestibular hypofunction, and

vestibulitis, have been used in the literature to describe the clinical syndrome presented with acute onset and severe dizziness that lasts days or weeks, which is occasionally associated with MRI enhancement of the vestibular nerve. Vestibular neuritis can affect almost any combination of afferent pathways in the vestibular nerve (48, 49).

The video head impulse test has gained great popularity as a frontline vestibular testing tool. The ease of performing vHIT during acute vertigo, especially in cases of acute vestibular syndrome, its ability to measure the VOR gain of the six semicircular canals, and its ability to detect overt, covert, and anti-compensatory saccades made it a crucial part of routine vestibular assessment.

Different commercial vHIT systems are available in the market, with a significant amount of research based on their clinical use (11). Acute unilateral vestibular hypofunction is a condition that is frequently encountered in clinical practice. VOR gain is typically reduced in one or more of the semicircular canals ipsilateral to the side of hypofunction. The literature showed that the main differential diagnosis of acute unilateral vestibular hypofunction is posterior circulation stroke specifically AICA and PICA. A VOR gain of lateral canal vHIT can differentiate between dysfunction of the vestibular end organs or their afferents and its central mimics: PICA and AICA infarctions (17).

The results of the conducted systemic review in this study revealed that the VOR gain of horizontal SCC ranged between 0.15 and 0.89 ipsilesional in cases of vestibular neuritis. On the contrary, the VOR gain of the lateral canal is usually spared or minimally reduced in PICA infarctions. Variable VOR gain values were reported in very few cases of AICA infarction as indicated in the study by Manokoudis et al. This is expected as AICA infarction could be associated with labyrinthine ischemia, leading to damage of vestibular end organs or their afferents. It could also be associated with damage to vestibular nuclei or cerebellar structures as flocculus but it sometimes spares the integrity of the lateral canal VOR. Thus, different patterns of VOR gain values could be seen in cases of AICA (17). This agrees with findings reported by Chen et al. using a magnetic search coil (50).

Among the patients with vestibular neuritis, the various studies' results suggest a greater variability in the range of vestibule-ocular reflex gain. (18, 42). One of the studies included in the review reported the range of ipsilesional VOR gain in cases of vestibular neuritis to be between 0.15 and 1.18 (mean VOR gain $= 0.49 \pm 0.03$), and for the contralesional side to be ranged between 0.70 and 1.28 (37). This means some of the included subjects presented with spontaneous nystagmus, caloric weakness, normal lateral canal VOR gain, and no signs of posterior circulation stroke. These cases possibly do not have vestibular neuritis but rather Meniere's disease or these results may be due to faulty calibration during vHIT. In fact, this is the only study that reported occasional high VOR gain in vestibular neuritis.

Most studies suggest a reduced vestibular ocular reflex gain in patients with vestibular neuritis. The studies suggested that the most commonly affected SCC is the lateral canal, which is why this research focuses on lateral canal VOR gain because it is more clinically significant. (18, 43). Cherchi and Yacovino (49) explained why the lateral canal is the most vulnerable semicircular canal to different pathologies with the anatomical fact that it has a lower number of afferent neurons which are condensed in a limited space. Clinical protocols used to differentiate vestibular neuritis from stroke such as HINTS protocol mainly depend on lateral canal VOR gain loss and compensatory saccades (1).

In a healthy subject during an abrupt head turn to the left, receptors and afferents in the left horizontal canal are activated and *simultaneously* receptors and afferents from the right horizontal canal are inhibited. Also, increased activity in the ipsilateral vestibular nuclei leads to decreased activity in the contralateral vestibular nuclei which in turn decreases the inhibitory effect on the ipsilateral vestibular nuclei, leading to enhancement of ipsilateral activity. In this way, the functionally inhibitory commissural connections act to enhance the difference in neural activity between the two vestibular nuclei. This explains the slightly reduced contralateral VOR gain in cases of acute unilateral vestibular hypofunction as shown in different studies (11).

Based on the results of the systematic review of VOR gain values in acute unilateral vestibular hypofunction, the authors propose a clinically needed grading scale for the severity of VOR. Based on the data presented in this study, both mild and profound VOR gain loss can present as acute prolonged vertigo with spontaneous nystagmus but recovery, compensation, duration of the acute symptoms, and residual symptoms are not expected to be the same.

The proposed scale is as the following: ≥ 0.8 normal, 0.79–0.70 mild loss, 0.69–0.4 moderate loss, 0.39–0.2 severe, < 0.2 profound loss. This scale could be used similarly to the hearing loss grading scale (25) which is widely used for the adjective description of hearing loss.

Limitations of the study

The study is limited to lateral canal VOR gain and does not include anterior and posterior semicircular canal VOR gain. The included studies used different video head impulse test systems and, consequently, different VOR gain measurement methods. The inclusion criteria of subjects with acute unilateral vestibular hypofunction are not standardized in all the included studies. The study only included acute unilateral vestibular hypofunction due to vestibular neuritis, PICA, and AICA

but not due to other pathologies. Another limitation of this work is that it is focused on numerical values of VOR gain with a lack of information about the morphology of the oculomotor response and the presence of corrective saccades, which are considered clinically significant parameters of vHIT interpretation.

Conclusions

VOR gain loss grading could provide an easy adjective description of variable degrees of lateral canal VOR gain loss due to different pathologies. Calculated VOR gain value of the lateral canal using video head impulse test helps in the etiological diagnosis of acute vestibular syndrome. The adjective scaling proposed in this study would make this much easier. For example, if the VOR gain of the ipsilesional lateral canal shows moderate to profound VOR gain loss with normal or mild VOR gain loss on the contralesional side, this is most likely a case of vestibular neuritis. If the VOR gain is normal or mildly reduced on both sides, it is most likely a PICA stroke. For an AICA stroke, there is a variety of reported patterns, and different degrees of ipsilesional and contralesional VOR gain loss could be found.

Recommendations

Further studies applying the VOR gain loss scale in different disorders, e.g., Meniere's disease, migraine, and transient ischemic attacks, should be conducted. Further, more studies with a larger number of subjects should be conducted.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Author contributions

MAlf conceptualized the work, contributed to data collection, analysis, contributed to writing, and revising the manuscript. MAlg and SS contributed to data collection, analysis, writing, and revising the manuscript. AN contributed to data collection and the analysis of data. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Vestibular assessment in sudden sensorineural hearing loss: Role in the prediction of hearing outcome and in the early detection of vascular and hydropic pathomechanisms

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Introduction: Predicting hearing outcome in sudden sensorineural hearing loss (SSNHL) is challenging, as well as detecting the underlying pathomechanisms. SSNHL could be associated with vestibular damage since cochleo-vestibular structures share the same vascularization, along with being in close anatomical proximity. Whereas viral inflammations and autoimmune/vascular disorders most likely represent the involved aetiologies, early-stage Menière's disease (MD) can also present with SSNHL. Since an early treatment could beneficially influence hearing outcome, understanding the possible etiology plays a pivotal role in orienting the most appropriate treatment. We aimed to evaluate the extent of vestibular damage in patients presenting with SSNHL with or without vertigo, investigate the prognostic role of vestibular dysfunctions on hearing recovery and detect specific lesion patterns related to the underlying pathomechanisms.

Methods: We prospectively evaluated 86 patients with SSNHL. Audio-vestibular investigation included pure-tone/speech/impedance audiometry, cervical/ocular-VEMPs, vHIT and video-Frenzel examination. White matter lesions (WML) were evaluated on brain-MRI. Patients were followed-up and divided into "SSNHL-no-vertigo," "SSNHL+vertigo" and "MD" subgroups.

Results: Hearing was more impaired in "SSNHL+vertigo" patients who exhibited either down-sloping or flat-type audiograms, and was less impaired in "MD" where low frequencies were mostly impaired ($p < 0.001$). Otolith receptors were more frequently involved than semicircular canals (SCs). Although the "SSNHL-no-vertigo" subgroup exhibited the lowest vestibular impairment ($p < 0.001$), 52% of patients developed otolith dysfunctions and 72% developed nystagmus. Only "MD" subjects showed anterior SC impairment and upbeating spontaneous/positional nystagmus. They more frequently exhibited cervical-VEMPs frequency tuning ($p = 0.036$) and ipsilesional spontaneous nystagmus ($p < 0.001$). "SSNHL+vertigo" subjects presented with more frequently impaired cervical-VEMPs and posterior SC and with higher number of impaired receptors ($p < 0.001$). They mainly exhibited contralesional spontaneous and vibration-induced nystagmus ($p < 0.05$) and only they showed the highest WML score and "vascular" lesion patterns ($p < 0.001$). Concerning the outcomes, hearing was better in "MD" and worse in

"SSNHL+vertigo" ($p < 0.001$). Hearing recovery was mostly affected by cervical-VEMPs impairment and the number of involved receptors ($p < 0.05$). Patients with "vascular" lesion patterns presented with the highest HL degree and WML score ($p \leq 0.001$), while none of them exhibited a complete hearing recovery ($p = 0.026$).

Conclusions: Our data suggest that vestibular evaluation in SSNHL can provide useful information on hearing recovery and underlying aetiologies.

KEYWORDS

video head impulse (vHIT), vestibular evoked myogenic potentials (VEMPs), vestibulo-ocular reflex (VOR), labyrinthine ischemia, spontaneous nystagmus, sudden sensorineunal hearing loss, Menière's disease

1. Introduction

Sudden sensorineural hearing loss (SSNHL) represents a sensorineural hearing impairment ≥30 dB over at least three contiguous frequencies on audiometry occurring within a 72-h time span. Although it mostly occurs unilaterally with a higher incidence in the 3rd–5th decades of life, SSNHL can affect patients of any age, whereas it might rarely present in both ears (simultaneous or sequential) (1). According to the literature, SSNHL is often accompanied by additional inner ear symptoms (vertigo, dizziness, tinnitus and aural fullness) while the estimated prevalence of the sole vestibular symptoms is 30%−60%. SSNHL is thought to represent an inner ear disorder in the majority of cases, despite infarction in the territory supplied by the vertebra-basilar system might result in sudden deafness with or without vertigo (2, 3). Despite an accurate history taking, including the evaluation of specific risk factors, and the use of various diagnostic tests, including laboratory tests and brain magnetic resonance imaging (MRI), a definite aetiologic factor is not identified in the vast majority of patients. This is the reason why SSNHL is mostly considered an idiopathic condition. While systemic diseases, neoplasms, neurological and otologic disorders, toxic, and traumatic agents represent some of the identifiable causes, some etiopathogenetic theories have been proposed for idiopathic SSNHL, including viral inflammations, immune-mediated mechanisms and vascular damage to the inner ear (4–6). Epidemiologic studies highlighting a close relationship between SSNHL and vascular disorders and, on the other hand, the evidence that patients with SSNHL exhibit a higher risk to develop cardiocerebrovascular diseases support the latter theory (7, 8). It has also been documented a higher arterial stiffness and a higher prevalence of leukoaraiosis on brain MRI in subjects with SSNHL compared to controls, further strengthening a vascular hypothesis (9, 10). In fact, leukoaraiosis represents a diffuse alteration of the periventricular and subcortical white matter, correlated to the small vessel disease and characterized by hyperintensity of the white matter lesions (WML) on T2-weighted images (11). Nevertheless, also Menière's disease (MD), which represents a multifactorial and heterogeneous disease likely due to an underlining endolymphatic hydrops (EH) as documented by histopathological, radiological and physiological studies (12–17), can present with isolated SSNHL affecting low frequencies as first clinical manifestation of. In fact, only a minority of MD patients debuts with the full clinical triad, including concomitant ictal vertigo and tinnitus, since hearing could exhibit delayed fluctuations and vestibular symptoms might occur only at a later stage (18, 19). Since auditory function in MD behaves differently from other SSNHL, as it tends to recover spontaneously and better than other conditions, some Authors usually prefer to rule out patients with low-frequency HL from inclusion criteria of idiopathic SSNHL to avoid bias. Nevertheless, it is well-known how the first episode of acute HL in MD might not only affect the low tones, but also middle and/or higher frequencies (20, 21). In addition, it has been described that only part of subjects with low-tone SSNHL develops a clinical picture consistent with MD over time and, on the other hand, that an additional subgroup of patients with idiopathic SSNHL later develop MD in the ipsilateral ear (ipsilateral delayed EH) (19, 22–24). Therefore, considering low-frequency SSNHL as a certain manifestation of MD "*a priori*" does not seem to represent a safe approach.

Steroid therapy represents the current mainstay of treatment for SSNHL. Additional treatment strategies include antiherpetic therapy, rheologic agents, diuretics, hyperbaric oxygen therapy, fibrinogen/LDL-apheresis and intratympanic injections. Nevertheless, spontaneous hearing recovery has also been reported in up to 65% of patients with SSNHL (1, 5, 6, 25).

Predicting hearing outcome in SSNHL is still challenging. Patient's age, configuration and degree of HL, comorbidities and time between onset of symptoms and treatment have been widely accepted as the most influencing factors on hearing outcome (5, 6, 26). Additionally, the presence of vestibular symptoms and the involvement of the vestibular end-organs have been considered supplementary poor prognostic factors, as they are usually associated with a greater inner ear damage, deeper HL and worse

Abbreviations: AC, air-conducted; AR, asymmetry ratio; ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; CCA, common-cochlear artery; CMV, Cytomegalovirus; CN, cochlear nerve; CNS, central nervous system; CT, computed tomography; cVEMPs, cervical vestibular-evoked myogenic potentials; EH, endolymphatic hydrops; HL, hearing loss; HSC, horizontal semicircular canal; HSN, head-shaking nystagmus; HSV, Herpes Simplex virus; HVN, hyperventilation nystagmus; HZV, Herpes Zoster virus; IAA, internal auditory artery; MD, Menière's disease; MRI, magnetic resonance imaging; oVEMPs, ocular vestibular-evoked myogenic potentials; PN, positional nystagmus; PSC, posterior semicircular canal; PTA, pure tone average; SC, semicircular canal; SN, spontaneous nystagmus; SSNHL, sudden sensorineural hearing loss; VCA, vestibulo-cochlear artery; vHIT, video-head impulse test; VIN, vibration-induced nystagmus; VOR, vestibulo-ocular reflex; VCA, vestibulo-cochlear artery; VN, vestibular nerve; WML, white matter lesions; WRS, words recognition score.

hearing recovery (27–37). Several studies investigating the clinical significance of vertigo and data obtained from vestibular tests have been conducted, yielding some conflicting results (26–51). One of the reasons for these discrepancies is that vertigo is not a specific disease entity but a symptom, and similar vestibular abnormalities can result from different pathologies not sharing the same etiologies, leading to heterogeneous group of patients. Theoretically, given the various embryological and anatomical factors making the inner ear (cochlear and vestibular partitions) an anatomo-physiological unity, it is possible to expect different lesion patterns depending on the underlying etiologies in case of SSNHL. Thanks to the combined use of recently introduced tests for vestibular assessment, such as the video-Head Impulse Test (vHIT) (52) and vestibular-evoked myogenic potentials (VEMPs) (53), assessing semicircular canal (SC) and otolith reflexes, respectively, and both branches of the vestibular nerve (VN), it has become possible to assess overall labyrinthine receptors and afferents even in acute setting, outlining lesion patterns peculiar to specific pathomechanisms (32, 54–62). In fact, while some patterns closely overlapped sensors innervated by the two divisions of the vestibular nerve likely due to viral neuritis (54, 55, 63, 64), inner ear ischemia has been considered the most likely mechanism for those patterns overlapping the territories supplied by the terminal branches of the internal acoustic artery (IAA) (57–59, 61–63, 65–68).

It is well-known how an early treatment could beneficially influence hearing outcome and symptoms recovery in SSNHL, therefore the detection of the possible etiology could play a pivotal role in orienting the most appropriate treatment. In addition, since it has been demonstrated how labyrinthine vascular lesions may precede a major stroke involving posterior fossa structures, clinicians' awareness toward the eventuality of an inner ear ischemia should be risen (69, 70). The aim of this study is to address the following questions, comparing our results with the pertinent literature:

- Identifying the extent of vestibular dysfunction quantitatively in patients affected by SSNHL with or without vertigo;
- Addressing the prognostic factors, including instrumental data and oculomotor findings, for SSNHL over 6 months;
- Identifying peculiar lesion patterns associated to specific pathomechanisms and etiologies underlying SSNHL.

2. Materials and methods

2.1. Ethical statement

This study was approved by our Institutional Review Board (Area Vasta Emilia Nord, approval number 238/2020/OSS/AUSLRE) and was conducted according to the tenets of the Declaration of Helsinki (2002). Written informed consent was obtained from each patient enrolled in the study.

2.2. Cohort and study design

We prospectively enrolled all consecutive adult patients (≥18 years old) with unilateral SSNHL who were admitted in Day Service of the Audiology and Ear Surgery Department of our Institution from January 2020 to June 2021. The diagnosis of SSNHL was based on unilateral SSNHL of more than 30 dB at a minimum of 3 consecutive frequencies over a period ≤72 h (1) occurred within the previous 30 days. All patients with onset of symptoms ≤30 days were included in the study. All patients who were admitted after more than 7 days from symptoms onset had already started an uneventful treatment with oral steroids. Subjects with previous HL in the same ear were excluded to avoid possible debate about the assessment of outcomes. All patients were treated according to the current therapeutic protocol for SSNHL in our Institution and received the same detailed work-up within 1 week from admission, including history taking, blood laboratory tests, pure tone audiometry, impedance audiometry, speech audiometry, video-Frenzel examination, VOR-gain assessment for all semicircular canals with the vHIT and both cervical and ocular-VEMPs for air-conducted (AC) sounds. Brain gadolinium-enhanced magnetic resonance imaging (MRI) was scheduled over a 3-month period in all cases, whereas temporal bones high-resolution computed tomography (CT) scan was performed only if needed in selected cases. Clinical records were collected and analyzed.

2.3. History taking and blood laboratory tests

Accompanying vestibular symptoms (acute vertigo and/or unsteadiness) and cochlear symptoms (aural fullness and/or tinnitus) were investigated, along with neurologic, endocrinologic and rheumatologic comorbidities. Each patient was investigated for precise cardiovascular risk factors [arterial hypertension, hypercholesterolemia, previous acute cerebrovascular or heart diseases, diabetes mellitus, body mass index (BMI) >25, smoke habits] and the sum of these factors ("0" absence, "1" presence) was calculated to assess the "cardiovascular risk score" for statistical purposes. Blood laboratory test included white blood cells count, PCR, TSH and biochemical assays for well-known biomarkers for cardiovascular disease associated to SSNHL (fibrinogen, homocysteine, total and LDL cholesterol, triglycerides, Apolipoprotein A1, Apolipoprotein B, Apolipoprotein A1/B ratio, Lipoprotein) (71). In case of at least one out-of-range laboratory assay among biomarkers for cardiovascular disease, the patient was assigned "+1" in the "cardiovascular risk score." Virological screening test including IgM and IgG antibodies against Herpes Simplex virus (HSV) type 1 and type 2, Herpes Zoster virus (HZV), and Cytomegalovirus (CMV) was also conducted.

2.4. Audiometry

Pure-tone audiometry was performed over the frequency range of 125–8,000 Hz for air-conduction (AC) and 250–4,000 Hz for bone-conduction (BC) in a soundproof room using standard clinical procedures, once normal status of tympanic membranes and external auditory meatus was ascertained on micro-otoscopic examination. Appropriate masking was used for BC testing and, when needed, for AC. The pure tone average (PTA) was calculated as the average of the BC thresholds of the four most impaired contiguous frequencies. Morphologies of audiometries were categorized as low-frequency, high-frequency or flat-type depending on the most affected tones. Audiometries were also classified according to the HL severity in four categories: "mild" (PTA ≤ 40 dB), "moderate" (PTA >40 and

≤70 dB), "severe" (PTA >70 and ≤90 dB) and "profound/anacusis" (PTA > 90 dB). In case of anacusis, PTA of 120 dB was assigned for statistical purposes. Standard tympanometry with a 226 Hz probe tone and ipsi/contralateral acoustic reflexes were administered to all patients. Speech audiometry with lists of disyllabic words was imparted on both ears to assess the words recognition score (WRS).

2.5. Video-Frenzel examination

Eye movements were recorded with a monocular ICS video-oculographic system (GN Otometrics, Denmark) on admission. Preliminary bedside oculomotor testing including smooth pursuit, saccades, vergence and skew deviation was assessed to rule out central nervous system (CNS) abnormalities. Horizontal, vertical, and torsional components of nystagmus were qualitatively assessed. Horizontal (right/leftbeating), vertical (up/downbeating) directions of nystagmus, and torsional (right/left) components were described from the patient's point of view. Bedside-examination included the assessment of spontaneous (SN), gaze-evoked and positional nystagmus (PN) evoked by the supine head-roll test, Dix-Hallpike positionings on both sides and straight head-hanging position. SN was classified according to the predominant features: absent, beating contralesionally (i.e., paretic nystagmus) or ipsilesionally to the side with SSNHL (i.e., either irritative or recovery nystagmus, depending on cases), upbeating and downbeating. Conversely, PN was classified in absent, either geotropic/apogeotropic (in case it could only be detected by positioning the patient's head on one side) or bigeotropic/biapogeotropic (in case it was direction-changing, i.e., detected by positioning the patient's head on both sides) at the supine head roll-test, either persistent upbeating/downbeating or paroxysmal upbeating/torsional consistent with ipsilesional benign paroxysmal positional vertigo (BPPV) at the Dix Hallpike and straight head hanging positions. Skull vibration, head-shaking and hyperventilation tests were conducted with the patient upright. Vibration-induced nystagmus (VIN) was elicited applying a hand-held 100-Hz vibrator (VVIB 100 Hz Synapsys, France) to both mastoids for at least 15 s. VIN was considered reliable only if vibrations in both mastoids resulted in the same oculomotor pattern. Then, 30 cycles of passive head rotations were imparted at a rate of 1–2 Hz with head tilted 30° forward in the plane of the HSC and the head-shaking nystagmus (HSN) was evaluated in the 30 s following the test. Finally, the patient was instructed to hyperventilate deeply for 40 s, taking about one breath per second, and hyperventilation nystagmus (HVN) was evaluated in the following 30 s. In patients without SN, we considered as pathologic response the onset of sustained unidirectional nystagmus (horizontal or vertical/torsional). In cases with SN, either a sustained increase, an inhibition or an inversion of nystagmus, or even a modification of SN plane were accepted as pathologic responses. SN, VIN, HSN, and HVN were classified for statistical purposes in absent, ipsilesional and contralesional to the ear with SSNHL, upbeating and downbeating.

2.6. vHIT

The vHIT was performed on admission to evaluate the high-frequency vestibulo-ocular reflex (VOR) gain for each semicircular canal (SC), using an ICS video-oculographic system (GN Otometrics Denmark). Passive, unpredictable 150°-250°/s and 3,000°-5,000°/s^2 head impulses were delivered manually on the plane of the horizontal and vertical SCs while the patient was asked to keep looking at an earth-fixed target, according to the standard protocol (52). At least 15 stimuli were delivered for stimulating each SC and averaged to get the corresponding mean VOR-gain. VOR-gain values <0.8 for HSC and <0.7 for ASC and PSC with corrective saccades (overt and/or covert) were considered pathological. Data corresponding to VOR-gain for the horizontal (HSC), anterior (ASC) and posterior SC (PSC) for each pathologic ear were considered in statistical analyses.

2.7. VEMPs testing

Cervical and ocular VEMPs (cVEMPs and oVEMPs, respectively) for AC sounds were recorded using 2-channel evoked potential acquisition systems (Viking, Nicolet EDX, CareFusion, Germany) with surface electrodes placed according to standardized criteria (53). Potentials were recorded delivering tone bursts (starting intensity: 100 dB nHL, frequency: 500 Hz, duration: 8 ms, stimulation rate: 5 Hz). Recording system used an EMG-based biofeedback monitoring method to minimize variations in muscles contractions and VEMPs amplitudes. A re-test was performed for each stimulus to assess reproducibility. The first biphasic responses on the ipsilateral sternocleidomastoid muscle (p13-n23) for cVEMPs (ipsilateral response) and under the patient's contralateral eye (n10-p15) for oVEMPs (crossed response) were analyzed by calculating the peak-to-peak amplitude. Inter-aural amplitude difference between the ipsilesional (Aipsi) and contralesional ear (Acontra) to SSNHL were calculated with the asymmetry-ratio (AR): (Acontra – Aipsi) / (Acontra + Aipsi) × 100. Otolith sensors on the pathologic side were considered damaged if potentials resulted in AR ≥33% for both cVEMPs and oVEMPs, according to our normative data and to literature references (53), or in cases of bilaterally absent responses. Threshold was then obtained decreasing in steps of 10 dB from 100 dB nHL; the lowest stimulus intensity resulting in a clear and repeatable biphasic wave was considered as threshold. cVEMPs were then tested with 100 dB tone bursts at 1 kHz bilaterally: frequency tuning was considered "positive" if the difference between the amplitude of potentials obtained at 1 kHz and the amplitude at 500 Hz was ≥ 0 μV (14).

2.8. Imaging

Brain gadolinium-enhanced MRI (1.5 Tesla) was completed by standard protocols for posterior fossa visualization. The extent of leukoaraiosis was assessed with the Fazekas scale (11) on T2-weighted images or FLAIR sequences and classified in four stages according to presence, size, and confluence of periventricular and deep WML: 0 "absent," 1 "foci," 2 "beginning confluent" and 3 "large confluent areas."

2.9. Treatment

According to the current uniform treatment protocol for SSNHL in our institution, each patient initially received the same standard treatment including i.v. Dexamethasone 0.15 mg/kg + i.v. Glycerol

(10%, 500 ml) for 10 days, followed by additional 10 days of oral steroid tapering. In case of treatment failure, salvage therapy with intratympanic steroid injections (Dexamethasone 24 mg/ml, five times in 3 weeks) and/or hyperbaric oxygen therapy (10 sessions in 2 weeks) and/or fibrinogen/LDL-apheresis (one session) were attempted. Only selected cases with highest WML scores according to the Fazekas scale were sent to neurological evaluation and only a subset of them started antiplatelet treatment accordingly.

2.10. Follow up and subgroups of patients

Pure tone, impedance and speech audiometries were scheduled according to the following timeline from admission to assess hearing recovery: 15 days, 3, 6, and 12. Audiometries performed on admission and at 6 months were considered to assess the final hearing improvement. Hearing recovery was considered either "complete" (if PTA returned within 10 dB HL of the unaffected ear, with WRS >50%), "partial" (PTA improvement >10 dB HL without returning within 10 dB HL of the unaffected ear, with WRS >50%) or "no recovery" (either PTA improvement <10 dB HL or greater improvement with a WRS ≤50%) (1). The amount of PTA recovered was calculated by the difference between presenting PTA (PTApre) and PTA at 6-month follow up (PTApost) for the four most impaired contiguous frequencies on the affected ear as follows: PTApre – PTApost. Conversely, the mean percentage of hearing recovery was calculated comparing the amount of PTA recovered to the difference between presenting PTA on the affected ear and the PTA for the corresponding affected frequencies on the contralateral ear (PTAcontra) as follows: (PTApre – PTApost) / (PTApre – PTAcontra) × 100. Even patients' symptoms were followed up over the 12 months from admission and three different subgroups were identified according to the clinical course. In case of lack of vestibular symptoms both on admission and throughout the whole follow up, the patient was assigned to the "SSNHL no vertigo" subgroup. Conversely, in case vestibular symptoms only occurred simultaneously with SSNHL, the patient was assigned to the "SSNHL + vertigo" subgroup. Finally, in case of fluctuating/relapsing HL, later onset of vertigo or recurrent vestibular symptoms consistent with "definite" or "probable" MD, according to the 2015 guidelines (72), the patient was considered as "MD." Finally, some patterns of vestibular impairment were identified as likely due to a "vascular" pathomechanism, based on the vascular supply to the inner ear and clinical descriptions (57–59, 61–63, 65–68). The following patterns were considered "vascular":

- High-frequency SSNHL associated with an impairment for cVEMPs and PSC VOR-gain, with or without concurrent abnormal oVEMPs, consistent with a selective ischemia in the territory mainly supplied by the vestibulo-cochlear artery (VCA).
- Severe or profound SSNHL associated with an impairment for cVEMPs and PSC VOR-gain, with or without concurrent abnormal oVEMPs, consistent with a selective ischemia in the territory mainly supplied by the common-cochlear artery (CCA).
- Severe or profound SSNHL associated with both otolith and SC impairment, consistent with a selective ischemia in the territory supplied by the IAA.

2.11. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics, version 20.0 for Windows (IBM Corp.; NY, USA). Categorical variables were presented as percentages. Quantitative variables were checked for normal distribution using both Kolmogorov–Smirnov and Shapiro-Wilk tests. Continuously distributed variables were described by mean ± 1 standard deviation or by median, interquartile range, and range. Pearson Chi-square test or Fischer exact test were used for categorical comparisons. A logistic regression model was used to evaluate the effects of prognostic factors on hearing recovery. The Kruskal–Wallis one-way analysis of variance (ANOVA) was used to compare median values of instrumental variables and *post-hoc* analysis was applied to compensate for multiple comparisons. Statistical significance was presented as *p*-value and assumed when a null hypothesis could be rejected at $p < 0.05$.

3. Results

3.1. Demographics and presenting clinical/instrumental findings of overall cohort

During the period examined, 147 patients were hospitalized. Sixty-one patients were excluded from the study either due to incomplete audio-vestibular assessment (18 patients), due to previous inner ear disease (40 patients) or known SSNHL etiology (three patients: vestibular schwannoma in one case, acoustic trauma in another case and multiple sclerosis in an additional case). Finally, 86 patients with complete instrumental assessment met the inclusion criteria for idiopathic SSNHL on admission and were included in the analysis: 49 were males (57%) and 37 females (43%), with a median age of 55.7 years ± 14.4 (range age 22–84 years old). None of them present with clinical or radiological signs of CNS involvement and none showed screening test consistent with active viral infection (HSV, HZV, CMV). SSNHL occurred on the right side in 41.9% of cases (36/86) and 45/86 (52.3%) patients complained of vestibular symptoms on admission. The average time between symptoms onset and the beginning of treatment was 14.4 ± 10.7 days (range 1–30 days). Hearing loss was mild in 12.8% of cases (11/86), moderate in 47.7% (41/86), severe in 18.6% (16/86) and profound/anacusis in 20.9% of cases (18/86). Hearing loss was down-sloping in 25.6% of cases (22/86), involved low-frequency tones in 24.4% (21/86) and was flat in 50% (43/86).

Otolith receptors were involved in similar percentage of cases as saccular function was impaired in 45.3% of cases (39/86), while utricular function in 43% (37/86) according to cervical and ocular VEMPs measurements, respectively ($p = 0.759$; Figure 1A). Similarly, HSC function was altered on vHIT in 16.3% (14/86), ASC in 11.6% (10/86) and PSC in 20.9% of cases (18/86) with no statistically significant difference ($p = 0.255$; Figure 1B).

3.2. Presenting clinical/instrumental findings in different subgroups

Once divided the overall cohort according to presenting symptoms and clinical course, 25/86 patients (29.1%) fit the "SSNHL

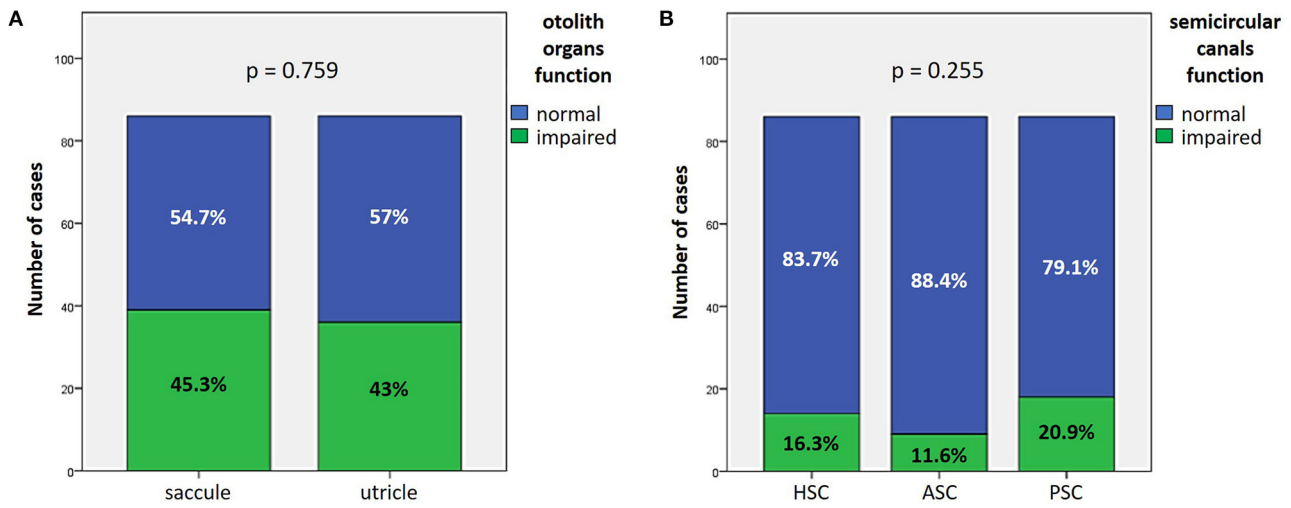

FIGURE 1
Bar plots showing the number of cases among overall cohort of 86 cases exhibiting different instrumental findings. **(A)** Normal or impaired function of otolith receptors. **(B)** Normal or impaired function of semicircular canals. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. ASC, anterior semicircular canal; HSC, horizontal semicircular canal; PSC, posterior semicircular canal.

no vertigo" subgroup, 27/86 patients (31.4%) were assigned to the "SSNHL + vertigo" subgroup and the remaining 34 patients (39.5%) in "MD." Compete clinical and instrumental data of overall patients from each subgroup can be in found in Supplementary Tables a–c. Subgroups did not significantly differ in terms of patients' age ($p = 0.092$), time between symptoms onset and beginning of treatment ($p = 0.979$) and number of cardiovascular risk factors ($p = 0.394$).

3.2.1. Cochlear function

Presenting cochlear function was more affected in "SSNHL + vertigo" patients and less impaired in "MD" ($p < 0.05$; Figures 2A, B). HL configuration and degree with corresponding statistically significant different distribution among subgroups are reported in Figures 2C, D. In particular, subjects without vestibular symptoms mainly presented either with down-sloping or flat HL and with moderate to severe HL. Similarly, presenting HL of patients with "SSNHL + vertigo" was either flat or down-sloping; nevertheless, HL degree was higher than the other subgroups, being mild in only 3.6% and profound/anacusis in 44.4% of cases. On the contrary, "MD" patients mainly presented either with low-frequency or flat HL with mean PTA mostly ≤70 dB.

3.2.2. Otolith function

Saccular impairment as assessed through cVEMPs was more frequently registered in the group of "SSNHL + vertigo" patients (20/27, 74.1%, $p = 0.001$; Figure 3A) and, similarly, the extent of abnormal AR for cVEMPs was greater in the same subgroup compared to the others ($p < 0.05$; Figure 3B). While a positive frequency tuning for ipsilesional cVEMPs was more frequently found in MD patients (10/34, 29.4%, $p = 0.036$), there were no significantly different distribution of positive frequency tuning among subgroups in the contralateral ear ($p = 0.974$; Figures 3C, D). Conversely, neither the prevalence of utricular impairment as assessed by oVEMPs ($p = 0.416$) nor the AR of oVEMPs amplitudes ($p = 0.516$) significantly differed among subgroups (Figures 3E, F).

3.2.3. Canal function

As for SC function, the percentage of cases with HSC impairment on vHIT significantly differed among subgroups, being more frequently impaired in "SSNHL + vertigo" (8/27, 29.6%) and in "MD" patients (5/34, 14.7%; $p = 0.042$), albeit without significant different mean VOR-gain values (Figures 4A, B). The percentage of subjects with ASC impairment significantly differed among subgroups ($p = 0.044$) as all patients without vestibular symptoms (25/25, 100%) exhibited spared ASC function, and "MD" patients presented with significantly lower ASC VOR-gain values than patients without vestibular symptoms ($p = 0.04$; Figures 4C, D). Finally, PSC function was significantly more affected in the "SSNHL + vertigo" subgroups compared to the others in terms of both percentage of cases presenting with PSC impairment (15/27, 55.6%, $p < 0.001$) and mean VOR-gain values on vHIT (Figures 4E, F).

3.2.4. Vestibular lesion patterns

Patterns of otolith and SC impairment were analyzed and reported in Figures 5A, B, respectively, with corresponding statistically significant difference in distribution among subgroups. Overall distribution of otolith lesion patterns significantly differed among subgroups ($p = 0.022$), as the "SSNHL + vertigo" subgroup exhibited a smaller percentage of patients without otolith involvement (6/27, 22.2%) than other subgroups and, on the other hand, a higher percentage of cases with both saccular and utricular damage (13/27, 48.2%; Figure 5A). Conversely, while in the vast majority of "SSNHL no vertigo" and "MD" patients overall SC function was spared (22/25, 88% and 25/34, 73.5%, respectively), 62.9% of patients with "SSNHL + vertigo" (17/27) presented with at least 1 SC damaged. In particular, patients without vertigo only presented at most with a selective impairment involving either

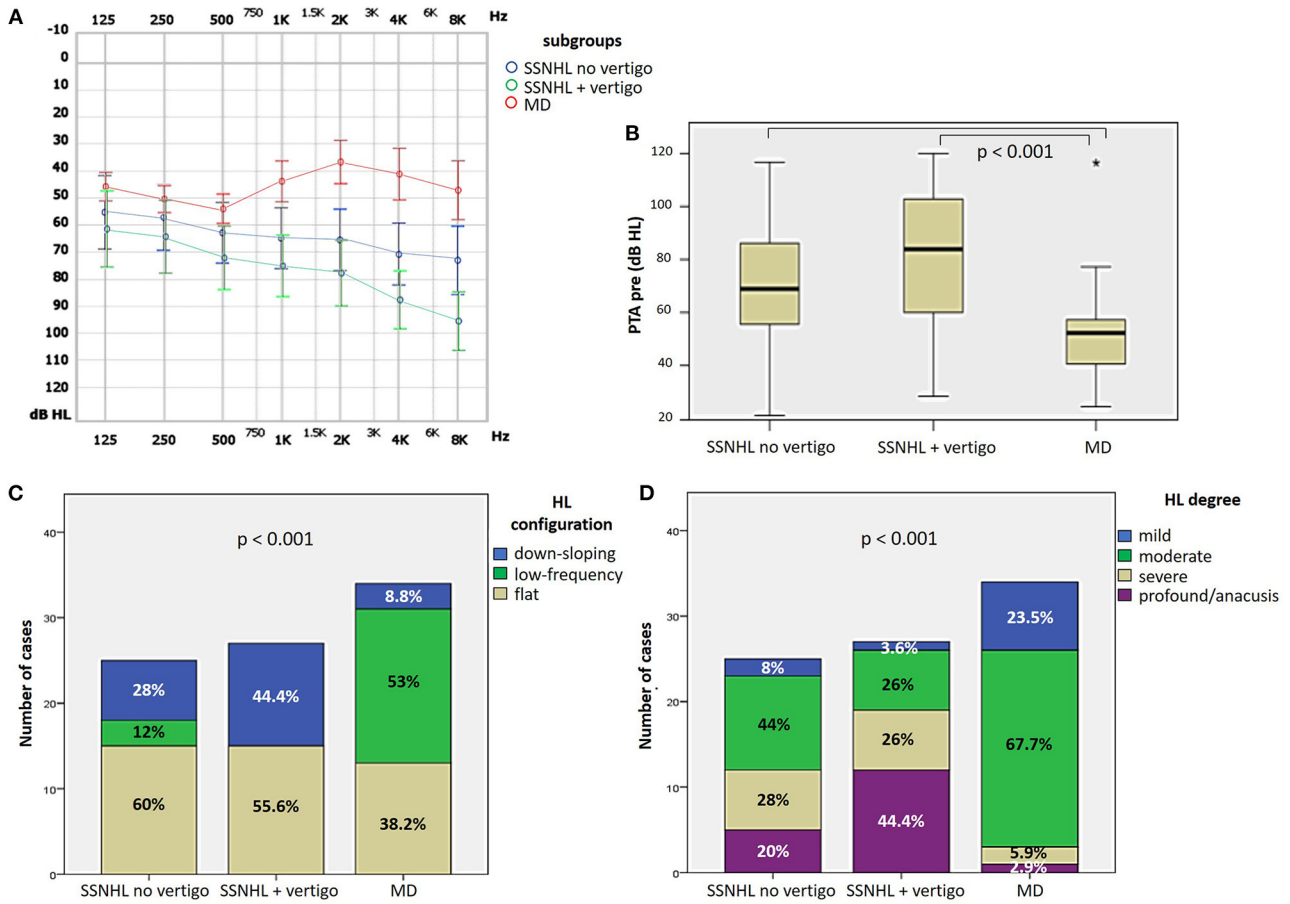

FIGURE 2
Presenting audiometric features of the affected ear of the overall cohort, divided in subgroups based on clinical course. **(A)** Audiogram. **(B)** Box plot correlating median values of PTA among subgroups. Statistically significant differences at the ANOVA test are shown. **(C, D)** Bar plots showing the number of cases presenting with different HL configurations **(C)** and different HL degree **(D)** among subgroups. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. HL, hearing loss; MD, Menière's disease; PTA pre, presenting pure tone average; SSNHL, sudden sensorineural hearing loss.

the HSC (1/25, 4%) or the PSC (2/25, 8%), whereas isolated PSC impairment represented the most frequent SC lesion pattern detected among "SSNHL + vertigo" patients (9/27, 33.3%). Conversely, the subset of "MD" patients presenting with canal dysfunction (9/34, 26.5%) most frequently exhibited a selective HSC impairment on vHIT (4/34, 11.8%) and represented the only cohort displaying a selective ASC damage (2/34, 5.9%). Furthermore, while simultaneous impairment of HSC and ASC could be only detected in "MD" patients (2/34, 5.9%), only the "SSNHL + vertigo" subgroup exhibited a SC impairment involving all the three SC (6/27, 22.2%; Figure 5B). Furthermore, the distribution within subgroups of the end organ lesion patterns and overall number of impaired vestibular receptors with the corresponding value of statistical significance ($p = 0.001$) is reported in Figures 5C, D, respectively. While the vast majority of patients included in the "SSNHL no vertigo" subgroup exhibited at most 1 impaired vestibular sensor (22/25, 88%), 91.2% of "MD" patients (31/34) exhibited at most 2 lesioned vestibular end-organs, whereas 66.7% of "SSNHL + vertigo" patients (18/27) displayed at least two involved sensors. Similarly, while more than three affected sensors could be detected in none in the "SSNHL no vertigo" subgroup, 2.9% (1/34) of "MD" patient presented with four impaired sensors and 22.2% (6/27) of patients with "SSNHL + vertigo" showed a complete vestibular damage. Noteworthy, no functional impairment of vestibular end-organs could be detected in five patients included in this latter subgroup (18.5%).

3.2.5. Video-Frenzel findings

As for spontaneous/positional nystagmus on video-Frenzel examination, none of the patients showed gaze-evoked nystagmus or other oculomotor signs attributable to CNS involvement. SN could be detected in 39.5% (34/86) of patients (Table 1), while PN could be found in only 20.9% of cases (18/86), presenting as horizontal apogeotropic PN in 11.6% (10/86), horizontal geotropic PN in 3.5% (3/86), paroxysmal upbeating PN consistent with ipsilesional PSC-BPPV in three cases (3.5%), persistent downbeating PN in one case and persistent upbeating PN in an additional case. While the distribution of SN greatly differed among subgroups ($p = 0.001$), a similar minority of patients among the 3 subgroups exhibited PN ($p = 0.101$; Figures 6A, B). In particular, in "SSNHL no vertigo" subgroup, while most patients presented neither with SN (21/25, 84%) nor with PN (19/25, 76%), a subset of patients exhibited either contralesional (i.e., paretic; 2/25, 8%) or ipsilesional SN (2/25, 8%) despite denying vestibular symptoms, and PN could be found in

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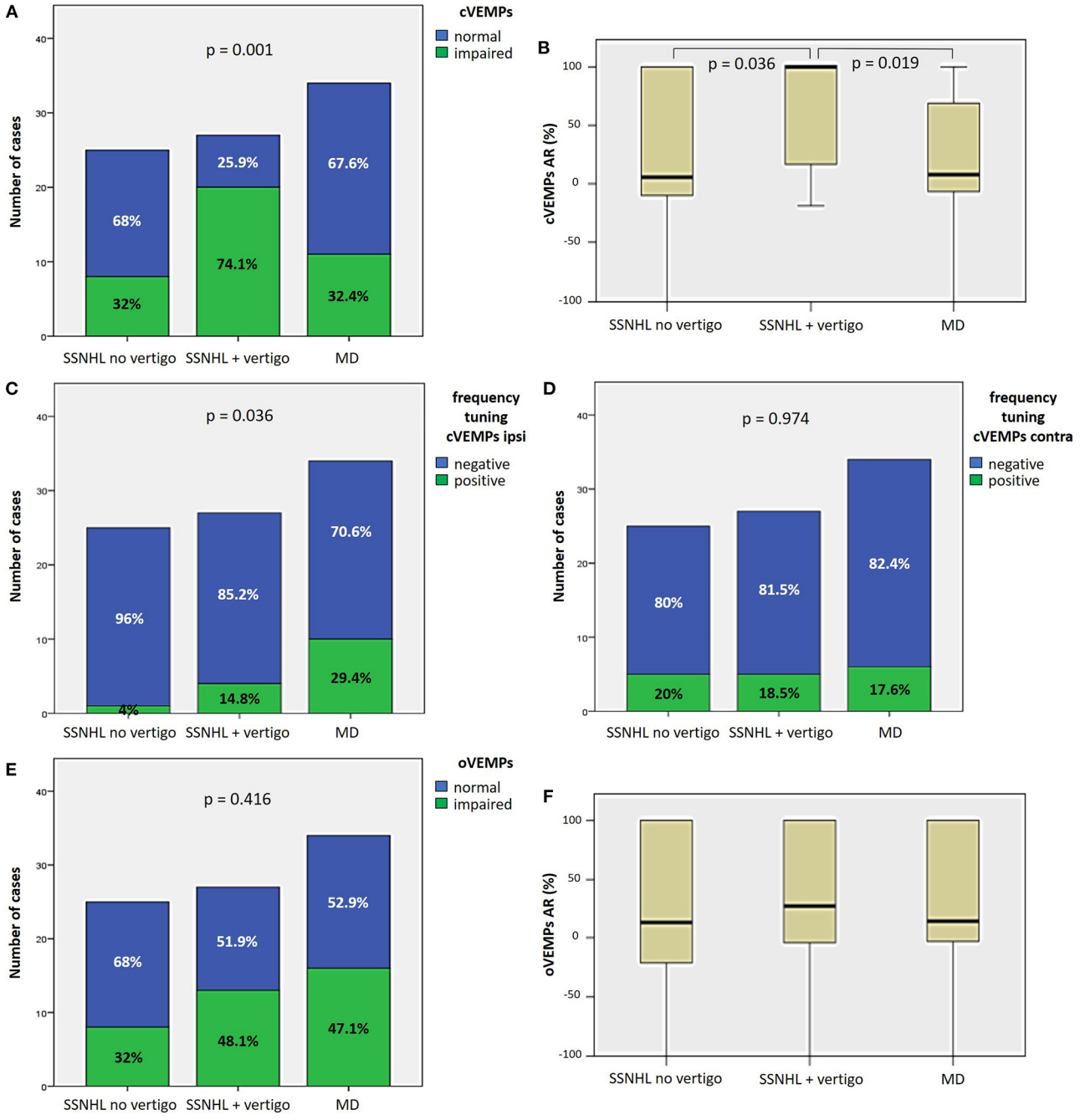

FIGURE 3
Different distribution of saccular **(A–D)** and utricular dysfunction **(E, F)**, as assessed by c and oVEMPs, respectively, among different subgroups based on clinical course. **(A)** Bar plot showing the distribution of impaired saccular function of the side affected by SSNHL among different subgroups. Relative percentages are reported in each column and *p*-value of categorical comparisons is reported. **(B)** Box plot correlating median values of cVEMPs AR among subgroups. Statistically significant differences at the ANOVA test are shown. Bar plots showing the distribution of positive frequency tuning of cVEMPs of the side affected by SSNHL **(C)** and of the contralesional side **(D)** among different subgroups. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. **(E)** Bar plot showing the distribution of impaired utricular function of the side affected by SSNHL among different subgroups. Relative percentages are reported in each column and *p*-value of categorical comparisons is reported. **(F)** Box plot correlating median values of oVEMPs AR among subgroups. No statistically significant differences at the ANOVA test are shown. AR, asymmetry ratio; contra, contralesional ear; cVEMPS, cervical vestibular-evoked myogenic potentials; ipsi, affected ear; MD, Menière's disease; oVEMPs, ocular vestibular-evoked myogenic potentials; SSNHL, sudden sensorineural hearing loss.

additional 6/25 patients (24%). On the other hand, the majority of "SSNHL + vertigo" patients presented with SN (16/27, 59.2%), being contralesional in most cases (13/27, 48.1%) while ipsilesional in only two cases and downbeating in 1; all patients with PSC-BPPV were included in this subgroup accounting for 11.1% of cases (3/27). Conversely, less than half of "MD" patients (14/34, 41.2%) presented with heterogenous types of SN, exhibiting mainly ipsilesional (i.e., either irritative or recovery) SN in 23.5% of cases (8/34), paretic SN

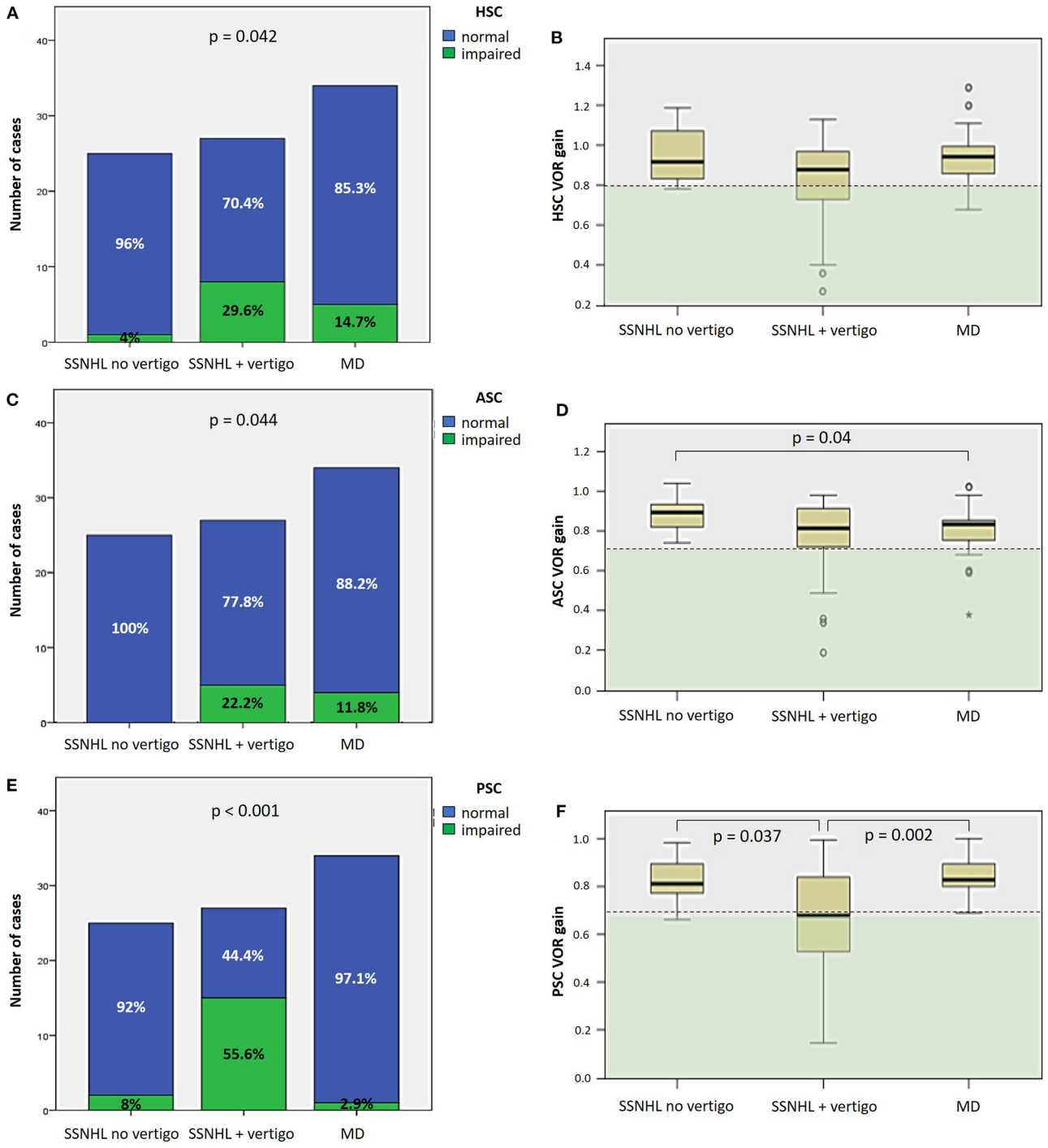

FIGURE 4
Different distribution of semicircular canal dysfunction, as assessed by vHIT, among different subgroups based on clinical course. **(A, C, E)** Bar plots showing the distribution of impaired HSC **(A)**, ASC **(C)** and PSC function **(E)** of the side affected by SSNHL among different subgroups. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. **(B, D, F)** Box plots correlating median values of HSC **(B)**, ASC **(D)**, and PSC VOR gain **(F)** among subgroups. Statistically significant differences at the ANOVA test are shown. ASC, anterior semicircular canal; HSC, horizontal semicircular canal; MD, Menière's disease; PSC, posterior semicircular canal; SSNHL, sudden sensorineural hearing loss; VOR, vestibulo-ocular reflex; vHIT, video-head impulse test.

in 8.9% (3/34), upbeating SN in 5.9% (2/34) and downbeating SN in 2.9% (1/34). The vast majority of them showed no PN (30/34, 88.2%), while only three (8.8%) presented with apogeotropic PN and only one case with persistent upbeating PN. Noteworthy, both upbeating SN and persistent upbeating PN could only be detected in "MD" patients. Details of remaining oculomotor findings on video-Frenzel examination for overall cohort including HSN, VIN and HVN are summarized in Table 1. HSN did not significantly differ among subgroups ($p = 0.424$), despite only in the "SSNHL no vertigo" subgroup head shakings neither elicited any detectable

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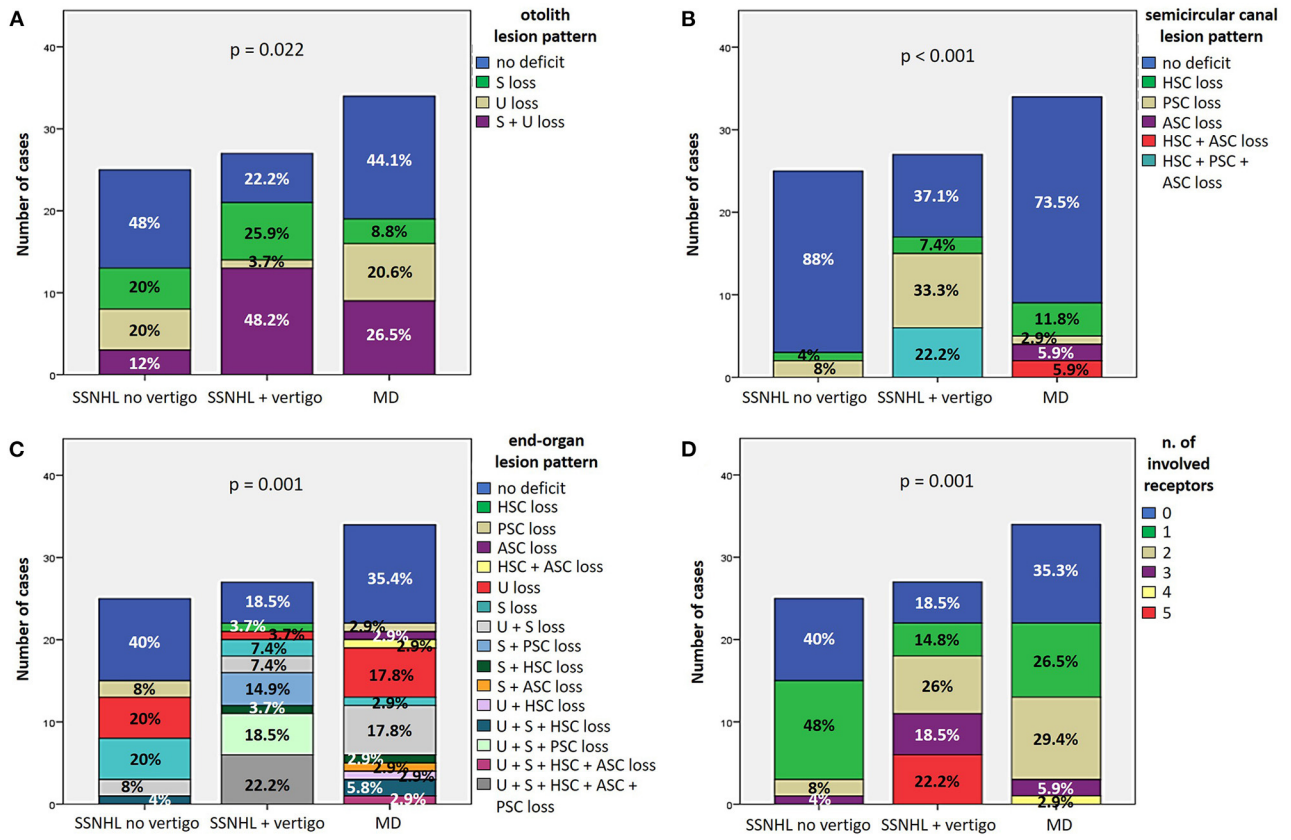

FIGURE 5
(A, B) Bar plots showing the different distribution of otolith **(A)** and semicircular canal **(B)** lesion patterns among different subgroups based on clinical course. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. **(C, D)** Bar plots showing the different distribution of end-organ lesion patterns **(C)** and the amount of impaired vestibular receptors **(D)** among different subgroups. Relative percentages are reported in each column and *p*-value of categorical comparisons is reported. ASC, anterior semicircular canal; HSC, horizontal semicircular canal; MD, Menière's disease; PSC, posterior semicircular canal; S, sacculus; SSNHL, sudden sensorineural hearing loss; U, utriculus.

TABLE 1 Video-Frenzel findings of the overall cohort of 86 patients.

	Absent (*n*, %)	Contra (*n*, %)	Ipsi (*n*, %)	Downbeating (*n*, %)	Upbeating (*n*, %)
SN	52/86 (60.5%)	18/86 (20.9%)	12/86 (14%)	2/86 (2.3%)	2/86 (2.3%)
HSN	53/86 (61.6%)	15/86 (17.4%)	8/86 (9.4%)	10/86 (11.6%)	0/86 (0%)
VIN	63/86 (73.2%)	12/86 (14%)	10/86 (11.6%)	1/86 (1.2%)	0/86 (0%)
HVN	75/86 (87.2%)	5/86 (5.8%)	5/86 (5.8%)	1/86 (1.2%)	0/86 (0%)

Contra, contralesional; HSN, head shaking nystagmus, HVN, hyperventilation nystagmus; ipsi, ipsilesional; SN, spontaneous nystagmus; VIN, vibration-induced nystagmus.

nystagmus nor significantly modified ongoing SN in the majority of cases (13/25, 52%). Conversely, contralesional HSN was more frequent among "SSNHL + vertigo" patients (11/27, 40.7%) while ipsilesional HSN was more frequently found among "MD" (6/34, 17.6%; Figure 6C). On the other hand, VIN significantly differed among subgroups ($p = 0.001$). In particular, whereas 25.9% (7/27) of "SSNHL + vertigo" subjects developed ipsilesional VIN, it was mainly contralesional in this subgroup (14/27, 51.9%), while it was absent in the majority of cases for the other subgroups (Figure 6D). Even HVN features and distribution did not significantly differ among subgroups ($p = 0.532$), as in the vast majority of cases hyperventilation test neither resulted in detectable eye movements nor modified ongoing SN (Figure 6E). Interestingly, only one case in the "SSNHL no vertigo" subgroup exhibited downbeating nystagmus after skull vibration and hyperventilation tests.

3.3. Hearing recovery

27.9% of cases (24/86) exhibited complete hearing restoration, 32.6% (28/86) developed partial recovery and 39.5% (34/86) had not hearing recovery, according to current guidelines (1). "MD" patients resulted in the best hearing function at 6-month follow up after treatment compared to the other subgroups ($p < 0.05$), as reported in Figures 7A, B. Even though "MD" exhibited a greater

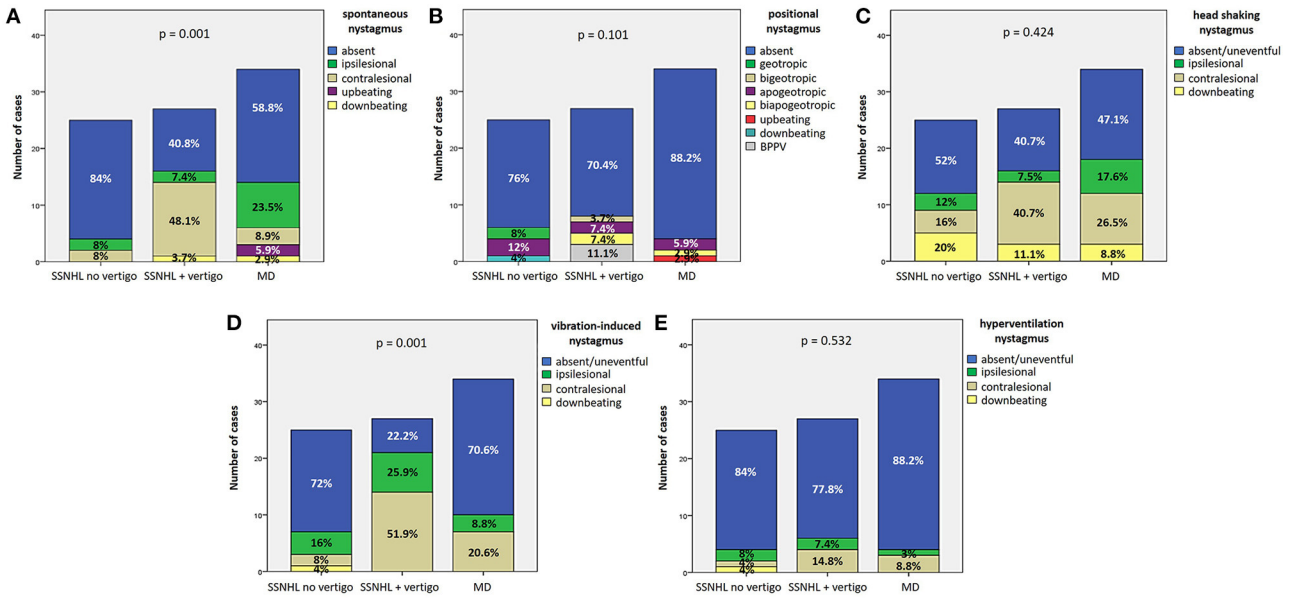

FIGURE 6
Bar plots showing the different distribution of the features of spontaneous **(A)**, positional **(B)**, head shaking **(C)**, vibration-induced **(D)**, and hyperventilation nystagmus **(E)** among different subgroups based on clinical course. Relative percentages are reported in each column and *p*-values of categorical comparisons are reported. MD, Menière's disease; SSNHL, sudden sensorineural hearing loss.

proportion of complete recovery (14/34 of cases, 41.2%) compared to other subgroups, no statistically relevant difference could be found in the distribution of different degree of hearing recovery among subgroups (Figure 7C). Once divided the overall cohort according to hearing outcome in "complete," "partial" and "no recovery," only saccular dysfunction resulted to be significantly associated with a poor prognosis ($p = 0.009$; Figure 8A). Even though the function of all sensors was more frequently impaired in cases with no hearing recovery and spared in cases with complete auditory restoration, nor utricular neither SC impairment significantly correlated with hearing outcome ($p > 0.05$; Figures 8B–E). The extent of inner lesion was significantly associated with hearing recovery; in particular, while the distribution of different types of hearing recovery did not significantly differ among patients divided according to the number of impaired vestibular receptors ($p = 0.301$; Figure 9A), there was a statistically significant negative correlation trend between the number of damaged sensors and the mean percentage of hearing recovery ($p = 0.002$; Figure 9B). The distribution of Fazekas score significantly differed among subgroups ($p = 0.02$; Figure 10A). Notably, while 88% (22/25) of subjects in "SSNHL no vertigo" subgroup and 88.2% (30/34) of "MD" patients exhibited at most grade 1 WML, "SSNHL + vertigo" patients exhibited the highest amount of WML, as 85.2% (23/27) of cases presented with at most grade 2 WML and all 4 patients with grade 3 lesions were included in this subgroup.

3.4. Vascular patterns: Association with presenting hearing loss and hearing recovery

Instrumental lesion patterns most likely consistent with an ischemic lesion of the inner ear were identified in 17.4% (15/86) of patients. Notably, two patients exhibited instrumental dysfunctions consistent with a VCA ischemic lesion (Figure 11, Supplementary Video 1), seven presented with clinical findings most likely due to a vascular lesion in the territory supplied by the CCA (Figure 12, Supplementary Video 2) and remaining six fulfilled diagnostic criteria of IAA occlusion (Figure 13, Supplementary Video 3). Interestingly, all of them belonged to the "SSNHL + vertigo" subgroup, accounting for more than half (15/27, 55.6%) of patients herein included (Figure 10B). Even HL configuration and degree significantly differed between patients presenting either with "vascular" or "non-vascular" lesion patterns. In particular, while all cases presenting with low-frequency SSNHL (21/71) were included only in the "non-vascular" subgroup, accounting for 29.6% of cases ($p = 0.007$), patients in "vascular" subgroups only presented either with down-sloping (8/15, 53.3%) or flat HL (7/15, 46.7%; Figure 10C). On the other hand, in more than half of patients presenting with "non-vascular" lesion patterns (39/71, 54.9%) a moderate SSNHL could be detected, and all cases with mild SSNHL (11/71) were included in this category, accounting for 15.5% of cases. Conversely, "vascular" cases never presented with mild SSNHL but mostly with either severe HL (6/15, 40%) or profound HL/anacusis (7/15, 46.7%; $p = 0.001$; Figure 10D). Additionally, different lesion patterns were found to have a significantly different impact on hearing recovery, as a full hearing restitution could only be obtained in patients exhibiting "non-vascular" lesion patterns (24/71, 33.8%), while all "vascular" cases could only reach either a partial (6/15, 40%) or no hearing recovery (9/15, 60%; $p = 0.026$; Figure 10E). Finally, we could confirm a clearly different distribution of MRI findings between patients either with "vascular" or "non-vascular" patterns of instrumental impairment ($p < 0.001$; Figure 10F). In fact, while almost half of "non-vascular" patients were lacking in WML on MRI (35/71, 49.3%), the vast majority of "vascular" patients (11/15, 73.3%) exhibited WML, including overall four patients with grade

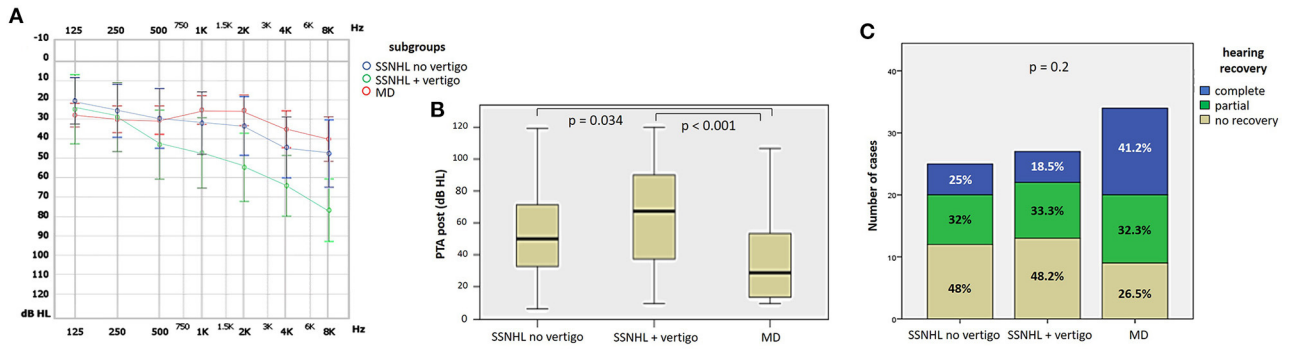

FIGURE 7
Final audiometric features at 6-month follow up of the affected ear of the overall cohort, divided in subgroups based on clinical course. **(A)** Audiogram. **(B)** Box plot correlating median values of PTA among subgroups. Statistically significant differences at the ANOVA test are shown. **(C)** Bar plot showing the different distribution of hearing recovery among different subgroups. Relative percentages are reported in each column and *p*-value of categorical comparisons is reported. MD, Menière's disease; PTA post, pure tone average at 6-month follow up; SSNHL, sudden sensorineural hearing loss.

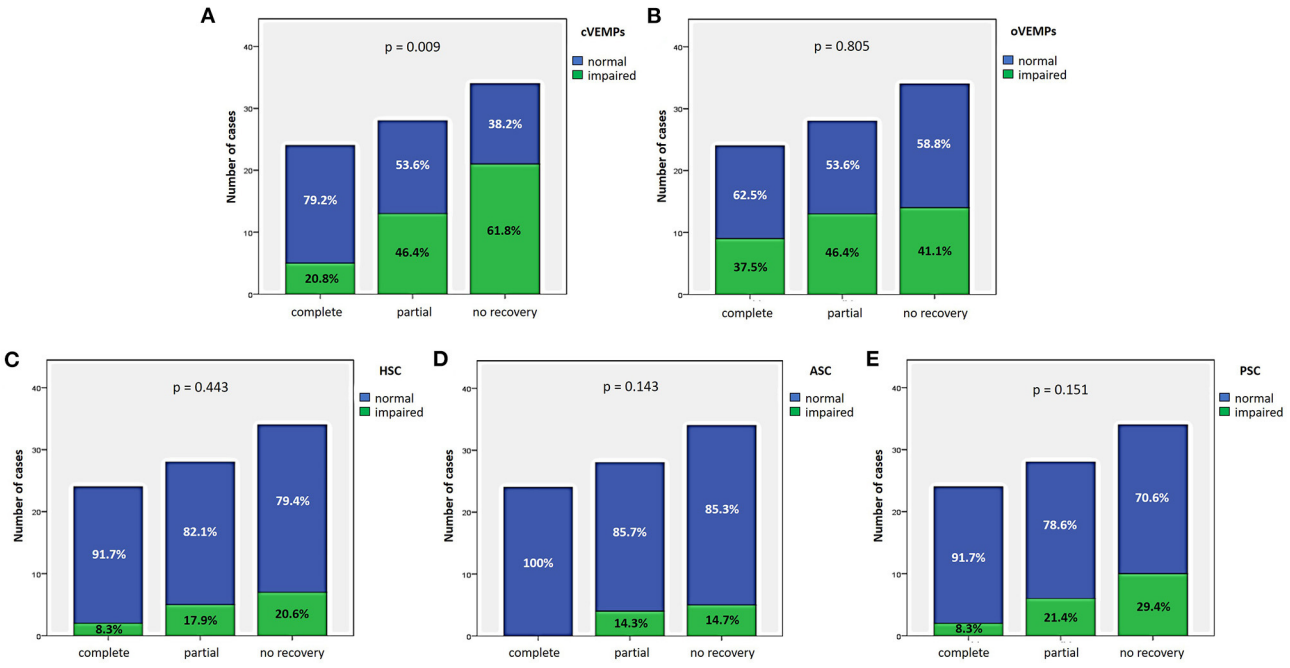

FIGURE 8
Bar plots showing the different distribution of otolith **(A, B)** and semicircular canal impairment **(C–E)** ipsilesionally to SSNHL, as measured by cVEMPs, oVEMPs, and vHIT, respectively, once divided the cohort according to hearing recovery. Relative percentages are reported in each column and *p*-value of categorical comparisons are reported. ASC, anterior semicircular canal; cVEMPs, cervical vestibular-evoked myogenic potentials; HSC, horizontal semicircular canal; oVEMPs, ocular vestibular-evoked myogenic potentials; PSC, posterior semicircular canal; SSNHL, sudden sensorineural hearing loss; vHIT, video-head impulse test.

3 WML according to Fazekas score, accounting for 26.7% of cases herein included.

4. Discussion

Predicting hearing outcome in SSNHL is still challenging, as well as detecting the precise pathomechanism accounting for symptoms and clinical findings. SSNHL could be associated with vestibular lesions since cochlear turns, otolith receptors and SCs share the same embryological origin and vascular supply. Moreover, besides being in close anatomical proximity, vestibular and cochlear hair cells provide afferents running through the internal acoustic canal in different but closely attached branches of the VIII cranial nerve. In fact, the VIII cranial nerve is composed by the cochlear nerve (CN) and the VN: while the latter receives fibers from both the superior and inferior VN, CN collects afferents from the entire spiral ganglion. In turn, the superior VN is composed of the lateral and anterior ampullary nerves and the utricular nerve, whereas the inferior VN is composed of the posterior ampullary nerve and the saccular nerve (63). On the other hand, the inner ear is supplied by the IAA, which branches from the anterior-inferior cerebellar artery (AICA) and divides into

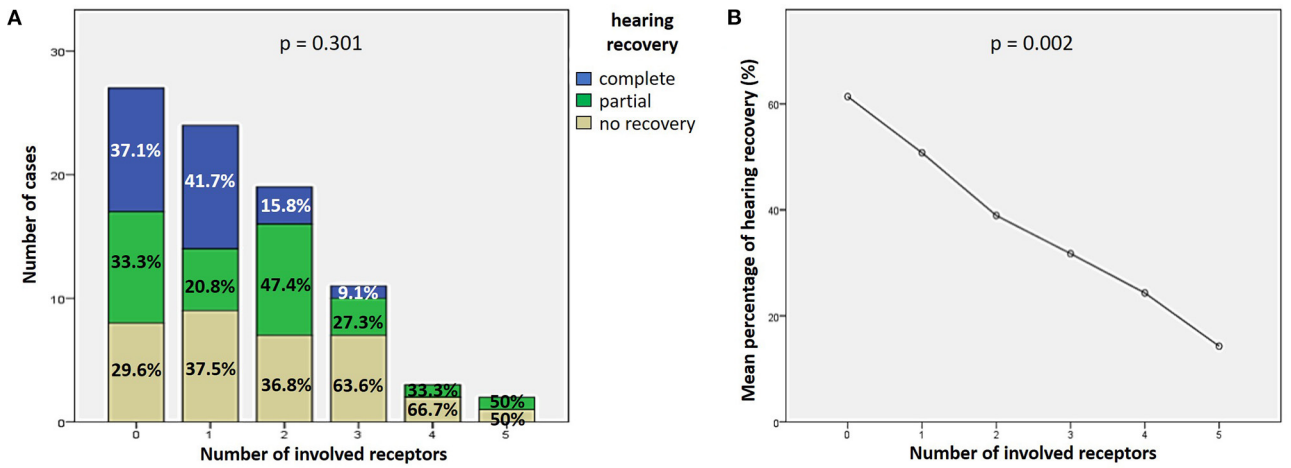

FIGURE 9
Correlation between the number of impaired vestibular receptors ipsilesionally to SSNHL and hearing recovery. **(A)** Bar plots showing the different distribution of hearing recovery among the study cohort divided according to the number of affected sensors. **(B)** Correlation trend between the number of impaired vestibular receptors and mean percentage of hearing recovery.

two main terminal branches: the anterior vestibular artery and CCA. Whereas, the first mostly supplies the utricle, the upper part of the saccule and both ASC and HSC, the latter mainly serves the cochlea, saccule, the lower part of the utricle and PSC. The VCA branches from the CCA and divides into the posterior vestibular artery, which provides blood supply to saccule and PSC, and the cochlear ramus that serves the basal turn of the cochlea. The main cochlear artery supplies the rest of the cochlear neuroepithelium. (63, 65–68). While selective damages to inner ear sensors (either cochlear or vestibular) could be attributed with certainty neither to neural nor to vascular damage, being possible both neuritis involving portions of VN/CN afferents and ischemia involving vestibular/cochlear end-organs, when SSNHL accompanies acute vestibular symptoms the lesion site should be searched within the labyrinth itself and an ischemic damage should be always suspected (73, 74). For example, while a selective lesion involving the sole PSC and saccule should orient toward a neural damage involving the inferior VN (54, 55), in the case of associated SSNHL a vascular damage should be considered, as the shared susceptibility of these structures may reflect the common vascular supply of the pars inferior of the labyrinth given by the CCA (29, 32, 57–59, 61, 62). Clinicians should be aware of this eventuality as it has been demonstrated how peripheral ischemic lesion may precede a posterior fossa stroke (69, 70). Even though neuritis involving both CN and VN have been described, likely due to a spreading of the damage through the anastomosis between the CN and the IVN (75–77), as well as an isolated ischemia involving the end-organs giving afferents into the superior VN or the inferior VN, likely due to an occlusion either of the anterior or posterior vestibular artery, respectively (73, 78, 79), the most easily assumable pathomechanism accounting for an acute cochleovestibular damage seems to be ischemia, in particular in the case an extensive instrumental assessment detects a precise lesion pattern overlapping the territories supplied by the IAA or its main branches. The lesion site of vestibular disorders in SSNHL with vertigo appeared to be within the labyrinth even on the basis of galvanic-VEMP findings (38). Configuration of HL might also provide useful informations in terms of pathophysiology. In fact, while low-frequency SSNHL is thought to be caused by the damage of the apical turns of the cochlea, an impairment of the higher frequencies should identify a damage of the basal turns. The latter cochlear portion is anatomically closer to vestibular organs, in particular the saccular macula, therefore it is easy to understand why high-frequency SSNHL tend to be more related to vestibular damages (27, 32, 39, 46). Nevertheless, some researches showed that also patients with low-frequency SSNHL tend to develop vertigo attacks (18, 19, 22). This data suggests that the anatomical position of the labyrinthine sensors and their topographical organization based on innervation and vascular supply may not fully explain the whole spectrum of symptoms in patients with SSNHL. In some of these cases, chemical and/or density alterations of perilymph and/or endolymph should be considered among pathomechanisms, since cochlear and vestibular partitions share the same inner ear fluids and are interconnected by surrounding membranes. Although its exact pathophysiology remains unclear, MD has been recognized as an idiopathic syndrome related to EH resulting in episodic vertigo attacks, fluctuating hearing loss, tinnitus, and aural fullness (18, 19, 22). Therefore, when SSNHL and vestibular symptoms coexist, in particular with an impairment of low tones on audiometry, EH and related disorders should always be investigated. Nonetheless, MD is a fluctuating disease, accounting for transient vestibulo-cochlear dysfunctions, and EH likely represents a common stage of different abnormalities presenting with similar symptoms. All these factors might account for the extreme heterogeneity of instrumental data related to MD, preventing the identification of specific patterns of audio-vestibular dysfunction for MD. In fact, different types of oculomotor findings, SC involvement and otolith alterations have been described based on the stage of the disease and the extent of EH (16, 20, 80–87). Although 3T MRI with delayed acquisition following Gadolinium infusion has demonstrated to detect EH in most patients with MD (13, 16, 17, 21, 24), physiological confirmation of EH is still useful for the diagnosis of MD in clinical setting. Due to the anatomical alterations that the hydropic inner ear develops over time, the coexistence of a reduced caloric response and normal HSC-VOR gin at the vHIT has been considered a hallmark of MD (17, 88).

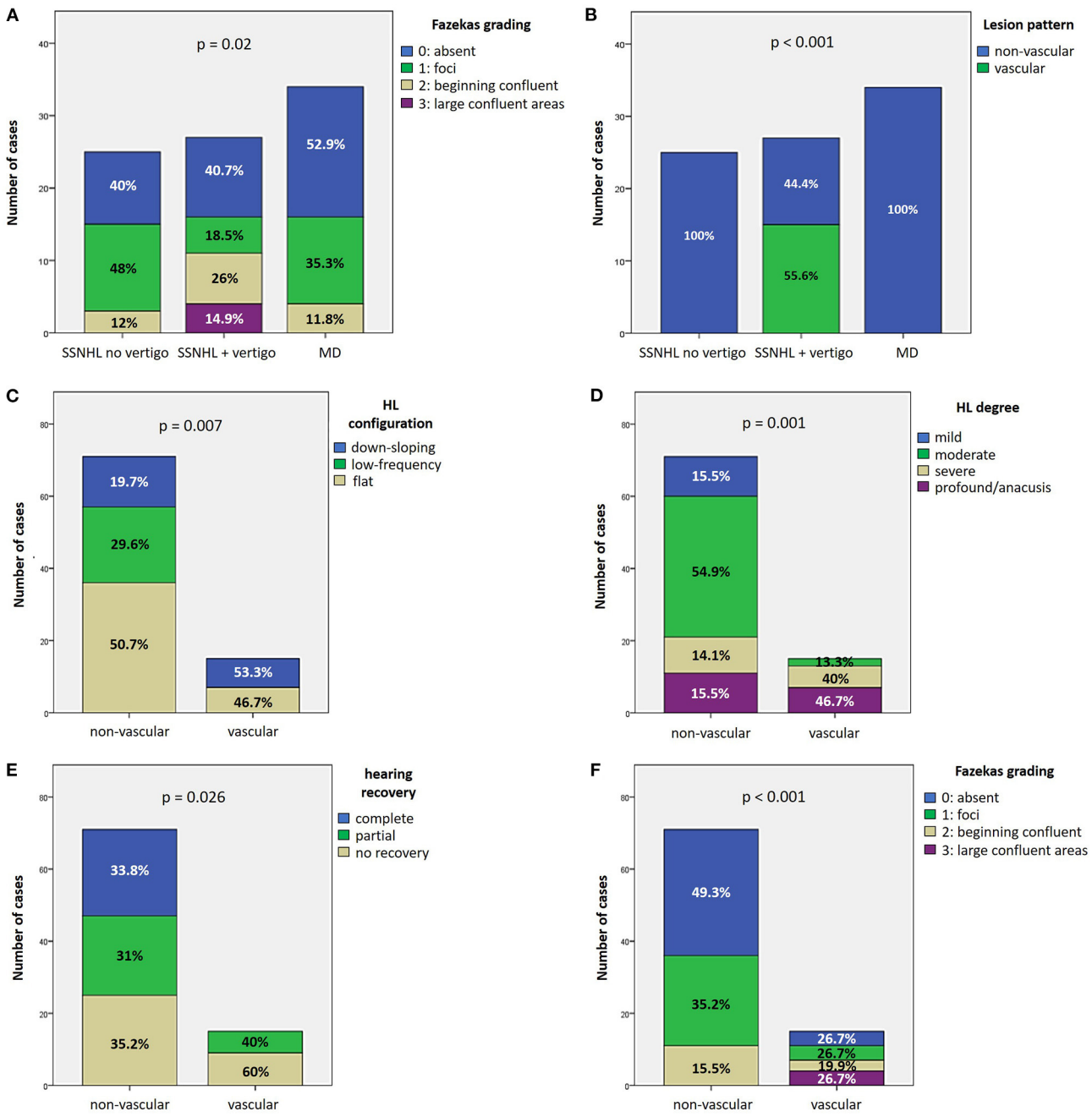

FIGURE 10
Vascular patterns. **(A, B)** Bar plots showing the different distribution of Fazekas grading of WML on MRI **(A)** and instrumental lesion patterns consistent with a vascular lesion **(B)** among the study cohort divided according to the clinical course. **(C–F)** Bar plots showing the different distribution of HL configuration **(C)**, HL degree **(D)**, hearing recovery **(E)**, and Fazekas grading of WML on MRI **(F)** among the study cohort divided according to the instrumental lesion patterns consistent with a vascular lesion. Relative percentages are reported in each column and *p*-value of categorical comparisons are reported. HL, hearing loss; MD, Menière's disease; SSNHL, sudden sensorineural hearing loss; WML, white matter lesions.

The tuning property test seems to represent another interesting and peculiar data supporting EH in MD, as these patients tend to show 1-kHz dominant VEMPs responses in comparison with VEMPs responses to 500 Hz due to saccular hydrops, while healthy subjects show 500-Hz dominant VEMPs responses (14, 15).

Given the aforementioned basis, it is easy to understand why vestibular assessment in SSNHL and its role in clinical presentation and hearing outcome have been widely explored in the literature. Most studies evaluated the vestibular function mainly through caloric testing, cVEMPs and oVEMPs, reporting contrasting data, in particular regarding its prognostic role. While most studies found that both abnormal caloric responses and, in general, the extent of inner ear damage correlate with the severity of HL and with poor recovery, there is no consensus on which vestibular end-organ is mostly involved and whether canal or otolith impairment is more closely related to worse hearing recovery (26, 28, 30, 31, 34–36, 38–50). One of the possible factors accounting for these discrepancies could be that comparing caloric test (which assess

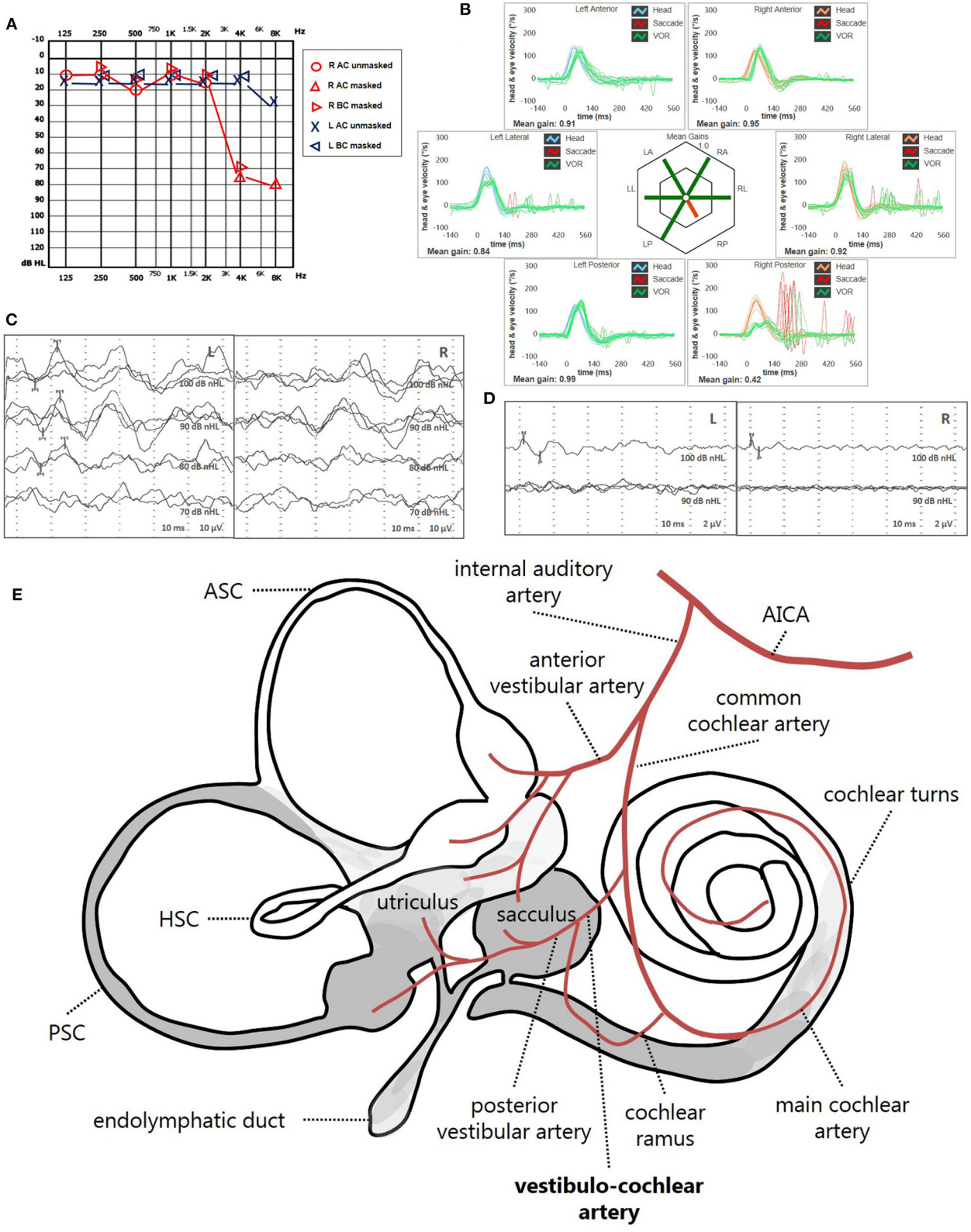

FIGURE 11
Presenting scenario of patients #42 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the right VCA (see also the Supplementary Video 1). **(A)** Pure-tone audiometry exhibiting high-frequency sensorineural HL on the right side. **(B)** vHIT showing a selective VOR-gain impairment for the right PSC (0.42) with overt saccades. **(C)** cVEMPs revealing absent potentials on the right side and normal responses on the left side (AR = 100%). **(D)** oVEMPs with potentials on both sides with an amplitude asymmetry within normality range (L > R, AR = 29%). **(E)** Schematic representation of the vascular supply of the inner ear, highlighting the assumed ischemic pathomechanism [modified from Schuknecht (63)]. Labyrinthine receptors mainly supplied by the VCA are represented in gray. AC, air-conduction; AICA, anterior-inferior cerebellar artery; ASC, anterior semicircular canal; BC, bone-conduction; cVEMPs, cervical vestibular-evoked myogenic potentials; HSC, horizontal semicircular canal; L, left; LA, left anterior; LL, left lateral; LP, left posterior; oVEMPs, ocular vestibular-evoked myogenic potentials; PSC, posterior semicircular canal; R, right; RA, right anterior; RL, right lateral; RP, right posterior; VCA, vestibulo-cochlear artery; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

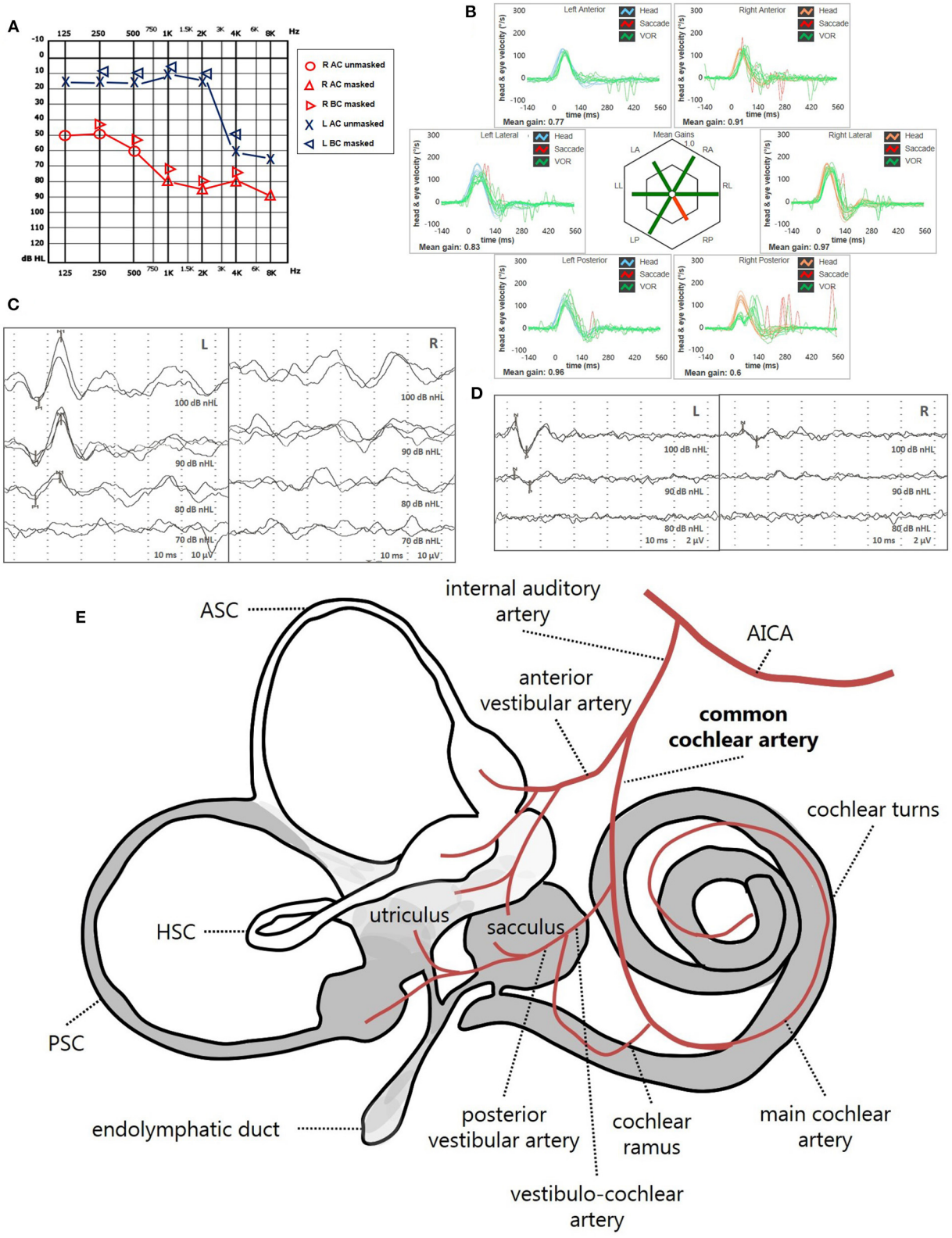

FIGURE 12
Presenting scenario of patients #64 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the right CAA (see also the Supplementary Video 2). **(A)** Pure-tone audiometry exhibiting severe down-sloping sensorineural HL on the right side. **(B)** vHIT showing a selective VOR-gain impairment for the right PSC (0.6) with both overt and covert saccades. **(C)** cVEMPs revealing absent potentials on the right side and normal responses on the left side (AR = 100%). **(D)** oVEMPs with potentials on both sides with an abnormal amplitude asymmetry (L > R, AR = 33%). **(E)** Labyrinthine receptors mainly supplied by the CCA are represented in gray. AC, air-conduction; AICA, anterior-inferior cerebellar artery; ASC, anterior semicircular canal; BC, bone-conduction; CCA, common-cochlear artery; cVEMPs, cervical vestibular-evoked myogenic potentials; HSC, horizontal semicircular canal; L, left; LA, left anterior; LL, left lateral; LP, left posterior; oVEMPs, ocular vestibular-evoked myogenic potentials; PSC, posterior semicircular canal; R, right; RA, right anterior; RL, right lateral; RP, right posterior; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

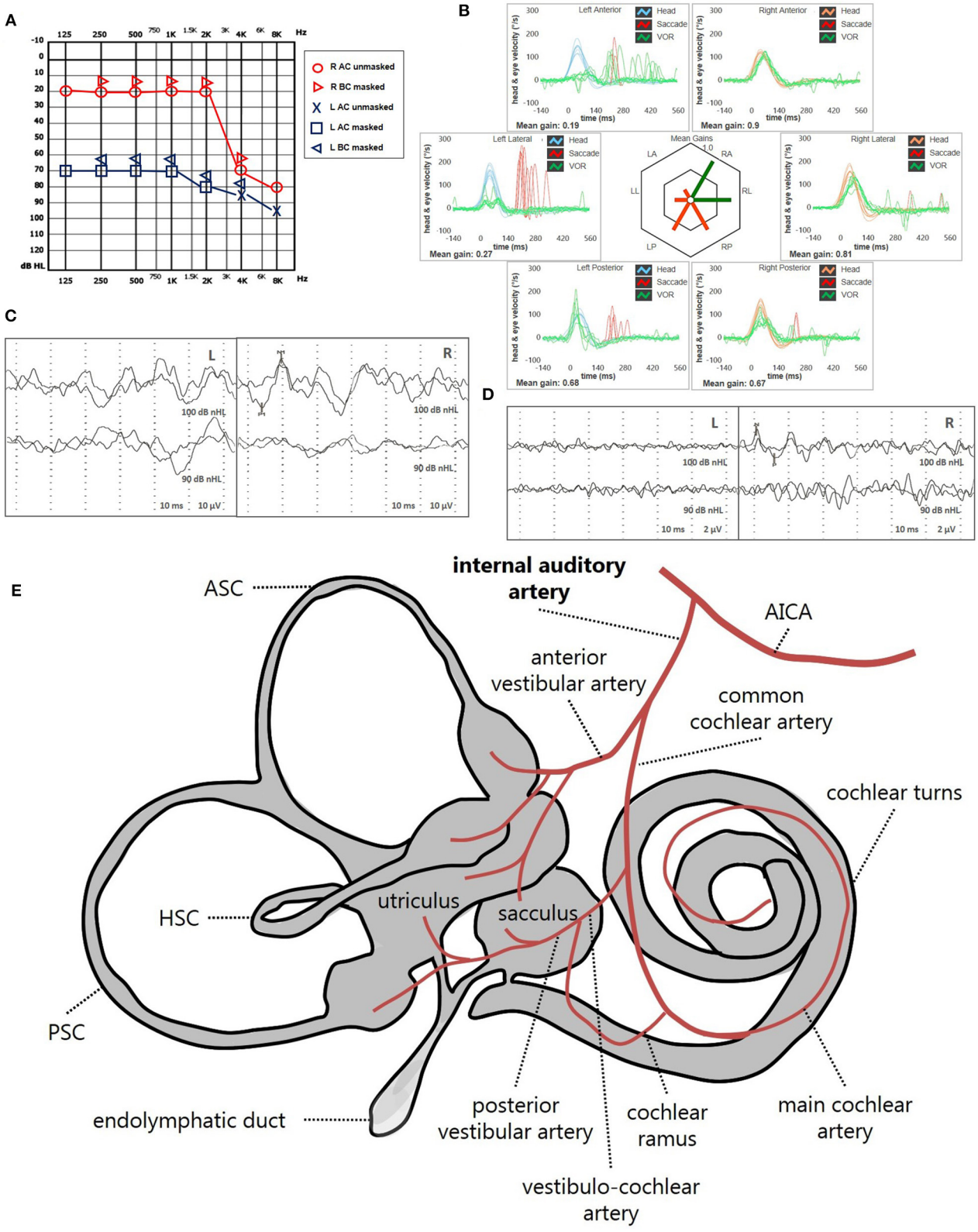

FIGURE 13
Presenting scenario of patients #59 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the left IAA (see also the Supplementary Video 3). **(A)** Pure-tone audiometry exhibiting severe flat sensorineural HL on the left side. **(B)** vHIT showing VOR-gain impairment for all the left SCs with mainly overt saccades. cVEMPs **(C)** and oVEMPs **(D)** revealing absent potentials on the left side and normal responses on the right (AR = 100%). **(E)** Labyrinthine receptors mainly supplied by the IAA are represented in gray. AC, air-conduction; AICA, anterior-inferior cerebellar artery; ASC, anterior semicircular canal; BC, bone-conduction; CCA, common-cochlear artery; cVEMPs, cervical vestibular-evoked myogenic potentials; HSC, horizontal semicircular canal; L, left; LA, left anterior; LL, left lateral; LP, left posterior; oVEMPs, ocular vestibular-evoked myogenic potentials; PSC, posterior semicircular canal; SC, semicircular canal; R, right; RA, right anterior; RL, right lateral; RP, right posterior; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

the low-acceleration response of the sole HSC) with VEMPs (which measures otolith reflexes in the high-frequency domain) does not seem to represent the most proper way to test vestibular end-organs. In fact, the higher vulnerability to various disorders of caloric responses might lead to biased topographic data on inner ear damage, as well as the different recovery behavior of different hair-cell populations might affect prognostic data. In recent years, since when the vHIT replaced the scleral search-coil system in the measurements of ampullary reflexes in the high frequency domain (52), the vestibular test battery in clinical setting has been extended to the evaluation of vertical SCs (29, 32, 34, 37, 49, 50, 57). According to the vast majority of the most recent investigations, PSC represents the most frequently involved SC in SSNHL, in particular when acute vertigo accompanies hearing symptoms (29, 32, 34, 37, 50, 57). Moreover, PSC hypofunction on vHIT appears to be a specific prognostic factor for incomplete hearing recovery, while impaired HSC VOR-gain has been related to mild and moderate SSNHL (34, 49). Oculomotor findings, including SN, PN and other evoked nystagmus, have also been investigated in SSNHL. According to the literature, the detection of SN seems to be related to PSC impairment, while it correlates with a higher incidence of recurrent HL in cases with low-frequency SSNHL. Additionally, BPPV seems to be associated with deeper HL and worse recovery rate (28, 50, 89). In particular, if the occurrence of BPPV ipsilesionally to SSNHL has been easily explained either with arterial occlusions or selective multiple vascular or neural involvement causing HL and otoconial release from the utricle, a change in density and viscosity of the endolymph by inner ear hypoperfusion or light/heavy debris attached to the cupula has been suggested as a possible cause of buoyancy mechanisms generating geotropic/apogeotropic PN, respectively (80–93). Similar biochemical alterations in the inner ear fluid exerting initially excitotoxic effect and then inhibition to vestibular afferents, along with central reorganization due to vestibular compensation, have also been assumed to explain spontaneous conversion of SN in SSNHL (94). Similar nystagmus behavior (both spontaneous and positional) has been registered both in the ictal and inter-ictal stage of MD, raising the question of whether the patients with SSNHL associated either to spontaneous direction-changing or positional direction-changing nystagmus should be considered as MD (80, 87, 94, 95).

In the present study, we aimed to evaluate the vestibular function in patients with SSNHL with or without vertigo and to explore its role in the prediction of hearing recovery and in the early detection of the underlying pathomechanisms. We hypothesized that the assessment of the vestibular function by means of vHIT, cVEMPs, and oVEMPs and the evaluation of SN, PN, HSN, VIN, and HVN through Video-Frenzel goggles might provide prognostic information and might suggest meaningful information for understanding the pathophysiology of the disease. We therefore divided the patients according to the clinical presentation and the evolution of symptoms, defining three different profiles: isolated SSNHL without vertigo ("SSNHL no vertigo"), SSNHL with acute vertigo ("SSNHL + vertigo") and MD ("MD"). Since it is well-known how patient's age, vascular comorbidities and time between onset of symptoms and treatment are considered the most influencing factors on hearing outcome (5, 6, 26, 96, 97), we preliminarily verified that those factors did not show statistically significant differences among subgroups in order to avoid bias during statistical analysis. As for vestibular function in the overall cohort, our data confirmed previous studies and systematic review stating that otolith organs were the most susceptible to damage in SSNHL (33, 35, 38), even if we did not find significant differences between otolith organs and among SCs ($p > 0.05$). Once exploring the differences among subgroups, hearing was more impaired in "SSNHL + vertigo" patients, who exhibited either down-sloping or flat-type audiogram, and was less impaired in "MD," where low frequencies were mostly impaired ($p < 0.001$). These results are consistent with previously reported data highlighting how HL is worse, in particular the highest frequencies, in patients with vertigo compared to non-vertigo (27, 32, 37, 51). Nevertheless, even a part of patients with MD exhibited down-sloping and flat HL, in accordance with other reports on "MD-like" patients (20, 21). Among otolith receptors, cVEMPs were more affected in patients with "SSNHL + vertigo" than other subgroups ($p = 0.027$) and, similarly, this population exhibited the highest rate of combined impairment of both cVEMPs and oVEMPs and showed the lowest percentage of isolated utricular deficit ($p = 0.022$), confirming how vestibular end-organs close to the cochlea tend to be preferentially affected in patients with vertigo (46). When exploring the tuning frequency of cVEMPs, in accordance with literature, we found that the rate of 1-kHz dominant VEMPs responses were higher in "MD" patients ipsilesionally to HL ($p = 0.036$) (14, 15). Nonetheless, only 29.4% of ears with MD exhibited a positive frequency tuning, while a small percentage of contralesional ears and of patients not fitting diagnostic criteria for MD presented with the same behavior. These discrepancies might be explained considering that all patients in our study cohort presented with the first episode of audio-vestibular symptoms, implying that MD patients herein investigated were at the earliest stage of the disease. Additionally, we gathered subjects with "definite" and "probable" MD in the same group; according to studies where potential differences between individuals with "definite" and "probable" MD were explored, Authors found that the dominant frequency shifted toward 1 kHz only in individuals with "definite" MD (14, 15). On the other hand, the visualization of EH through 3T Gadolinium-enhanced brain MRI in 65% of asymptomatic contralateral ears could account for the presence of a tuning shift toward higher stimulation frequencies also in non-MD subjects (13, 17). Another factor accounting for the presence of a positive tuning curve in non-MD patients might be the evidence of EH even in a subgroup of patients with idiopathic SSNHL, likely as a secondary reaction following a damage of inner ear sensors (21, 24). Interestingly, 14 patients exhibited an AR $\leq$-33% either for cVEMPs or oVEMPs. This peculiar lesion pattern due to an enhanced otolith reflexes of the affected ear has been described in the early stage of MD patients, likely due to an increased endolymphatic stiffness induced by an hydropic state of the vestibular compartment (81, 98). In line with this assumption, six of these patients were "MD," while five belonged to the "SSNHL no vertigo" subgroup and only three to the "SSNHL + vertigo" subgroup. Since 11 of these patients presented either with low-frequency or flat SSNHL, 10 of them with mild to moderate HL, while none of them exhibited a WML score >1, it is possible to assume that most of these cases developed EH in the affected ear. Although these patients exhibited neither a reduced VEMPs threshold nor conductive HL, and two of them developed a VOR-gain impairment for ipsilesional SCs (PSC in one case and ASC in the other), temporal bone high-resolution CT scan was scheduled to exclude a third window disorder. In fact, it has been

demonstrated how SC dehiscence might account for low-frequency HL, enhanced VEMPs responses and functional impairment of the affected SC at the vHIT on the same ear (99). As for vHIT data, the "SSNHL + vertigo" subgroup exhibited a higher prevalence of PSC loss compared to the others ($p < 0.001$), confirming previous results on SCs function in patients with sudden deafness and vestibular symptoms (29, 32, 34, 37, 49, 50, 57). Conversely, patients with "SSNHL no vertigo" exhibited the lowest rate of SC impairment even for HSC and ASC ($p < 0.05$). Only MD developed a SC lesion pattern consistent with isolated ASC involvement and HSC + ASC damage, while only patients with vertigo presented with all SCs impaired. Considering overall vestibular lesion patterns, patients with "SSNHL no vertigo" mainly presented either with no deficit, with isolated utricular loss or with isolated saccular loss, while "SSNHL + vertigo" subjects mainly developed either functional loss for overall receptors or PSC + saccular loss with/without utricular impairment. Conversely, despite MD exhibited the most heterogeneous findings, the most frequent patterns included either no sensor impairment, isolated utricular impairment or hypofunction of both otolith receptors ($p = 0.001$). Overall number of involved sensors was lowest for patients without vertigo and highest for those with vertigo ($p = 0.001$). As already reported in the literature, we noted that not all patients showing some degree of vestibular impairment complained of vertigo (in particular, 52% of cases without vertigo developed otolith dysfunctions) and, on the contrary, patients with vestibular symptoms did not always have vestibular function abnormalities on instrumental test (18.5%) (34, 37, 49). Either previous asymptomatic dysfunctions or damages with a slowly progressive onset leading to central compensation mechanisms could likely account for the lack of vestibular symptoms in subjects with altered vestibular data. Conversely, normal instrumental tests for patients with vestibular complaints strengthen the significance of data collected from temporal bones of patients with SSNHL where no direct relationship between the presence of vertigo and damage to the vestibular apparatus could be found. In these cases, it has been hypothesized that vertigo might be due to the transmission of biochemical changes in the inner ear fluid between cochlear and vestibular partition or that the damage could involve the extracellular superstructure (100, 101). It should also be considered the possibility that a fast functional recovery might occur in some damaged receptor, as the time span between the onset of symptoms and the evaluation was $\geq$3 days for all these patients.

SN behaved differently in the three subgroups, being absent in most patients without vertigo and MD, and mostly contralesional in the "SSNHL + vertigo" subgroup. Furthermore, MD subgroup exhibited higher rate of ipsilesional SN compared to others and was the sole subgroup exhibiting upbeating SN, while both "SSNHL + vertigo" and "MD" subgroups presented small percentages of downbeating SN ($p = 0.001$). These findings are in accordance with previous investigation (32, 50, 61, 80, 87, 94). Conversely, the three subgroups exhibited similar small rates of PN with some exceptions; in fact, only one patient without vertigo developed downbeating PN and only one MD patient exhibited upbeating PN. As reported in other studies (28, 32, 50), also three patients from the "SSNHL + vertigo" subgroup developed ipsilesional PSC-BPPV that resolved in all cases after appropriate canalith repositioning maneuvers. Noteworthy, only one patient exhibited utricular and HSC/ASC impaired as expected from an ischemic involvement of the anterior vestibular artery or from a neural damage involving the superior VN leading to an otolith dislodgment from the utricle. Irrespective of the underlying cause, this discrepancy can be explained with a faster recovery of these structures during the time between the onset of symptoms and clinical testing. Conversely, since the utricle receives a dual vascular supply, it might be assumed that otolith dislodgement might result from an ischemic lesion involving the territory supplied by a branch of the CCA. Additionally, two of the three patients who developed PSC-BPPV exhibited reduced VOR gain for the PSC involved. This apparently incongruent finding might be explained assuming a functional dissociation between "transient" and "sustained" vestibular system encoding angular accelerations (102). In particular, paroxysmal PN despite SC impairment on vHIT might imply a selective damage for type I hair-cells and irregular canal afferents (measured by vHIT) sparing the activity of type II hair-cells and regular fibers encoding cupular displacements which generates nystagmus (103–105). On the other hand, it may be assumed a different recovery time for damaged end-organs/afferents following acute labyrinthine injury, resulting in faster restoration for low-frequency responses compared to higher-frequency VOR (106, 107). Nevertheless, a possible role of the residual function of irregular afferents in the genesis of paroxysmal PN could not be excluded, as these patients did not develop a complete PSC loss on vHIT. Another interesting finding closely related to the aforementioned assumption is that only 50% (17/34) of patients presenting with SN exhibited a canal dysfunction at the vHIT, whereas at least an otolith receptor was impaired (mainly the utricle) in 11 cases. This atypical pattern was most frequently observed in "MD" subgroup, where 10/14 patients with SN did not exhibit canal impairment and the utricle was involved in five cases. Though this data might strengthen the hypothesis that SN might be generated by a selective utricular damage (108), it could also be assumed that in most of these patients an underlying EH could more likely dampen the activity of type II hair cells and regular afferents encoding low-frequency inputs, resulting in SN and in the classical dissociation between vHIT (spared) and caloric responses (abnormal) (17, 88). Unfortunatey, we could not confirm these hypotheses since caloric irrigations were not performed in our study. Another interesting finding is that nystagmus was detected in 72% of cases without vertigo, raising the hypothesis that some of them might develop in future a clinical picture consistent with MD.

Though HSN did not provide useful information to distinguish the three different subgroups, it is worthwhile to highlight that it elicited downbeat nystagmus in a small percentage of subjects. This finding, along with horizontal SN with no HSC VOR-gain impairment on vHIT or the sole vertical SN, could have been misdiagnosed as central disorders (2, 3, 109). Conversely, it has already been already demonstrated how vertical components perverted HSN in MD and acute vertigo with SSNHL might be related either to asymmetrically impaired vertical SCs (PSC more than ASC) or misorientation of the velocity storage mechanism (55, 62, 82). On the other hand, VIN behaved highly differently among subgroups. Given that it is known to represent a sensitive and simple clinical test for detecting peripheral vestibular asymmetry, it makes sense that it was mainly elicited in "SSNHL + vertigo" patients with contralesional direction ($p = 0.001$). Even though this group exhibited mainly PSC hypofunction, no downbeating VIN was detect as expected from an asymmetrical activation of the opposed

paired vertical SCs, but rather it was mostly horizontal as reported in the literature (77). This data might be explained assuming either an extent of ischemic damage to the only HSC hair-cells encoding low-frequency signals (thus not detectable with the vHIT) or by a previous wider damage involving the HSC, where only type-I hair-cells have recovered over time (61). The relatively lower percentage of VIN in MD patients in our cohort (29.4%) compared to literature might be explained recalling that all our patients were at the earliest stage of the disease and that SVIN is correlated with the severity of caloric hypofunction, likely mild in early-stage MD (110). Finally, rates of HVN were extremely low in all subgroups, strengthening the assumption that most pathomechanisms underlying SSNHL involve inner ear structures rather than VN/CN fibers (77, 111). In fact, HVN has been reported to occur in the case of alterations in the neuronal excitability in the vestibular system. In particular, ipsilesional HVN might be due to a transitory improvement of axonal conduction in partially demyelinated nerve fibers resulting from an increase in cerebrospinal fluid pH by hyperventilation, while brain vasoconstriction resulting from high-velocity deep breaths might affect the velocity storage mechanism which had restored the resting neuronal excitability after peripheral vestibular deficit, accounting for contralesional HVN (112). Nevertheless, it is well-known how hyperventilation can induce ipsilesional nystagmus in vestibular neuritis in the acute stage. The significance of our findings needs to be scaled back since a stratification of the behavior of HVN according to the time span from the onset of symptoms and evaluation was not pursued.

As for hearing recovery, the final HL was less impaired in "MD" and more impaired in "SSNHL + vertigo" subgroup ($p < 0.001$). Nevertheless, rates of hearing recovery did not significantly differ among subgroups. These data are in agreement with previous data on the better recovery low-tones SSNHL (19, 22, 42) and in that SSNHL patients with vertigo have a worse prognosis, while there is no difference in whole rate of hearing recovery between the different groups (27, 28, 37). Our data are also consistent with the literature on the correlations between vestibular function and hearing recovery. In particular, we confirmed that an incomplete hearing recovery is significantly associated with saccular impairment ($p = 0.009$) and with the number of impaired vestibular receptors ($p = 0.002$) (31, 33, 35, 37–39, 41, 42, 46, 51). Finally, we aimed to investigate whether "vascular" lesion pattern correlated with the worst hearing impairment at presentation and poorest prognosis. According to studies on inner ear vascularization and clinical reports, three specific lesion patterns seem to be assumable as "vascular" with cautious confidence, being otherwise hardly explainable (57–59, 61–63, 65–68):

- High-frequency SSNHL associated with an impairment for PSC VOR-gain, cVEMPs and with or without concurrent abnormal oVEMPs, due to a lesion involving the cochlear basal turn, the PSC, the saccule and possibly a part of the utricle, consistent with a selective occlusion of the VCA (Figure 11).
- Severe or profound SSNHL associated with an impairment for PSC VOR-gain, cVEMPs and with or without concurrent abnormal oVEMPs, due to a lesion involving more extensively the cochlear turns, the PSC, the saccule and possibly a part of the utricle, consistent with a selective ischemia in the territory mainly supplied by the CCA (Figure 12).
- Severe or profound SSNHL associated with an impairment of cVEMPs, oVEMPs and all three SC-VOR-gain, due to a complete inner ear damage, consistent with an IAA infarct (Figure 13).

According to our data, 17.4% of overall cohort exhibited a "vascular" lesion pattern. They were all part of "SSNHL + vertigo" subgroup and accounted for most patients herein included ($p < 0.001$), consistent with previous reports (29, 32). In general, these patients seemed to represent the part of the overall cohort with the worst hearing performance and prognosis, and the category with the highest WML score ($p < 0.001$), confirming the close relationship between these types of lesion pattern and vascular disease, and highlighting their poor HL at presentation ($p = 0.001$) and worse hearing recovery ($p = 0.026$). These findings are in line with animal studies on cochlear vulnerability to ischemia showing that 30 min hypoxia can induce irreversible cochlear damages (113), and also confirm previous data on the correlations among vascular disorders, severe SSNHL and worst outcome (7–10). These data should encourage further studies related to causes of ischemia and its therapy.

The prospective nature of the study with a complete vestibular assessment, along with the number of consecutive patients managed with a uniform treatment protocol, give strength to data obtained from the present study. Nevertheless, even though a substantial portion of SSNHL patients with/without vertigo seems to be related either to vascular disorders or MD, a considerable part of subjects with non-specific audio-vestibular findings still remains as unknown significance. Further clinical trials are needed to provide insights into unknown pathogenesis of the disease and establish evidence-based management. In addition, some limitations for this study exist. First, the inclusion of both "definite" and "probable" MD patients in both acute and inter-ictal stages could have affected the power of the statistical analysis. The use of well-recognized diagnostic tool for EH, such as electrocochleography and 3T brain MRI with delayed acquisition following Gadolinium infusion, could have surely helped in better differentiating MD patients from the other subgroups. Nevertheless, MD itself represents a multifactorial disease and a fluctuating disorder, resulting in heterogeneous findings. Continuous changings of inner ear function depending on the labyrinthine compartments involved and on the stages of the disease, including SC VOR-gain, cVEMPs and oVEMPs amplitudes, SN direction and other oculomotor findings, might have further ruined the data collection. Additionally, we did not include caloric test and rotatory test data to identify VOR lesions in the low frequency domain and for the midrange VOR function, respectively, even though they represent the tests mainly impaired in MD patients. Moreover, we could only test otolith pathways with AC sounds as it represents the only setting at our disposal in our institution, whereas it is well-known how bone conduction likely represents the best stimulus to obtain oVEMPs especially in elderly patients. Therefore, the applied method might have missed otolith pathology. Another shortcoming is represented by the wide range of days from the onset of symptoms and clinical evaluation (0–30). Asymmetrical recovery of the activity of different vestibular end-organs over time might have accounted for heterogenous data not fitting well established lesion patterns. Moreover, since both otolith organs receive a dual vascular supply from both the anterior vestibular artery and the

CCA, it might be possible that our definition of "vascular" pattern (always including saccular involvement) might have underestimated the prevalence of other labyrinthine ischemia sparing the saccular macula. Additionally, it should be considered that a transient inner ear ischemia may cause an incomplete pattern of labyrinthine damage according to individual inner ear organ susceptibility to ischemia. Nonetheless, we did not consider the possible lesion patterns matching the venous drainage system of the inner ear and it branches, which seems to play a pivotal role in defining the areas of highest vulnerability according to recent studies (114). It should also be considered that brain-enhanced MRI was completed within 3 months after the evaluation in all patients, which represents a large time span to potentially detect CNS lesions in a timely manner; for this purpose, an early inner ear MRI might have had more suggestive value for the determination of vascular lesions. Moreover, using the Fazekas score to detect a vascular burden in these patients might have introduced potential confounders in the analysis of results, considering that WML might be hard to classify as vascular or non-vascular or caused by different etiologies (i.e., migraine, arterial hypertension) and that the time correlation of SSNHL and WML could not be established. Finally, though we prospective enrolled consecutive SSNHL patients who were managed with a uniform treatment protocol, some biases might have arisen from different salvage treatments according to personal and logistical issues.

5. Conclusions

SSHL is a disorder which includes various clinical scenario and results from a variety of etiologies. Our data confirm that the assessment of vestibular function represents a valuable method to explore underlying pathomechanisms as it provides additional data on the involvement of inner ear receptors, supporting further understandings in labyrinthine function. Vestibular assessment should always be pursued in case of SSNHL, irrespective to vestibular symptoms, as it could be useful in the detection of the possible underlying pathophysiological mechanisms, in orienting treatment strategies and protocols aimed at preventing further inner ear impairment, and in the prediction of hearing recovery. Nevertheless, further studies are needed to confirm the clinical relevance of vestibular assessment in SSNHL.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Area Vasta Emilia Nord. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AC and CB led the conception of the study and conducted most data acquisition, data interpretation, data analysis, and made significant contributions to the writing and editing of the manuscript. AC conducted the creation of figures. SD, MB, FL, PB, RR, and LG contribute to data acquisition. PM, SM, and EA were involved in project conception and manuscript editing. LR, AG, and GB were involved in manuscript review. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1127008/full#supplementary-material

SUPPLEMENTARY TABLE a
Clinical-instrumental findings of the 25 patients fitting the "SSNHL no vertigo" subgroup.

SUPPLEMENTARY TABLE b
Clinical-instrumental findings of the 27 patients fitting the "SSNHL + vertigo" subgroup.

SUPPLEMENTARY TABLE c
Clinical-instrumental findings of the 34 patients fitting the "MD" subgroup.

SUPPLEMENTARY VIDEO 1
Video-Frenzel examination of patients #42 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the right VCA.

SUPPLEMENTARY VIDEO 2
Video-Frenzel examination of patients #64 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the right CAA.

SUPPLEMENTARY VIDEO 3
Video-Frenzel examination of patients #59 with an instrumental lesion pattern consistent with an ischemic damage in the territory mainly supplied by the left IAA.

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Binocular video head impulse test: Normative data study

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Introduction: The video head impulse test (vHIT) evaluates the vestibulo-ocular reflex (VOR). It's usually recorded from only one eye. Newer vHIT devices allow a binocular quantification of the VOR.

Purpose (Aim): To investigate the advantages of simultaneously recorded binocular vHIT (bvHIT) to detect the differences between the VOR gains of the adducting and the abducting eye, to define the most precise VOR measure, and to assess gaze dys/conjugacy. We aimed to establish normative values for bvHIT adducting/abducting eye VOR gains and to introduce the VOR dysconjugacy ratio (vorDR) between adducting and abducting eyes for bvHIT.

Methods: We enrolled 44 healthy adult participants in a cross-sectional, prospective study using a repeated-measures design to assess test–retest reliability. A binocular EyeSeeCam Sci 2 device was used to simultaneously record bvHIT from both eyes during impulsive head stimulation in the horizontal plane.

Results: Pooled bvHIT retest gains of the adducting eye significantly exceeded those of the abducting eye (mean (SD): 1.08 (SD=0.06), 0.95 (SD=0.06), respectively). Both adduction and abduction gains showed similar variability, suggesting comparable precision and therefore equal suitability for VOR asymmetry assessment. The pooled vorDR here introduced to bvHIT was 1.13 (SD=0.05). The test–retest repeatability coefficient was 0.06.

Conclusion: Our study provides normative values reflecting the conjugacy of eye movement responses to horizontal bvHIT in healthy participants. The results were similar to a previous study using the gold-standard scleral search coil, which also reported greater VOR gains in the adducting than in the abducting eye. In analogy to the analysis of saccade conjugacy, we propose the use of a novel bvHIT dysconjugacy ratio to assess dys/conjugacy of VOR-induced eye movements. In addition, to accurately assess VOR asymmetry, and to avoid directional gain preponderance between adduction and abduction VOR-induced eye movements leading to monocular vHIT bias, we recommend using a binocular ductional VOR asymmetry index that compares the VOR gains of only the abduction or only the adduction movements of both eyes.

KEYWORDS

binocular video head impulse test, conjugate gaze, adduction, abduction, ductional VOR asymmetry index, dysconjugacy ratio, monocular VOR asymmetry index, vestibuloocular reflex

Introduction

Accurate control of binocular eye movements is essential to direct the fovea of each eye at an object in the visual field. During locomotion, visual exploration requires coordination between gaze-stabilizing reflexes and gaze-shifting eye movements to ensure clear vision and depth perception. Failure of either system, or failure to achieve binocular coordination, results in blurred vision, diplopia, and loss of stereo acuity (1, 2).

The reflex that stabilizes gaze on a target, for example, during locomotion, by rotating the eyes in the opposite direction to head movement is the vestibulo-ocular reflex (VOR). The traditional measure of angular VOR function is gain, defined as the ratio of eye and head angular velocity.

Depending on the distance and eccentricity of the visual target during VOR-induced eye movements, the two eyes' lines of sight should be parallel when viewing distant objects (conjugate gaze) or intersect (converge) at the location of a near target. VOR gain increases as the fixated target moves closer to the observer (3–5), reflecting the interaction between the version and vergence systems in the VOR.

The video head impulse test (vHIT) directly quantifies VOR function by assessing VOR gain, and it objectively detects both covert and overt refixation saccades as an indirect sign of canal paresis. To date, the vHIT has mostly been used monocularly. Binocular vHIT would allow simultaneous recording of the movements of both eyes resulting from VOR activation by a head impulse. Importantly, the nasal movement of the ADducting (AD) eye and the temporal movement of the ABducting (AB) eye could be analyzed separately. The need for an accurate binocular head impulse test was highlighted in 2008 in a study using a gold standard scleral search coil to measure head and binocular eye movements (6). The study showed that the difference between the gains of the adducting and abducting eye reached 15.3% at head accelerations greater than 3,234 °/s^2 (6). However, when only abduction gains were compared between both eyes, VOR symmetry was stable across all head accelerations. While accurate VOR measurement is a prerequisite for the diagnosis of unilateral vestibular loss, the disadvantage of using a monocular vHIT system is a directional gain preponderance of adduction over abduction VOR eye movement responses (6, 7). Therefore, it is crucial to minimize this bias, for example, by calculating the adduction- or abduction-related gains from the binocular recordings. Based on the lower variability, the search coil study recommended analysis of the VOR gains of the abducting eyes to obtain directional symmetry of VOR gain measurements in normal subjects.

Study aims

Although these findings highlighted the need for binocular vHIT, normative ranges for binocular vHIT (bvHIT) have not yet been established.

The HIT has the potential to assess not only peripheral vestibular function by evaluating the VOR gain response but also the complete VOR arc with its nuclear, internuclear, and infranuclear pathways, including the oculomotor nerves and muscles. Simultaneous binocular recording adds the ability to assess the central pathways by comparing centrally controlled conjugate eye movements between the adducting and abducting eyes. Our study aimed to establish normative ranges for adduction-and abduction-related VOR gains and to introduce a dysconjugacy ratio (vorDR) (8) between the two.

Methods

Participants

We measured 44 healthy adults (22 male, 22 female, 20 to 70 years of age, mean age 35, SD 12.5) in a prospective cross-sectional study using a repeated-measures design.

Standard protocol approvals, registrations, and patient consent

Before including a participant in this study, we received their written informed consent. The protocol was approved by a local ethics committee and was in accordance with the Declaration of Helsinki (Reference number 202106 P08). The inclusion criterion was a negative history of any balance disturbance or of any oculomotor deficit due to an underlying neurological condition.

Study device

For simultaneous recordings of head and binocular eye movements, we used a binocular EyeSeeCam Sci 2 device (EyeSeeTec, Munich, Germany) (Figure 1). The study device is a successor version of the previous EyeSeeCam Sci 1 and Interacoustics EyeSeeCam vHIT (Interacoustics, Middelfart, Denmark) systems. Attached to the new goggles, there was a pair of synchronized high-speed cameras which tracked the pupil to determine eye position at sampling rates of either 500 Hz or 250 Hz. For this study we used the lower sampling rate of 250 Hz. An inertial measurement unit integrated into the left camera measured angular head velocity at the same sampling rate.

Study methods

Participants were seated 3 meters in front of a fixation dot on a white wall. The fixation dot was black, it contained two lines crossing at the center, and had a diameter of 5 cm, which provided a good fixation target also for myopic participants. The target distance of 3 m was chosen to minimize the effect of vergence on

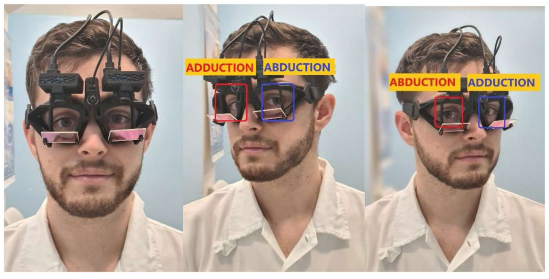

FIGURE 1
Binocular vHIT (EyeSeeTec Sci 2): Two high-speed cameras are attached to tightly fitting goggles. Note the ductions of the right (red) and left (blue) eyes during rightward and leftward impulses.

VOR gain, as it is well known that VOR gain increases with decreasing target distance (3, 9) and that this effect vanishes at distances of more than 2 meters (4). First, the study device was calibrated with the participants sequentially fixating five laser dots on the wall 3 meters in front of them. The dots were projected from a goggle-mounted laser and a diffraction grating. After calibration, 14 horizontal head impulses were completed (7 to both sides) during each test. The examiner grasped the head of a participant from behind and moved it briskly from center to each side with unpredictable timing and direction, aiming at an angular displacement amplitude of 20° and a peak velocity in the range of 150° to 250°/s. To assess test–retest reliability, the sequence consisting of calibration and seven impulses in both the left and right directions was repeated a second time by the same examiner (MS), who had a seven-year clinical experience in using vHIT. The sequence was repeated immediately if any technical error was noted. Test–retest was applied to all participants within one session to avoid biases caused by changes in their health status.

Invalid impulses, artifacts, goggle slippage

The proprietary algorithm classified impulses as valid if no eye blinks or other artifacts were detected. Invalid impulses were discarded from the analysis. The remaining valid impulses were subsequently inspected visually for remaining artifacts. Impulses with artifacts not detected automatically were manually removed using the interactive Traces Editor of the EyeSeeCam Sci 2 software. Only goggle slippage or pupil detection artifacts, but not VOR gain or the presence of corrective saccades, were used as criteria to remove impulses. On average, 6.5 (range four to seven) out of seven impulses per measurement were considered valid to remain in the data set for analysis. The recordings of five subjects were excluded from the study due to an insufficient number (less than four) of valid impulses without artifacts. Thirty-nine subjects were used in the data set (20 male, 19 female, mean age 36, SD 13).

Metrics

Our study used vHIT gains, dysconjugacy ratios, and asymmetry indexes as continuous quantitative metrics. We analyzed the binocular results of three different vHIT gain calculation methods reported by the EyeSeeCam Sci 2 system: (1) Regression gain (10, 11); (2) Instantaneous gain at 60 ms (10, 11); (3) Median gain 0–100 ms calculated as the median of the ratios of eye and head velocity medians in a window between 0 and 100 ms. For all metrics, the EyeSeeCam Sci software also reported the standard deviations (SD) calculated from the four to seven valid stimulations.

Furthermore, the question of how conjugate and symmetrical the VOR eye movements are was addressed by deriving further ratios and indexes from the reported gain values for both the left and right eyes as well as for both leftward and rightward head impulse directions. Asymmetry indices were calculated in analogy to previous definitions of VOR asymmetry indices (6, 9). Abbreviations used in the succeeding equations are defined in the contingency table in Table 1.

Monocular VOR asymmetry index

To assess the possible directional gain preponderance between AD and AB eyes, we first evaluated the monocular recordings of each of the two cameras separately. As most head-mounted vHIT devices provide only one camera, clinicians are familiar with the evaluation of such monocular recordings. We compared left- and rightward impulse gains monocularly analyzed from each eye to evaluate monocular VOR asymmetry (Figure 2). We calculated the monocular VOR asymmetry index (m-vorAI) by using Eq. 1 and the abbreviations from Table 1. The equation contains the absolute value of the difference between gains in the numerator.

Eq. 1:

(a) Right Eye (RE) Monocular VOR asymmetry:

$$RE\_m\text{-}vorAI = | AD_{RE} - AB_{RE} | / (AD_{RE} + AB_{RE}) \times 100\%.$$

(b) Left Eye (LE) Monocular VOR asymmetry:

$$LE\_m\text{-}vorAI = | AD_{LE} - AB_{LE} | / (AD_{LE} + AB_{LE}) \times 100\%.$$

Ductional VOR asymmetry index

To avoid the effects of directional gain preponderance on VOR asymmetry typically obtained from monocular recordings (6, 7), and to assess the most precise VOR asymmetry metric, we computed ductional VOR asymmetry indices (vorDAI) separately for ADduction and ABduction eye movement responses to left- and rightward head impulses. Specifically, the ADduction asymmetry is calculated from only adducting eyes during impulsive testing: rightward impulses from the right eye and leftward impulses from the left eye (Figure 3), and vice versa for ABduction (calculated from both ABducting eyes). The vorDAI were calculated using the abbreviations from Table 1 in Eq. 2, which contains the absolute value of the difference between ductional gains in the numerator:

Eq. 2:

(a) ADduction VOR asymmetry index:

$$AD\_vorDAI = | AD_{RE} - AD_{LE} | / (AD_{RE} + AD_{LE}) \times 100\%.$$

(b) ABduction VOR asymmetry index:

$$AB\_vorDAI = | AB_{RE} - AB_{LE} | / (AB_{RE} + AB_{LE}) \times 100\%.$$

Binocular vHIT dysconjugacy ratio

To assess eye movement dysconjugacy and to evaluate the contribution of central inter- and infra-nuclear oculomotor

TABLE 1 Contingency table mapping leftward and rightward impulse directions as well as left and right eyes to color-coded abbreviations for AD- and ABduction.

		Impulse direction	
		Rightward	Leftward
Eye	Right (RE)	AD_{RE}	AB_{RE}
	Left (LE)	AB_{LE}	AD_{LE}

During the rightward impulse, the right eye (red) ADducts, and the left eye (blue) ABducts (in the "Rightward" column) to follow the target. During the leftward impulse, the right eye (red) ABducts, and the left eye (blue) ADducts.

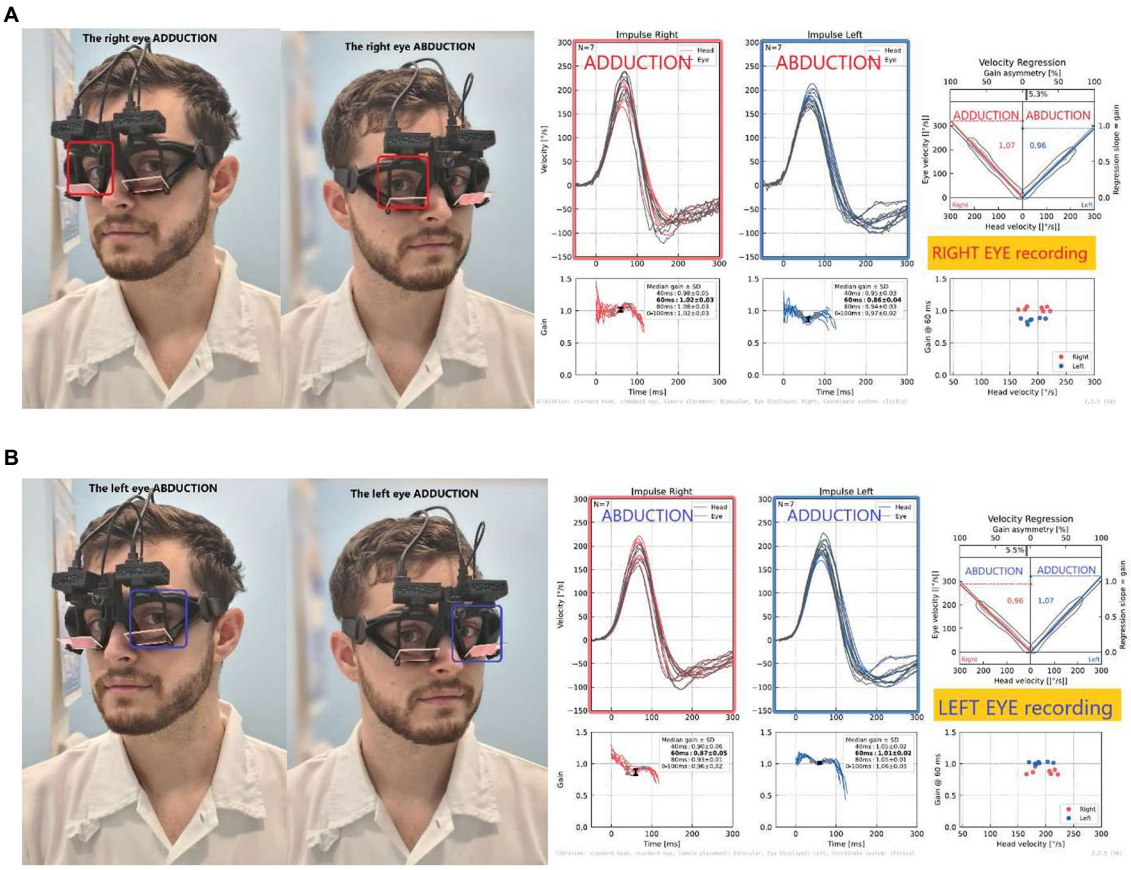

FIGURE 2
Monocular recordings from the right **(A)** and left **(B)** eyes: Note the higher gain during right impulse on the right ADducting eye **(A)**, while opposite on the left eye **(B)**, demonstrating the directional gain preponderance when recorded only from one eye (left or right). Monocular VOR asymmetry calculated for the right eye; in this case, RE_m-vorAI was 5% asymmetry, the same for the left eye.

pathways to the execution of vestibularly-induced conjugate eye movements, we compared the same direction impulses recorded simultaneously from both eyes. For example, during a leftward head impulse, we measured the adduction response of the left eye, and the abduction response of the right eye (Figure 4). To quantify eye movement dys/conjugacy during impulsive testing, we propose the use of a bvHIT dysconjugacy ratio (vorDR) between ADducting and Abducting eyes during the same direction impulse recorded from both eyes, as previously suggested in the literature (8). We defined the vorDR for bvHIT such that ADduction is in the numerator, giving a value >1 when the ADduction (AD) gain is greater than the ABduction (AB) gain. The calculation is based on the direction of an impulse, which allows the assessment of both unidirectional dysconjugacy, such as an isolated oculomotor deficit in unilateral INO, or bidirectional dysconjugacy, such as bilateral INO.

Eq. 3:

(a) Rightward impulse dysconjugacy ratio:

$$\text{Rightward\_vorDR} = AD_{RE} / AB_{LE} .$$

(b) Leftward impulse dysconjugacy ratio:

$$\text{Leftward\_vorDR} = AD_{LE} / AB_{RE} .$$

Statistical analysis

A repeated-measures study design with three within factors, each with two levels, was used: duction (ABduction, ADduction), eye (left, right), and repetition (test, retest). Continuous normally distributed data are reported as mean (SD), with standard deviation in parentheses. Indices are reported as median (IQR), with interquartile range in parentheses. Statistical computations were conducted with JASP (JASP Team, 2022), Python (Version 3.9) with Pandas (Version 1.3.2), and R (R Core Team, 2022). All metrics were tested for normality by visual inspection of qq plots and subsequent Shapiro–Wilk testing. Levene's test was used to verify variance homogeneity. Differences and interactions in VOR gains between factor levels were assessed with a repeated measures analysis of variance (ANOVA). Both frequentist and Bayesian analyzes were performed for repeated measures ANOVA. For frequentist analyzes, $p < 0.05$ was considered statistically significant. Separate tests were performed for the metrics instantaneous gain, median gain, and regression gain.

The distributions of gains as well as derived dysconjugacy ratios and asymmetry indexes were assessed visually using qq plots and tested for normality using Shapiro-Wilks tests. F-tests of within-subject SD were used to answer the questions of (1) which gain calculation method, (2) which duction level

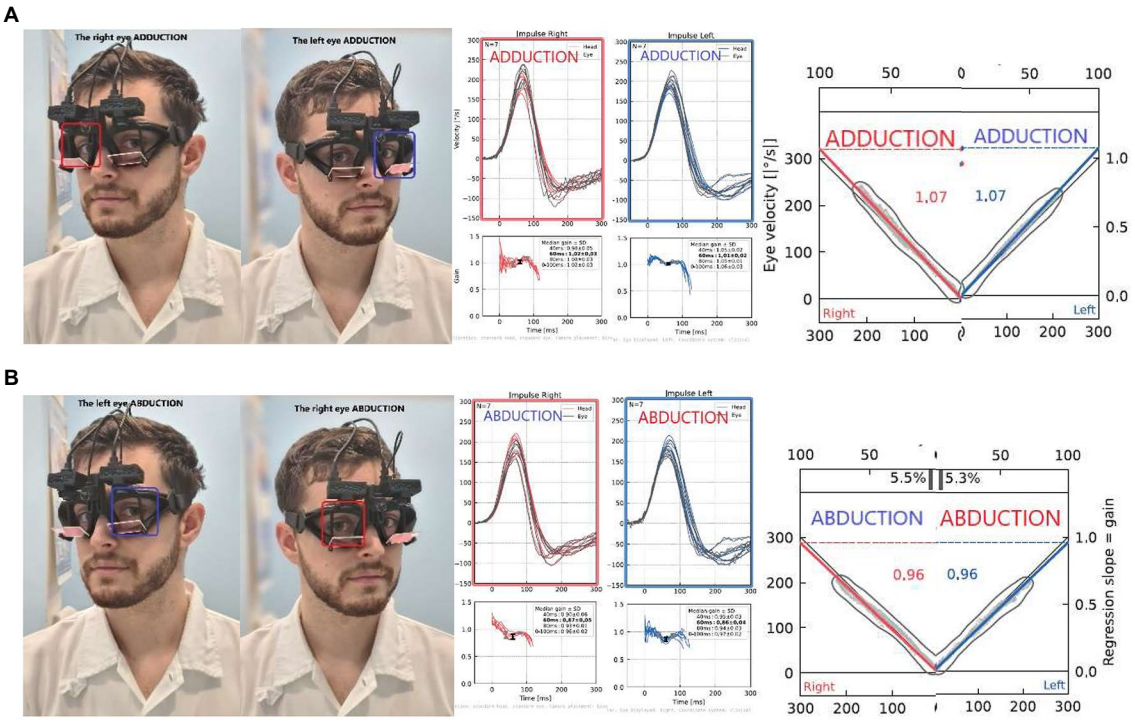

FIGURE 3
Ductional VOR asymmetry of one participant: Comparison of left and right impulses recorded from only ADducting **(A)** or ABducting **(B)** eyes: In this case, symmetrical VOR responses can be observed, calculated as 0% asymmetry for both **(A)** AD gains (AD vorDAI=0%), as well as **(B)** AB gains (AB vorDAI=0%).

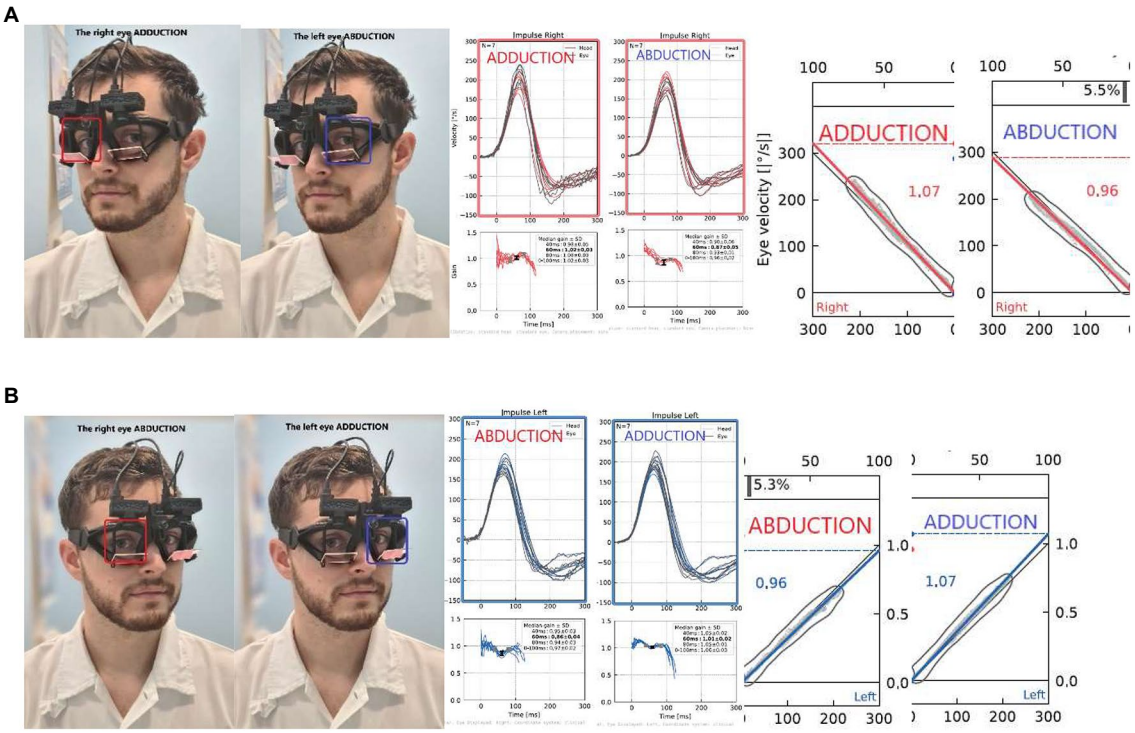

FIGURE 4
Dysconjugacy ratio (vorDR) of leftward gaze during rightward impulse **(A)** and rightward gaze during leftward impulse **(B)**. The calculation is based on the direction of an impulse: In this exemplary case, the **(A)** rightward dysconjugacy ratio (Rightward vorDR) is 1.07/0.96=1.11, and the same result is calculated for **(B)** leftward dysconjugacy ratio (Leftward vorDR) is 1.07/0.96=1.11.

(ABduction, ADduction), and (3) which repetition level (test, retest) yielded the better precision for future use in bvHIT.

Results

Normative values

The normative values and ranges for the regression gain, instantaneous gain, and median gain metrics, and bvHIT dysconjugacy ratio are shown in Table 2. Normative values and ranges for the monocular and ductional VOR asymmetry indices are shown in Table 3. The gain and ratio metrics were normally distributed ($W = 0.95$, $p > 0.08$), and their between-subject SDs were F-distributed. Nonparametric normative values are reported for the VOR asymmetry indices. The distributions of the three different gain metrics can be visually assessed from Figure 5. Levene's test indicated equality of variances [$F(7,304) = 0.66$, $p > 0.71$].

The main effect found by the frequentist statistical analysis was a highly significant difference between ADduction and ABduction gains [$F(1,38) = 350$, $p < 0.001$]; the ADduction gains exceeded the ABduction gains (see Table 2 and Figure 5). The Bayes factors were $BF_{10} > 10^{17}$, indicating "extreme evidence" for differences rather than equality. This finding holds for all three gain methods analyzed (see Table 2). Correspondingly, the monocular directional VOR asymmetry is also increased (see Table 3).

The regression and median gains analysis also showed significant differences between the levels of the eye (left, right) and repetition (test, retest) factors ($p < 0.014$), but the Bayes factors BF_{10} were < 7.5, indicating only "moderate evidence" for differences rather than equality. The regression and instantaneous gains also showed a significant interaction [$F(1,38) = 12.85$, $p < 0.001$] between the eye and duction factors, as shown in the interaction plots on the right of Figure 5. From these plots it can be concluded that the differences in ABduction gains between the left (0.97) and right (0.94) eyes, although significant, are small and clinically irrelevant compared to the main effect of duction.

It is noteworthy that the instantaneous gain of 0.95 (0.09), resulting from averaging over both eyes and duction directions, is comparable to the previously reported normal gain of 0.94 (0.1) from monocular vHIT recordings (5). However, the between-subject SD of the instantaneous gains of 0.09 was slightly lower than the standard deviations of 0.1 typically reported in the literature for normal vHIT gains (5). This may be due to the examiner's 7 years of experience in administering the vHIT. The SDs of the regression and median gains of approximately 0.06 are considerably lower than the SDs of the instantaneous gain, reflecting a better inter-individual precision of these gain calculation methods.

We also calculated the averaged intra-individual SD as a measure of precision for the different gain calculation methods to answer the question of which metric should be used to report the results of future bvHIT examinations. Regression and median gain showed a significantly lower SD [$F(77,77) = 1.46$, $p < 0.003$] than the SD of instantaneous gain (0.02, 0.03, and 0.04, respectively).

The question of whether ABduction gain or ADduction gain is the more precise metric to assess VOR gain asymmetry was also addressed by analyzing the intra-individual SDs of the regression gains. Both duction directions showed SDs of 0.02, with no significant difference [$F(77,77) = 1.46$, $p = 0.59$]. Similarly, both ABduction and ADduction had comparable inter-individual SDs of 0.05. Therefore, in terms of precision, both directions of duction appear to be equally suitable for assessing VOR asymmetry. Similarly, the SDs for test and retest also showed the same values of 0.02 [$F(77,77) = 1.46$, $p > 0.55$], suggesting that no improvement in precision is to be expected from repeating a test. However, from test to retest, the pooled regression gain decreased slightly but significantly from 1.03 to 1.015 (0.06) [$F(1,38) = 6.875$, $p = 0.013$], possibly indicating an improvement in accuracy from retesting.

TABLE 2 Normative values and ranges for the three VOR gain methods and for the dysconjugacy ratio (vorDR).

		Impulse direction						
		Rightward			Leftward			
		Rightward dysconjugacy ratio	Eye				Leftward dysconjugacy ratio	
			Right	Left	Right	Left		
	Equation	AD_{RE}/AB_{LE}	AD_{RE}	AB_{LE}	AB_{RE}	AD_{LE}	AD_{LE}/AB_{RE}	
Gain Method	Regression	**1.12 (0.05)**	**1.08 (0.06)**	**0.97 (0.05)**	**0.94 (0.06)**	**1.07 (0.06)**	**1.14 (0.05)**	Mean (SD)
	Instantaneous	1.15 (0.08)	1.03 (0.09)	0.9 (0.09)	0.86 (0.08)	1.01 (0.08)	1.18 (0.07)	
	Median	1.10 (0.05)	1.06 (0.06)	0.96 (0.05)	0.94 (0.06)	1.06 (0.06)	1.13 (0.05)	
	Regression	**[1.02; 1.22]**	**[0.96; 1.2]**	**[0.87; 1.07]**	**[0.82; 1.06]**	**[0.95; 1.19]**	**[1.04; 1.24]**	Range
	Instantaneous	[0.99; 1.31]	[0.85; 1.21]	[0.72; 1.08]	[0.70; 1.02]	[0.85; 1.17]	[1.04; 1.32]	
	Median	[1.00; 1.2]	[0.94; 1.18]	[0.86; 1.06]	[0.82; 1.06]	[0.94; 1.18]	[1.03; 1.23]	
	Metric	Rightward_vorDR	VOR Gain				Leftward_vorDR	

Values for gains and ratios are reported as mean (SD). Normative ranges are reported with the lower and upper limits in parentheses. Values resulting from the calculation method with the best precision, regression gain, are highlighted in bold.

TABLE 3 Normative values and ranges for VOR asymmetry indices.

		VOR asymmetry index				
		Monocular		Binocular		
		Eye		Ductional VOR asymmetry index		
		Right	Left	AD_vorDAI	AB_vorDAI	
	Equation	$\lvert AD_{RE}-AB_{RE}\rvert / AD_{RE}+AB_{RE}$	$\lvert AD_{LE}-AB_{LE}\rvert / AD_{LE}+AB_{LE}$	$\lvert AD_{RE}-AD_{LE}\rvert / AD_{RE}+AD_{LE}$	$\lvert AB_{RE}-AB_{LE}\rvert / AB_{RE}+AB_{LE}$	
Gain Method	Regression	**7.0 (2.8)**	**4.5 (3.0)**	**1.3 (1.3)**	**2.2 (2.8)**	Median (IQR)
	Instantaneous	8.4 (3.8)	5.7 (4.0)	1.9 (1.9)	2.0 (3.8)	
	Median	5.6 (3.4)	4.8 (3.8)	2.0 (1.2)	1.6 (2.2)	
	Regression	**[3.4; 11.3]**	**[0.9; 11.0]**	**[0.0; 4.3]**	**[0.0; 6.1]**	Range
	Instantaneous	[4.3; 15.6]	[1.0; 17.2]	[0.0; 6.6]	[0.0; 8.5]	
	Median	[1.5; 13.4]	[0.5; 8.8]	[0.0; 4.9]	[0.0; 8.1]	
	Metric	m-vorAI [%]		vorDAI [%]		

Index values are reported as median with the interquartile range (IQR) in parentheses. Normative ranges are reported as percentile ranges from 2.5 to 97.5%, with lower and upper limits in parentheses. Index values resulting from the most precise gain calculation method, regression gain, are highlighted in bold.

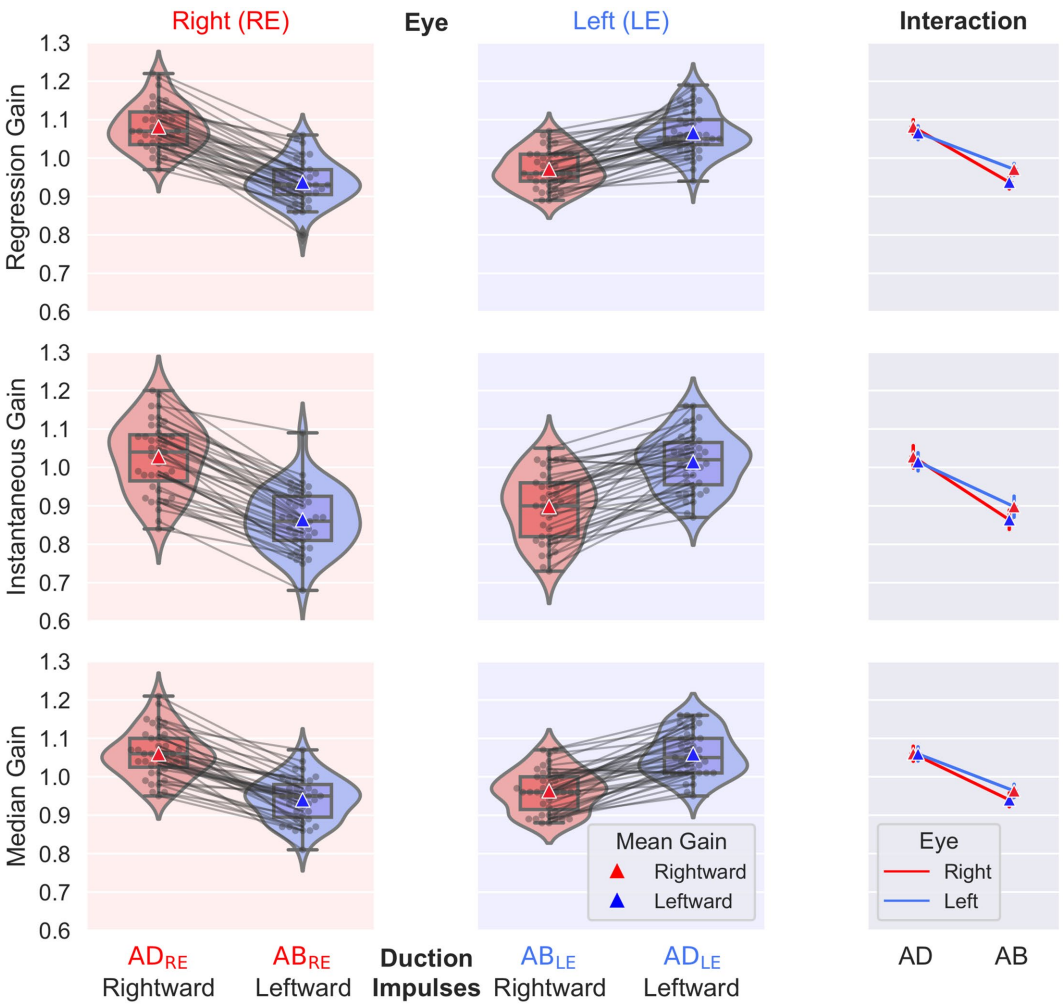

FIGURE 5
Individual gain values, box plots of descriptive statistics, and distributions for the factors eye (left, right) and duction (abduction, adduction). The results of the regression gain (top), instantaneous gain (middle), and median gain (bottom) calculations are shown. The interaction plot on the right presents the interaction between the factors eye and duction.

The repeatability coefficients for the three gain calculation methods are 0.06 for regression gain, 0.09 for instantaneous gain, and 0.07 for median gain. As regression gain was found to be the most precise metric, with the lowest values for both intra-and inter-individual SDs and repeatability coefficient, we recommend its use for future bvHIT gain reporting. Therefore, we focus our analysis and discussion on this metric. Accordingly, the regression gains are highlighted with bold letters in Tables 2, 3, which provide normative values and ranges.

Monocular VOR asymmetry

For regression gain, the median monocular VOR asymmetry recorded from one eye was 7.0% (IQR 2.8%) for the right eye and 4.5% (3.0%) for the left eye. The results reflect an ADduction-ABduction bias in monocular vHIT measurements, resulting in a directional gain preponderance (ADduction gains were always higher than ABduction gains in monocular recordings).

Ductional VOR asymmetry

We calculated ductional VOR asymmetry indices separately for ADduction and ABduction eye movement responses to leftward and rightward head impulses (Figures 3A,B). For the regression gain, the ADduction asymmetry index was 1.3% (IQR 1.3%) and the ABduction asymmetry was 2.2% (2.8%) (Table 3). These results indicate that ADduction asymmetry is less variable than ABduction asymmetry in the healthy subjects. Therefore, it provides a more precise assessment of peripheral vestibular function asymmetry. ADduction vHIT gains were not significantly different between the left and and right eyes, whereas ABduction vHIT gains were [$F(1,38) = 12.85$, $p < 0.001$] (Table 3 and interaction plot in Figure 5).

Binocular vHIT dysconjugacy ratio

The bvHIT dysconjugacy ratio (ADduction/ABduction) pooled for leftward and rightward head impulses was calculated as 1.08 (0.06) /0.95 (0.06). The resulting ratio of 1.13 (0.05) reflects the higher ADduction gains and should therefore be consistently greater than 1. Accordingly, the normative range, calculated as mean + -2xSD, is from 1.03 to 1.23. The dysconjugacy ratio is calculated separately for leftward and rightward impulses to assess the dysconjugacy during leftward or rightward VOR-induced eye movements. This would allow, for example, to identify unilateral or bilateral central oculomotor lesions.

Discussion

We report normative ranges for the horizontal binocular video head impulse test (bvHIT) in 39 healthy participants aged 20 to 70 years.

Difference between adducting and abducting eye VOR gains

Our results are consistent with a previous study using a gold standard scleral search coil to measure binocular eye movement responses to horizontal head impulse testing. In both studies, adduction gains exceeded those of abduction, resulting in directional gain asymmetry when recorded from only one eye (6).

Mechanistic explanation of adduction delay with higher velocities during HIT

Different synaptic arcs

In the scleral search coil study (6), longer latencies were observed in the adducting eye but steeper velocity slopes than in the abducting eye. These have been interpreted as a result of the synaptic delay with a longer trisynaptic pathway and the different firing characteristics of the additional abducens internuclear neuron for adduction (1, 12, 13). The central neural pathways connecting the two horizontal semicircular canals to the recti eye muscles to mediate the horizontal VOR have been described in detail elsewhere (8).

Vergence system influence

The vergence system could also shape the differences between the velocity trajectories of the adducting and abducting eyes. Distance to the visual target is known to modulate the VOR gain, presumably via the vergence system (3–5). Conjugate gaze shifts between two distant targets at optical infinity, which require both eyes to rotate around the same angle, have been assumed to be driven solely by the conjugate subsystem. However, more recent studies have shown that such saccades are consistently accompanied by transient intrasaccadic vergence movements (the eyes initially diverge and then subsequently converge) resulting from dynamic asymmetries in the right and left eye movements (14).

Differences in muscle forces

There is evidence in the literature that the maximum active force of the medial rectus muscle responsible for adduction is approximately 25% greater than that of the lateral rectus muscle, which is responsible for abduction (15). The adduction force can be supported by a vergence command and by the tertiary muscle actions innervated by the same third cranial nerve. The abduction (sixth cranial nerve) can be supported by additive tertiary muscle actions innervated by the fourth and third cranial nerves.

Our study

Our study showed partially similar results to the scleral search coil study with higher adduction gains compared to abduction gains of VOR eye movement responses to head impulse testing, resulting in a monocular VOR directional gain asymmetry. The binocular vHIT device used reflected this ADduction pattern in 100% of the recorded regression gains.

Contribution to the field

bVHIT VOR asymmetry

Our data support the need to simultaneously record and compare vestibulo-oculomotor responses from both eyes during one impulse to obtain a more accurate vHIT asymmetry measure by comparing only adduction or only abduction gains of both eyes. This approach would avoid the preponderance of adduction over

abduction, which is the cause of VOR asymmetry in monocular vHIT (6, 7). The previous search coil study (6) showed less variability in abduction gains. Our study showed similar within-subject and between-subject SD in both abduction and adduction. Considering that the abducting gains reflect a shorter three-neuron reflex arc with possibly less neural processing than in the four-neuron reflex arc of the adducting gains, we recommend the use of abduction for the assessment of VOR asymmetry (between the two eyes during abduction).

bvHIT gaze conjugacy

An additional advantage of the bvHIT is the assessment of gaze conjugacy during head impulse testing as a potential innovation in oculomotor assessment in otoneurology patients suffering from balance complaints accompanied by oculomotor disturbance. Therefore, we established a normative bvHIT dysconjugacy ratio (vorDR) dataset to describe the eye movement patterns during head impulse testing. Based on our normative data, the bvHIT dysconjugacy ratio should be in the range of 1.03 to 1.23 for regression gain. Thus, a vorDR of 1 or less could reflect adduction weakness, whereas a vorDR greater than 1.24 could be present in an abduction deficit.

The bvHIT dysconjugacy ratio can prove useful in supporting challenging diagnoses of dysconjugate eye movement disorders that may be accompanied by symptomatic diplopia or blurred vision. Loss of conjugacy during horizontal eye movements is a common and useful clinical sign of lateral or medial muscle palsies or weaknesses in different conditions such as stroke, in diabetic patients, internuclear ophthalmoplegia due to multiple sclerosis or stroke, Gradenigo syndrome in petrosal apicitis, intracranial hypertension, one and a half syndrome, and other ophthalmoplegias due to stroke or myasthenia gravis (16–18). The vorDR calculation is based on the direction of an impulse, which allows the assessment of both unidirectional (unilateral muscle palsies) or bidirectional dysconjugacy (such as bilateral INO).

Artifacts

Mechanical factors, such as the translation of the adducting eyeball by pulling on the skin or the inertia of the eyeball itself, have been tested previously and are well addressed in the search coil study (6).

Conclusion

Our study provides normative values for binocular vHIT (bvHIT) in healthy subjects. The ADducting eye has a higher vHIT gain than the ABducting eye. This AD-AB preponderance causes a directional gain bias in monocular vHIT. The binocular bvHIT measurement eliminates this bias by comparing the VOR gains of the abduction-only or the adduction-only movements of both eyes.

We also provide a novel bvHIT dysconjugacy ratio that adds a new advantage to vHIT testing: an assessment of inter- and infra-nuclear vestibulo-oculomotor central pathways and muscle action to vHIT. The dysconjugacy ratio reflects the action of horizontal gaze-yoked muscles and associated synaptic arcs. In conclusion, the main advantages of binocular bvHIT over monocular vHIT are, on the one hand, a more accurate measurement of vHIT gain asymmetry by an analysis of ductional VOR gains, and, on the other hand, an additional oculomotor assessment by evaluation of gaze conjugacy during head impulse testing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was performed according to the ethical standards of the Declaration of Helsinki and following procedure approval of the Ethics Committee of the University Hospital Hradec Kralove (Reference number 202106 P08). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

MS designed the study. MS and ES conducted the study and measurements and wrote the manuscript. ES and TS provided statistical analysis. MC, VC, OP, JK, and MV provided critical revisions to the draft and read and approved the final manuscript.

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Conflict of interest

ES is the general manager and a shareholder of EyeSeeTec GmbH.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The incidence of vestibular neuritis in Italy

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Objective: This study aims to estimate the incidence of Vestibular neuritis (VN) in three different districts in Italy, its epidemiological features, and the prevalence of comorbidities associated with it.

Methods: An observational prospective study of 198 patients referred to ENT departments in Siena, Grosseto, and Cuneo was carried out over a 2-year period. Each patient underwent a complete otoneurologic examination in the first 48 h from the onset of symptoms and a brain MRI in the early stages of the disease. The follow-up lasted for 1 year.

Results: The total VN incidence rate of the three municipalities was 48.497 (95% CI: 48.395–48.598) and its standardized value was 53.564 (95% CI: 53.463–53.666). The total VN incidence rate for the whole sample (municipality and district of the three centers) was 18.218 (95% CI: 18.164–18.272), and its standardized value was 20.185 (95% CI: 20.129–20.241). A significant difference was highlighted between patients living in the city compared to those living in the surrounding area ($p < 0.000$), this may be due to the ease of reaching the otoneurological referral center.

Conclusion: The total incidence rate for the three municipalities was 48.497. This result is higher than previously reported studies.

KEYWORDS

acute vestibular neuronitis, dizziness, prospective study, epidemiology, incidence

1. Introduction

Vestibular neuritis (VN), also known as acute unilateral peripheral vestibulopathy or unilateral sudden vestibular loss, is one of the most impairing acute vestibular disorders and a common cause of peripheral vertigo in adults. The etiology is thought to be viral, though in rare cases, the cause may be labyrinthine ischemia (1). Sudden and severe vestibular symptoms, often debilitating, require clinical attention to differentiate them from acute vascular lesions such as cerebellar infarction (1). Although it is considered one of the most frequent and invalidating causes of vertigo in specialized dizziness units (2, 3), the scarcity of epidemiological data is surprising as reported by a recent review by Neuhauser et al., possibly due to the lack of standardized interviews/questionnaires for its diagnosis (2). The most reliable data come from a prospective, population-based study performed in Croatia in the years 2011 and 2012. According to that study, the annual incidence of VN ranged from 11.7 to 15.5 per 100.000 inhabitants per year with an uneven distribution throughout the different seasons of the year (4); previously Sekitani et al. estimated a lower incidence of VN of 3.5 per 100.000 based on population epidemiological survey by questionnaire in Japan

(5, 6). In specialized dizziness units, VN accounts for 3–10% of diagnoses among referred subjects (2, 4, 7). In a British general practice study, VN was reported to be the second most common diagnosis after BPPV among subjects suffering from dizziness. According to Literature, too much variability seems to exist in the epidemiological data. The age of onset ranges usually from 30 to 60 years but existing data reported very different mean ages [61.4 (3), 52.3 (4), 44 in male patients and 46 in female patients (5, 6); some studies reported a female predominance (3, 5) while others reported no gender difference (4–6)]. Recurrence rates are ranging from 2 to 11% (8–11) with pathological sequelae such as persistent or chronic disequilibrium, benign paroxysmal positional vertigo (BPPV) (10), and chronic anxiety (11). The present study aims to estimate the incidence of VN in three different districts in Italy, its epidemiological features, and the prevalence of comorbidities associated with it.

2. Materials and methods

This prospective cohort study was performed over a 2-year period in the areas of Siena (in 2015), Grosseto (in 2015), and Cuneo (in 2016). Given the relatively low populations in these cities, patients with severe vertigo are referred to a single otoneurological unit in their district. Patients were added to the study according to clinical and diagnostic inclusion criteria and followed for up to 1 year from the onset of symptoms. All the patients were seen by an experienced otoneurologist. Most were sent to the units in the acute stage by emergency departments, and some were sent directly to the respective units by general practitioners. All patients underwent a complete otoneurologic examination in the first 48 h from the onset of symptoms [bedside eye movements examination (12), caloric stimulation, video head impulse (VHIT), Romberg and Fukuda test, subjective visual vertical (bucket test)] (13). Bedside eye movements examination was performed with Frenzel goggles and/or videonystagmography. Caloric irrigation was performed with hot, cold, and ice water, and the asymmetry of vestibular function was calculated using the Jongkees formula (12). The VHIT was performed with a video system (vHIT GN Otometrics, Denmark) on the plane of each canal. The normal gain was >0.8 for lateral canals and >0.7 for vertical canals. Vestibular myogenic evoked potentials (VEMPs) were not performed because not available in all centers at the time of the study. Thus, isolated inferior vestibular neuritis was excluded from this study. Since the exact diagnostic criteria for vestibular neuritis were non-standardized at the time of the study and it is still unclear whether vestibular neuritis is a disorder of the end organ (posterior labyrinth) or nerve (5, 14–17), a very comprehensive diagnostic protocol with strict inclusion criteria was adopted. Vestibular neuritis was diagnosed according to the following major criteria: (a) acute vertigo lasting for at least 24 h; (b) dominantly horizontal-rotatory spontaneous nystagmus beating toward the non-affected ear with a torsional component (beating with the pole at the 12-o'clock position directed toward the non-affected ear); (c) pathologic HIT of VOR function toward the affected side and in the planes of the horizontal canal, (d) pathological caloric stimulation (paresis or paralysis) and VHIT (gain < 0.8); (e) postural unsteadiness with Romberg toward the affected ear; (f) normal otoscopic examination and no unilateral hearing loss or tinnitus associated with vertigo; (g) no additional neurologic signs and symptoms; (h) normal brain images: (MRI in all subjects and CT scan when performed in the emergency setting); and (i) no other vestibular or neurological disorders. Patients with concomitant vestibular disorders, such as Ménière's disease, acute stage lateral semicircular canal paroxysmal positional vertigo, postural phobic vertigo, central vestibular disorders or bilateral vestibular hypofunction, and vestibular migraine, were excluded from the study. If HIT was normal at first referral and a stroke or a transient ischemic attack was suspected, neurologic evaluation and MRI or CT scan were performed in an emergency setting. The majority of the patients underwent a cerebral CT scan according to the internal emergency protocol. All patients underwent brain MRI, during the first 2 months from the onset of symptoms, to exclude brainstem and cerebellar lesions. Furthermore, follow-up lasted for 12 months to check for recurrences, the onset of positional vertigo, or chronic dizziness. The diagnostic criteria adopted fit very well the diagnosis of acute unilateral vestibulopathy/VN defined by the Consensus document of the committee for the International Classification of Vestibular Disorders of the Barany Society (18). Epidemiological data were collected and integrated between the three municipalities, similar from a demographic and climatic point of view, and each with a single otoneurologic unit representing the local center of reference for vestibular disorders (Siena and Grosseto, Tuscany, Central Italy; Cuneo, Piemonte, Northern Italy). Large areas with multiple otoneurological referral centers might be a bias in defining the incidence of VN beacause of a higher leakage in data collection. This was overcome by choosing smaller municipalities and districts with a single emergency department and direct access from the emergency department and general practitioners (24/7 hours a day) to the only otoneurological referral center for the area. Age at onset, sex, and affected side have been analyzed. The following comorbidity conditions were considered: hypertension, diabetes, hyperlipidemia, and migraine. Migraine was diagnosed according to the criteria of the International Headache Society (IHS) (19, 20).

2.1. Statistical analysis

Data were analyzed through descriptive statistics (frequency, mean, and standard deviation) to assess the variables' characteristics. The crude and standardized incidence rates were calculated for each area concerning the municipality alone and with its surrounding larger district. The standardization of the incidence rate was assessed for age, using the population data (ISTAT) within the same patient's range. A 95% confidence interval was computed for each estimation. The difference in the mean ages among the samples was verified using the Kruskal–Wallis test since violation of normality was detected by the Kolmogorov–Smirnov test. The two-tailed Z-test was used to analyze the difference in the prevalence of a patient's comorbidities compared to that of the population. The significance level was set at $p < 0.05$, and the analyses were performed

with IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA).

3. Results

In the study period, a total of 198 patients received the diagnosis of vestibular neuritis according to the criteria. Subjects enrolled met all the inclusion criteria. Of these, 68 were seen in the unit at Siena, 76 in Grosseto, and 54 in Cuneo. As shown in Table 1, 111 patients were male and 87 were female with a total sex ratio of 1.28:1 in favor of the men. The sex ratio showed a clear variability, ranging from 1.06:1 in the Siena district to 1.53:1 in the Grosseto district. The right side was involved in 104 patients and the left side in 94, with a total ratio R/L of 1.1:1, with homogeneous levels of the ratios among the districts. The mean age at onset was 54.13 years (SD: 16.65), ranging from a minimum of 12 years to a maximum of 87 years. Age did not show statistically significant differences among the three districts (K-W = 0.008; $p < 0.996$), but the three samples showed different patterns (Figure 1). The incidence of the VN onset reached its maximum between the ages of 40 and 70 years. Among the 198 subjects enrolled, 29 of them lived in Siena municipality and 39 in its surrounding district, 46 in Grosseto municipality and 30 in its surrounding district, and 18 in Cuneo municipality and 36 in its surrounding district (Figure 2). The cumulative incidence rate was assessed for the total sample of patients enrolled and each district, separating the estimations for the municipalities considered in the study (Table 2). The total incidence rate of the three municipalities was 48.497 (95% CI: 48.395–48.598), and its standardized value was 53.564 (95% CI: 53.463–53.666). The municipality of Grosseto showed the highest incidence rate (56.417; standardized: 62.070), very close to the incidence rate of Siena (53.579; standardized: 59.616), while the lowest value was found for the municipality of Cuneo with an incidence rate of 32.083 (standardized: 35.386). Considering all the patients living in the districts, the incidence rates decreased in magnitude. The total incidence rate was 18.218 (95% CI: 18.164–18.272) and its standardized value was 20.185 (95% CI: 20.129–20.241). The highest rate was again detected in the district of Grosseto and was 33.856 (standardized: 37.111), whereas the district of Cuneo showed a very low incidence rate (9.121; standardized: 10.140), probably because of its larger population resident in the district when compared to the districts of Siena and Grosseto. A group of comorbidities was assessed in a subset of patients, those living in the municipalities of Grosseto and Cuneo. The comparison with the population prevalence during the same period revealed that some of these comorbidities showed a significantly different prevalence than the population data (21–24). In the group of patients, diabetes mellitus, with a prevalence of 15.6% (95% CI: 14.6–16.6%; $p < 0.000$), and migraine-possible (17.2%; 95% CI: 16.2–18.2%; $p < 0.012$) were statistically significantly different from the prevalence of these comorbidities in the population (Supplementary Table 1).

4. Discussion

In our observational epidemiological study, the crude incidence rate of VN varied from 32.083 (Cuneo municipality) to 56.417 (Grosseto municipality), with a mean value of 48.497 in the three municipalities. This value is slightly higher than that reported previously by other authors (2, 4–6). In our opinion, this rate seems very realistic since we used strict diagnostic criteria, and all dizzy patients converge on a unique referral otoneurologic unit per district working 24/24 h. A significant difference was highlighted between patients residing in the cities compared to those residing in the surrounding area. In our opinion, this may be because general practitioners in the country sometimes manage patients with vertigo independently. In our study, the diagnosis of VN was performed, in most patients, with a bedside vestibular examination: spontaneous nystagmus, head impulse test (HIT), head shaking test (HST), and mastoid vibration. The caloric preponderance and VHIT confirmed the diagnosis. The peripheral origin of the disease was also confirmed by the exclusion of central causes by MRI, performed in all patients during the 2-month period from the onset of vertigo, and by a prolonged follow-up. Indeed, no patients with a diagnosis of VN developed symptoms or signs due to central involvement. Only patients with horizontal or horizontal/torsional spontaneous nystagmus were considered. Therefore, patients with inferior VN were not included in this study since this rarer subtype of VN is classically characterized by spontaneous torsional downbeat nystagmus, abnormal HIT for the posterior semicircular canal, abnormal cervical-VEMPs, normal HIT for the anterior and horizontal semicircular canals, and normal caloric test (15–17). According to our results, VN is 10 times less frequent than BPPV (25), that is, every year, there is a new patient with VN for every 10 with BPPV. When comparing the incidence of VN with that of Ménière's disease (MD), it is well-known that, in the general population, reliable prevalence and incidence estimates of MD are difficult to obtain. Many years ago, we conducted a perspective population-based survey and found that, in Siena, definite MD is

TABLE 1 Sex distribution, affected side distribution and their ratios in the three districts and in the whole sample of patients.

	Patients (*n*)	Gender*		M/F ratio	Affected side**		R/L ratio
		M	F		R	L	
Siena	68	35	33	1.06:1	37	31	1.19:1
Grosseto	76	46	30	1.53:1	40	36	1.11:1
Cuneo	54	30	24	1.25:1	27	27	1.00:1
Total	198	111	87	1.28:1	104	94	1.11:1

*M, male; F, female.
**R, right; L, left.

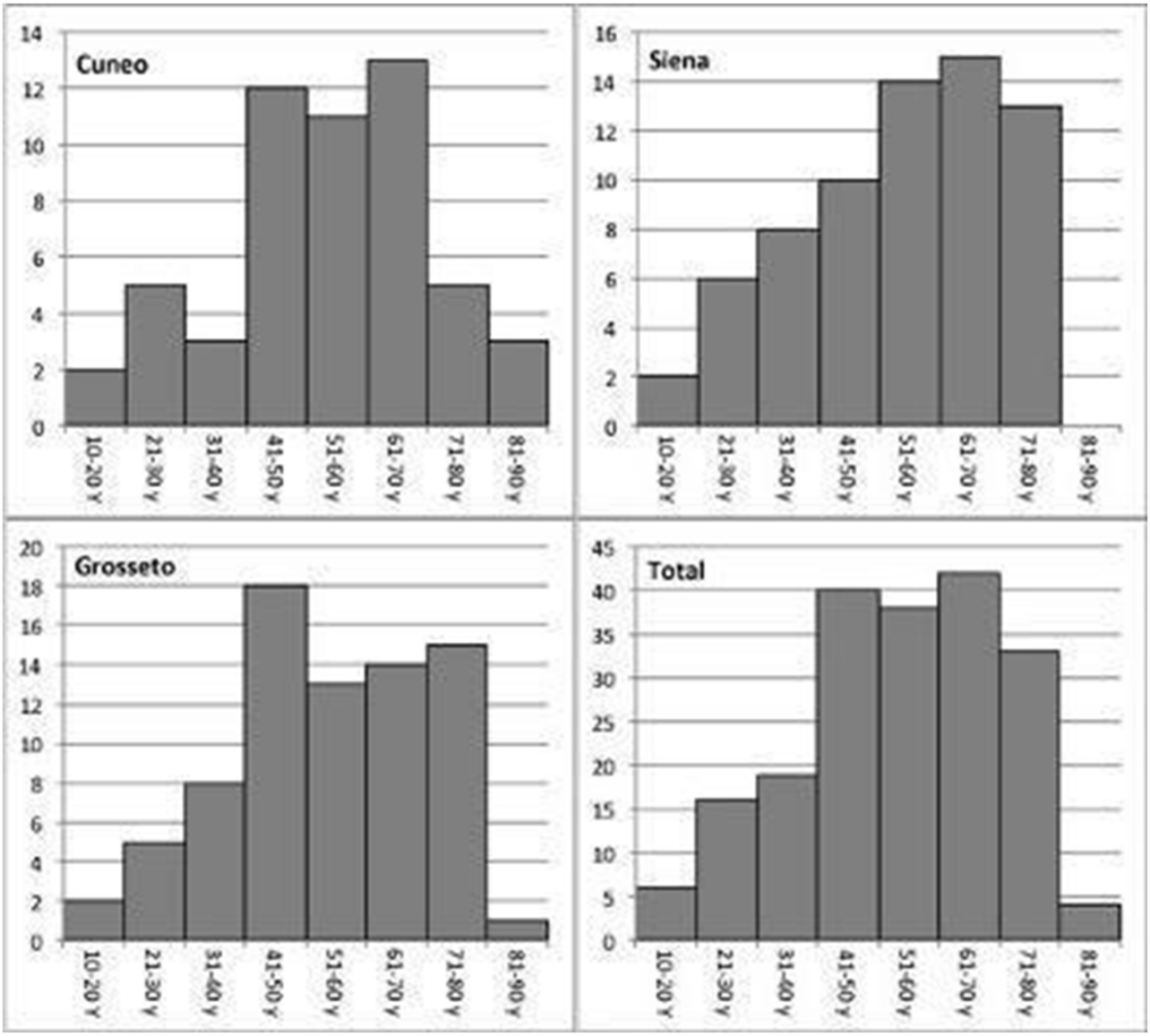

FIGURE 1
Comparison of age distributions of patients with vestibular neuritis.

rare, with an incidence rate of 5.6 per 100,000 inhabitants per year (26). That study was accurate, and we believe that "true" MD is a rare condition and our value is not far from reality. If so, every year, there is a new patient with MD for every 10 patients with VN. Interestingly, the incidence of VN is similar to that of Bell's palsy, another idiopathic disease probably viral in origin, reinforcing the common causal hypothesis. Indeed, the cumulative incidence of Bell's palsy was 53.3/100,000/year (27). The high incidence of VN documented in our study may be explained in part also with the possible overlap with the diagnosis of vestibular migraine, despite that no patients met the diagnostic criteria for definite VM in the 1-year follow-up. The mean age at the onset of VN was 54.13 years, similar to that in Croatian patients. VN is rare but possible in young people: five patients were teenagers and the youngest was 13 years old. In fact, VN mainly affects adults over 40 years of age, with more than 40% of patients between 40 and 70 years. There was no significant difference between these three decades, and the incidence of the disease does not seem to increase with age. A slight prevalence of the male population was detected in all three cities (111 male patients vs. 87 female patients) that is in accordance with a previously demonstrated study by Adamec et al. and Sekitani et al. (4, 6). This is in contrast to the general behavior of vestibular disorders in adults (BPPV, vestibular migraine, and Meniere's disease). Indeed, the prevalence and incidence rates of vestibular disorders are consistently higher in women than in men (2). There was no statistically significant difference in the site of the lesion with a right/left ratio of 1.11:1. Comorbidities, such as hypertension in 26.6% of patients or diabetes in 15.6%, could suggest shared potential risk factors of vascular origin. On the other hand, the lowest rates of VN in older people >

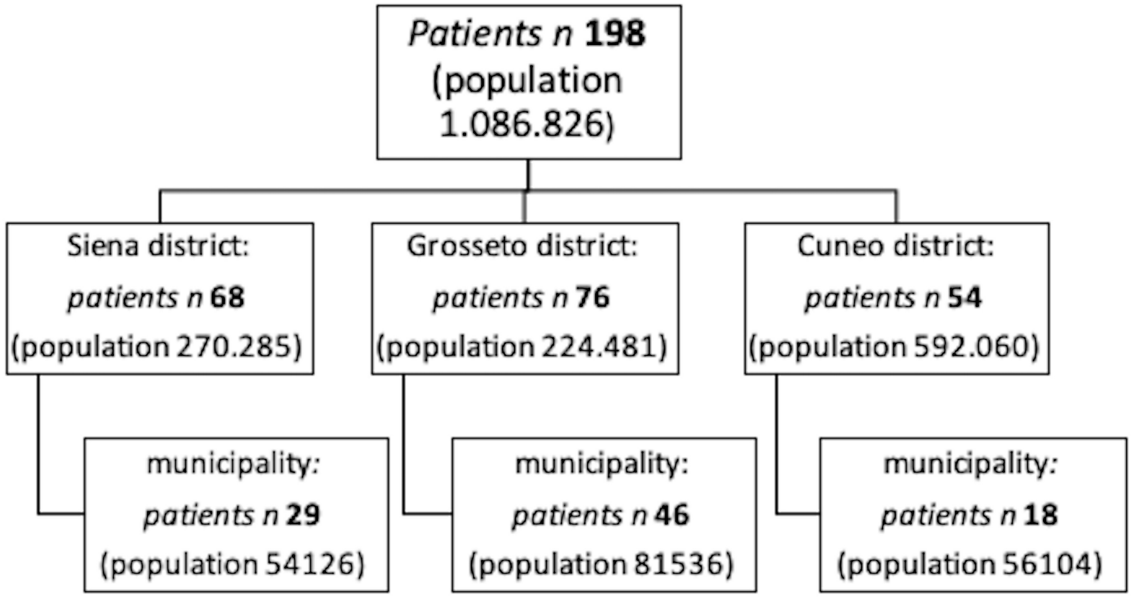

FIGURE 2
Flow chart of screened patients for each center.

TABLE 2 Crude incidence rates, standardized incidence rates (by age) and their 95% confidence interval.

	Patients	Inhabitants	Crude incidence rate (95% CI)	Standardized incidence rate (95% CI)
Siena (district)	68	270,285	25.159 (25.055–25.262)	27.912 (27.806–28.019)
Siena (municipality)	29	54,126	53.579 (53.397–53.760)	59.616 (59.437–59.794)
Grosseto (district)	76	224,481	33.856 (33.749–33.962)	37.111 (37.003–37.220)
Grosseto (municipality)	46	81,536	56.417 (56.273–56.560)	62.070 (61.930–62.210)
Cuneo (district)	54	592,060	9.121 (9.044–9.197)	10.140 (10.060–10.221)
Cuneo (municipality)	18	56,104	32.083 (31.868–32.299)	35.386 (35.165–35.607)
Total (all patients)	198	1,086,826	18.218 (18.164–18.272)	20.185 (20.129–20.241)
Total (municipalities)	93	191,766	48.497 (48.395–48.598)	53.564 (53.463–53.666)

70 years, when cardiovascular disorders are preponderant, seem to limit this hypothesis. Correlations between VN and migraine (14.1% ICHD-3 defined, 17.2% possible) are possible since the two clinical manifestations share common complaints such as visual vertigo and/or anxiety or phobic vertigo. The scarcity of epidemiological data on vestibular neuritis is however remarkable (2, 5–7). Furthermore, most experienced neurotologic centers all over the world do not have direct access to data from emergency departments making the incidence of VN difficult to estimate and evaluate. The most recent study on VN incidence (4) only evaluated patients over 20 years of age and the population in that study only included one center from the four emergency departments in the area. Finally, it is well-known that it is more difficult for severely impaired dizzy patients to reach the emergency department or neurotological unit promptly in large cities. These limitations may have had a bearing on the lower incidence with respect to our results. There are other limitations to our study. First of all, the sample size. Although the estimations were sufficiently accurate, this does not guarantee that the results can be generalized to the Italian population as a whole, since data were only collected in three small territories in the northwestern and central regions of Italy. Another limitation is related to the analysis of the comorbidities; we assessed them as the difference in prevalence compared to that of the population, but we did not investigate how was the burden of the comorbidities in VN pathogenesis. Finally, since VEMPs were not available in all centers, we excluded the diagnosis of isolated inferior VN from the study. Despite the rarity of isolated inferior VN, this limitation may have lowered the incidence of VN in the present study (16).

5. Conclusions

The total VN incidence rate was 18.218/100.000/year and its standardized value was 20.185/100.000/year. The observation of restricted and homogeneous population areas to collect

demographic data and a more accurate information from emergency centers and general practioners might lead to a more definite epidemiological observation survey, limiting the effects of diagnostic errors or incorrect pharmacological treatments. Usually, compensation occurs in the days after the acute onset of VN, especially if the patient is rapidly mobilized, so a prompt diagnosis should be made to avoid delays or late/partial recovery. A long-term follow-up of VN patients is however recommended in order to highlight spontaneous compensation/adaptation phenomena to modulate the best vestibular rehabilitation options and to monitor patients for possible recurrences.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MM, CF, and DN contributed to conception and design of the study. SP, SB, SA, and FV organized the database. FF, RG, and GG performed the statistical analysis. GC wrote the first draft of the manuscript. IB, FV, GC, and LS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1177621/full#supplementary-material

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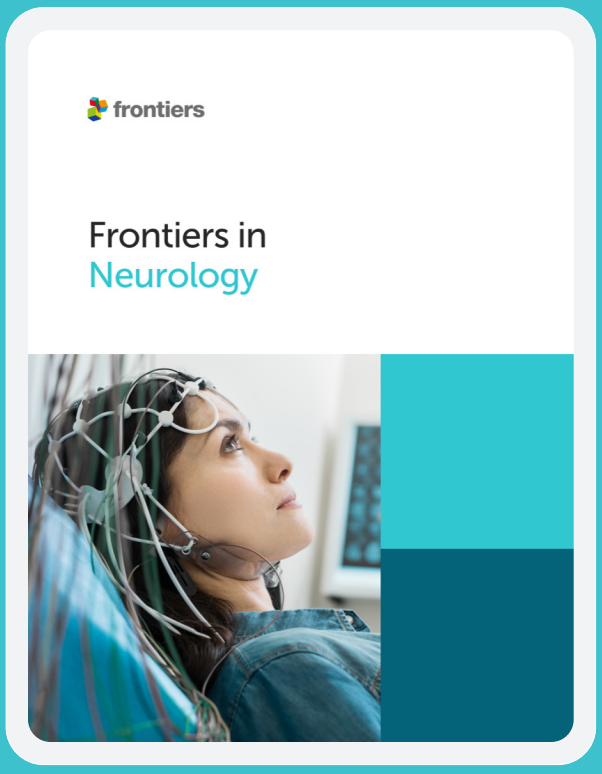

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