BILATERAL VESTIBULOPATHY - CURRENT KNOWLEDGE AND FUTURE DIRECTIONS TO IMPROVE ITS DIAGNOSIS AND TREATMENT

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BILATERAL VESTIBULOPATHY - CURRENT KNOWLEDGE AND FUTURE DIRECTIONS TO IMPROVE ITS DIAGNOSIS AND TREATMENT

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Many patients with bilateral vestibulopathy experience chronic oscillopsia due to failure of the vestibulo-ocular reflex and gait instability due to failure of vestibulo-spinal reflexes. There are numerous potential contributing factors, however, many cases remain idiopathic. The diagnosis of bilateral vestibulopathy is often delayed, placing patients at risk for unnecessary diagnostic tests and late initiation of treatment. Novel diagnostic tests offer new opportunities to characterize patterns of vestibular impairment. With the advent of new therapies, there is urgency to define and better understand patients with bilateral vestibulopathy. This collection includes topics such as an exploration of the large class of patients with bilateral vestibulopathy currently considered idiopathic, by identifying novel pathophysiologic mechanisms. Other topics include a historical perspective on early recognition, the impact of bilateral vestibular impairment on quality of life, and how advances in diagnostics are refining our understanding of what it means to have bilateral vestibulopathy. New developments in treatment strategies for patients with bilateral vestibulopathy are also featured.

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EDITORIAL
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Editorial: Bilateral Vestibulopathy - Current Knowledge and Future Directions to Improve its Diagnosis and Treatment

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Editorial on the Research Topic

Bilateral Vestibulopathy - Current Knowledge and Future Directions to Improve its Diagnosis and Treatment

Bilateral vestibulopathy has had several names, paralleling growing numbers of publications and interest in its pathophysiology and treatment. The condition was formerly Dandy syndrome, eponymously associated with neurosurgeon Walter Dandy who worked at the Johns Hopkins Hospital from 1918 to 1946. Having developed expertise in vestibular schwannoma surgery, Dandy became interested in vestibular nerve section to treat Meniere's disease. He achieved early success at controlling vertigo in patients with Meniere's disease after unilateral sectioning of the vestibular nerve, and then began performing bilateral vestibular nerve section. The first descriptions of the consequences of this surgery were in 1936 by neurologist Frank Ford and neuro-ophthalmologist Frank Walsh, who both worked with Dandy at the Johns Hopkins Hospital (1). They noted in a patient: "Objects seemed to move before his eyes unless his head was kept perfectly still." Dandy later synthesized these cases and reported them himself in 1941, leading to the term Dandy syndrome (2).

Although we understand the implications of cutting both vestibular nerves today, at the time, many clinicians had a poor knowledge of the role of the vestibular system. A popular notion held that the vestibular system was vestigial. Prominent English physician Edmund Hobhouse noted in a 1924 Lancet editorial: "We are driven to the somewhat painful conclusion that in the semicircular canals man possesses a beautiful and complex mechanism which has been superseded by higher development, and whose only positive function now is to produce some of the most disabling and distressing symptoms which the human body can experience; moreover, this mechanism is so bound up with the organ of hearing that it is impossible to remove it without inflicting the penalty of deafness (3)." If vestibular testing and disease produces vertigo and nausea in those with intact labyrinthine function, and no symptoms in those without, Hobhouse argued, then the labyrinth is superfluous. Since airplane pilots could be led asunder by normal vestibular perceptions, the United States military even expressed interest in bilateral vestibulopathy to make better pilots (4). Dandy began performing vestibular nerve section for Meniere's disease in 1924, the same year as Hobhouse's editorial (5), later expanding to sectioning both vestibular nerves (6). Dandy comments in his 1934 series: "One is amazed that almost no symptoms are induced by the abrupt loss of both semicircular canals in man." and provocatively states "It would be interesting indeed, to know whether this patient would be subject to seasickness." Ford and Walsh' 1938 article describing Dandy's patients was in response to the popular belief that an intact vestibular system could only do harm.

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This research topic highlights the significant progress our field has made since Ford and Walsh's first descriptions of Dandy syndrome (see Hain et al. for comprehensive review). Surgery is no longer a common cause of bilateral vestibulopathy, and the etiology of bilateral vestibulopathy is more varied than once believed (Kattah). Fortunately, idiopathic cases of bilateral vestibulopathy are becoming less common. Authors in this issue have identified new causes such as amiodarone (Gürkov) and environmental toxicities like a type of military jet fuel (Fife et al.). Others highlighted here include an accumulation of iron called superficial siderosis (Lee et al.), as well as central vestibular lesions that can mimic peripheral ones (Chen and Halmagyi).

New diagnostic tests like video head impulse testing (vHIT) and vestibular-evoked myogenic potentials (VEMPs, see Rosengren et al. for review) allow us to identify patterns of bilateral vestibular impairment (Tarnutzer et al.). For instance, patients with Wernicke's encephalopathy, show a predominantly horizontal semicircular canal impairment (Lee et al.). We also now have evidence for sequential episodes of superior vestibular neuritis leading to bilateral vestibulopathy (Yacovino et al.). Rotatory chair testing may have new applications as well, by combining gain and time constant in a new variable to help determine the severity of bilateral vestibulopathy and to track progress during treatment (Hain et al.).

Many patients with bilateral vestibulopathy suffer, and although these patients may be spared spinning vertigo and have similar rates visual height intolerance to the general population (Brandt et al.), they can be incapacitated by oscillopsia and unstable gait. Articles in this research topic show that patients with bilateral vestibulopathy depend heavily on other sensory cues such as vision and proprioception (Sprenger et al.; Medendorp et al.), and that covert saccades are triggered in order to decrease symptoms of oscillopsia (de Waele et al.). Vestibular physical therapy can be helpful. Lehnen et al. emphasize the importance of head motion while Ellis et al. propose newer cognitive interventions to improve self-motion perception.

New medical and surgical treatments are being investigated, including gene therapy to regrow hair cells and vestibular implantation. In order to determine whether new treatments are effective, well-defined and properly developed outcome measures are needed. Lucieer et al. and Anson et al. report early work toward developing new validated outcomes measures for bilateral vestibulopathy. We must also better understand the causes of bilateral vestibulopathy and establish clear diagnostic criteria. Recently the committee for the classification of vestibular disorders of the Barany society has made an important first step, defining the condition as bilateral vestibulopathy and publishing consensus diagnostic criteria (7). The manuscripts in this issue are a broad sample of the current efforts in our field to understand the pathophysiology of this disabling condition and to develop effective therapies.

AUTHOR CONTRIBUTIONS

BW and AT jointly contributed to this editorial.

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ORIGINAL RESEARCH
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The Gain-Time Constant Product Quantifies Total Vestibular Output in Bilateral Vestibular Loss

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Patients with inner ear damage associated with bilateral vestibular impairment often ask "how much damage do I have." Although there are presently three clinical methods of measuring semicircular canal vestibular function; electronystagmography (ENG or VENG), rotatory chair and video head-impulse (VHIT) testing; none of these methods provides a method of measuring total vestibular output. Theory suggests that the slow cumulative eye position can be derived from the rotatory chair test by multiplying the high frequency gain by the time constant, or the "Gain*Tc* product." In this retrospective study, we compared the Gain*Tc* in three groups, 30 normal subjects, 25 patients with surgically induced unilateral vestibular loss, and 24 patients with absent or nearly absent vestibular responses due to gentamicin exposure. We found that the Gain*Tc* product correlated better with remaining vestibular function than either the gain or the time constant alone. The fraction of remaining vestibular function was predicted by the equation $R = (\text{Gain}Tc/11.3) - 0.6$. We suggest that the Gain*Tc* product answers the question "how much damage do I have," and is a better measure than other clinical tests of vestibular function.

Keywords: bilateral vestibular loss, vestibular testing, rotatory chair, caloric testing, VHIT testing

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INTRODUCTION

Patients with inner ear damage associated with bilateral vestibular impairment often ask "How much damage do I have." They ask "Are my inner ears getting better or worse?" These questions can be difficult to answer because of our limited repertoire of vestibular tests. Although there are presently three clinical methods of measuring semicircular canal vestibular function; videonystagmography (VNG), rotatory chair and video head-impulse (VHIT) testing; none of these methods provides a method of measuring total vestibular output.

By total vestibular output we mean: the total ocular response for a given change in head velocity. This is not the same as the peak eye velocity, as the peak is a response at a particular time, that does not account for responses prior to and following the peak. The total response requires adding up all of the eye movement output over time. We will develop below the argument that a reasonable quantity to describe the total vestibular response is cumulative eye position.

One might argue that the caloric portion of VNG testing provides a "total response" parameter. However, this is a peak velocity measurement and thus is not a total response, which would require considering all eye movement elicited by the caloric stimulus. Furthermore, the caloric input corresponds to very low frequencies of vestibular stimulation, analogous to 0.003 Hz (1). Thus, the VNG doesn't cover the entire frequency range of the vestibular response.

The VHIT device has no total vestibular response parameter. This is again because it measures velocity rather than position. Furthermore, the VHIT is limited to high frequencies of vestibular stimulation, predominantly at 2.5 Hz (2). According to Patel et al., the output of the VHIT, high frequency gain, is not correlated with chronic symptoms of dizziness (3).

The rotatory chair test assesses a broad range of input frequencies, typically 0.01–0.64 Hz, and thus provides more information than either the caloric or the VHIT. However, the rotatory chair test does not provide a "total vestibular response" parameter. We will discuss how this can be computed.

The rotatory chair quantifies the velocity gain and phase of the vestibular-ocular reflex (VOR) in the horizontal plane. These values are obtained typically for at least four frequencies ranging from low (0.01 Hz) to high (0.64 Hz). The gain and phase values are plotted against the range of normal, and inferences are made concerning vestibular function from their pattern. As frequency ranges from high to low, individuals with peripheral vestibular disorders exhibit both reduced gain and increased phase, but there is considerable variability (4).

While recognition of specific patterns of gain and phase of rotatory chair plots is useful, it is often imprecise and it can also be challenging to explain to patients that their problem is "phase lead at low frequencies." Fortunately, the gain and phase plots such as are used in rotatory chair testing have a descriptive mathematics that can be used to simplify this situation. The dependence of output on input can be expressed as a "transfer function." For a linear system, the output for any stimulus can be predicted from the transfer function. As the vestibulo-ocular reflex (VOR) is largely linear for low velocities and accelerations (5), its transfer function can be represented by a linear mathematical construct, which for the VOR is a "single pole." The single pole has two parameters—gain (K) and time constant (*Tc*) (6). Although having only two values (gain and time constant) is simpler to interpret than the eight values contained within the gain/phase frequency plots, the gain, and time constant values do not answer the question often posed by patients with bilateral vestibular impairment: "How much of the vestibular system remains?"

A possible solution lies in the "Slow cumulative eye position," or SCEP. Equations (1) and (2) express the mathematics underlying the SCEP. This transfer function for the vestibulo-ocular reflex can be computed from the step response—an exponentially declining eye velocity that is produced by a sudden change, or "step" in head velocity. The SCEP is the integral of the VOR step response and represents the total angular displacement of the eye for a step of head velocity. Thus, the SCEP reflects total vestibular output, in units of ocular angular displacement, for a step change of head velocity. When the step response equation is normalized to a 1°/s step (Equation 1) and then is integrated over time (Equation 2),the total eye displacement is simply the product of K * *Tc*—the product of the gain and the time constant. We subsequently call this the "Gain*Tc*."

Equation 1: Eye velocity in response to a unit 1°/s step of head velocity.

$\dot{E}$ = eye velocity, K = High frequency gain, t = time, and Tc = Time constant:

$$\dot{E} = K \times e^{-t/Tc} \tag{1}$$

Equation 2: Slow cumulative eye position, or SCEP

$$E = \int \dot{E} = \int K \times e^{-t/Tc} = K \times Tc \tag{2}$$

The SCEP is computationally straightforward, being simply the product of the gain and time constant, and from Equations (1) and (2), one can see that this single number represents the total output, in terms of cumulative eye position, for a unit 1°/s step of head velocity.

For a group of subjects in whom the amount of remaining vestibular function was known we asked the question: How well does the Gain*Tc* correlate with remaining vestibular function?

METHODS

This was a retrospective study in which we computed the Gain*Tc* in three groups of subjects. The first group had good evidence for normal vestibular function. The second group had surgical unilateral hypofunction. The third group had near complete bilateral vestibular loss due to exposure to the ototoxic antibiotic, gentamicin. They are described in more detail below.

This study was reviewed and approved by the Northwestern University Institutional Research Board. A waiver of consent was granted for this retrospective review of data.

Most subjects were derived from the clinical practice of the first two authors (TCH, MC). These subjects underwent rotatory chair testing on a Micromedical Technology Rotatory chair system (Model 2000, GN-Otometrics, Chatham, Illinois), with a peak acceleration of 200°/s^2. Fifteen of the 25 surgical subjects were contributed by the third author (NPF). These subjects were tested on a similar device, the CHARTR® RVT system, ICS Medical Corporation, Schaumburg, IL). All subjects were tested using standard protocols that included sinusoidal stimulation up to 0.64 Hz, and step responses. The parameters used to compute the Gain*Tc* were produced by the commercial software for these two devices.

The VOR gain (*K* in Equations 1 and 2) was computed from the ratio of peak eye velocity/peak head velocity) for sinusoidal rotatory chair testing at 0.64 Hz, which is the highest frequency used for routine rotatory chair testing with these devices. The time constant, *Tc* was taken from the average computed time constant for per and post-rotatory measurements of two 100°/s step responses. The frequency of 0.64 Hz was chosen because it is the highest frequency available for these tests, and because while the VOR gain depends on frequency, it asymptotes to a constant level at higher frequencies (7).

RESULTS

Group 1, "normal," included 30 subjects. Six of these were normal volunteers with no complaints of dizziness or hearing

disturbance. The remaining 24 complained of dizziness but had entirely normal otoneurological examinations including bedside video Frenzel testing. The bedside exam included negative testing for spontaneous nystagmus, vibration induced nystagmus, and head-shaking nystagmus, and a negative eyes-closed tandem Romberg. This testing is very sensitive to unilateral and bilateral vestibular loss. In 21 of the "normal" subjects, the cause of their dizziness was attributed to migraine as they also had headaches as a prominent feature. In the remaining three, final diagnoses were epilepsy, anxiety, and syncope. Fifteen of these subjects also had caloric testing done. These subjects had normal caloric responses using conventional criteria (1). For patients where it was available, the average total caloric response was 76.11°/s. We assumed that these subjects had 100% of their vestibular system functioning and set the *R*-value to 1.

Group 2, "unilateral," included 25 subjects. Of these, 21 had undergone surgery to ablate vestibular function on one side. Six of these had vestibular nerve sections, and 15 were post labyrinthectomy. The remaining four had surgical removal of large acoustic neuromas followed by a caloric test that documented no remaining vestibular function. Twenty-four of these subjects had caloric testing done, and all but three had no caloric response on the operated side. In these three, the caloric paresis was very high (79, 91, 93%). In these cases, we accounted for the remaining residual function. Specifically, we assumed the remaining ear had an "*R*" of 0.5, and we solved the paresis equation of Jongkees (8) for the other ear. These adjustments were small and resulted in a mean value for "*R*" of 0.51, only slightly greater than the expected 0.5 for surgical lesions.

Group 3, "bilateral," included 24 patients with bilateral vestibular loss. These individuals had developed permanent oscillopsia and ataxia after exposure to gentamicin, a well-known ototoxin. Twenty-two of twenty-four of these had caloric responses available, and the average total caloric response was 10.05°/s. Rather than assume that they had no vestibular function at all, in the 22 where caloric results were available, we estimated their remaining vestibular function by dividing the sum of all four open water caloric irrigations by 100. The figure of 100 was chosen as it is the average sum of all caloric irrigations of normal persons to open water caloric testing (9). While this is called the "total caloric response," here the term "total" refers to an aggregate descriptor of the conventional caloric test, rather than the entire output of the caloric test (which would require an integral). As previously observed by Hess et al. (10), it is likely that the caloric underestimates the true remaining vestibular function, in as much as caloric testing is a test of low frequencies, and cannot assess the higher frequency VOR. Nevertheless, considering the lack of better data this is the most reasonable adjustment.

Table 1 shows that the average Gain*Tc*-value varied greatly between normal (11.25), unilateral (3.75), and bilateral (0.95) groups. As the values of the Gain*Tc* parameter were not normally distributed for each group we used the Kruskal-Wallis test to compare group differences (11). There was a statistically significant difference in Gain*Tc* parameter for the three groups [$H_{(2)} = 63.657$, $p < 0.001$], with a mean rank of 64.15 for the normal group, 35.42 for the unilateral group, and 14.58 for the bilateral group. Follow up pairwise comparisons revealed that the Normal group was significantly higher than both the unilateral ($H = 28.730$, $p < 0.001$) and bilateral-gent ($H = 49.567$, $p < 0.001$) groups, and the Gain*Tc* parameter was higher for the unilateral group than for the bilateral group ($H = 20.837$, $p = 0.004$).

Figure 1 is a scatter plot showing remaining vestibular function, on the X axis, plotted against the Gain*Tc* on the Y axis. The linear regression line shown in **Figure 1** is described in **Table 2.**

DISCUSSION

Our results suggest that the mean Gain*Tc*—the product of the VOR gain and time constant, differs significantly between the normal, unilateral loss and bilateral loss groups, and furthermore the Gain*Tc* correlates with remaining vestibular function. In particular, a reasonable estimate for the remaining fraction of vestibular function that an individual has, which we call "*R*," neglecting the small Y intercept, is the product of their VOR Gain and step-response time constant, computed as we described, divided by 11.3.

We have also shown that the correlation of Gain*Tc* with *R* is higher than either the VOR gain or the VOR time constant, *Tc*. Based on this analysis, we suggest that the Gain*Tc* product is a better measure of total vestibular function than either Gain or *Tc*. Because, as we have shown, the Gain*Tc* is proportional to the total vestibular output, the Gain*Tc* is also the measure most suitable to quantify bilateral vestibular damage such as resulting from ototoxicity. As mentioned in the introduction, the other tests of semicircular canal function contain less information than the rotatory chair because they assess low frequencies (i.e., caloric tests) alone, or primarily very high frequencies (i.e., VHIT test).

Although the Gain*Tc* product is not a complex construct, we were able to find only a single other mention of this parameter in the vestibular testing literature. Honrubia et al. (12), when describing the results of rotatory chair testing in subjects with bilateral vestibular weakness, reported the "coefficient of sensitivity of the pendulum equation," that was computed identically. They stated that the value for this parameter was 5.87 in normal subjects, while the mean value for the nine patients with bilateral vestibular weakness that they reported was 1.60. This result is smaller than ours, possibly because of their use

TABLE 1 | Summarizes the characteristics of the three groups of subjects as well as provides summary values for vestibular parameters from rotatory chair testing.

	n	*R*	Gain	*Tc*	Gain*Tc*	Age
Normal	30	1.00	0.75 ± 0.11	15.28 ± 5.34	11.25 ± 3.13	36.07 ± 12.9
Unilateral	25	0.50	0.51 ± 0.15	7.38 ± 2.76	3.75 ± 1.51	52.16 ± 10.0
Bilateral	24	0.09	0.35 ± 0.21	3.22 ± 1.28	0.95 ± 1.18	62.08 ± 11.11

n = number of subjects. Remaining function (R) = fraction of total vestibular function remaining (see text). Gain is the VOR gain for 0.64 Hz. Tc is the average time constant for step responses. GainTc = product of VOR Gain and Tc. Standard deviations are provided next to the mean values.

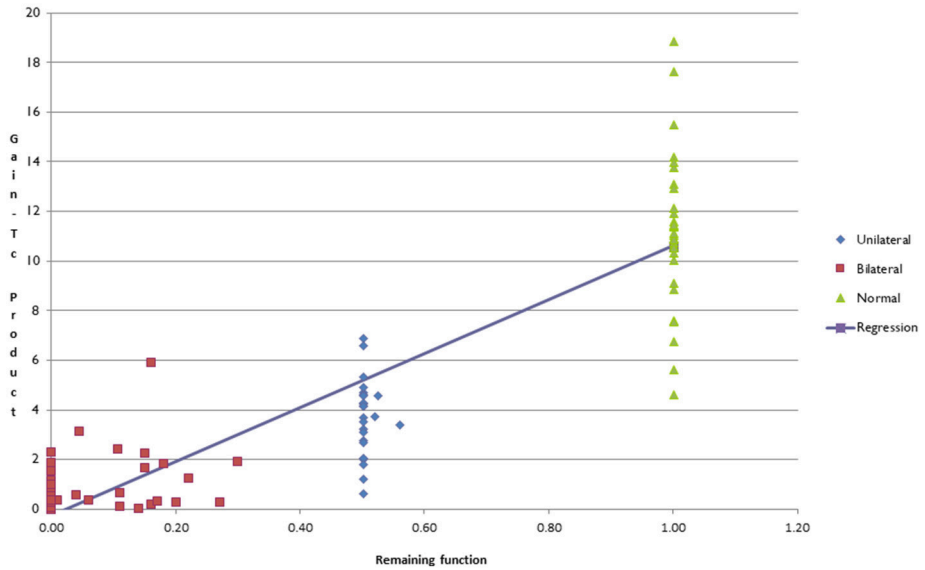

FIGURE 1 | Scatter plot showing inferred remaining vestibular function, on the X axis, against the Gain*Tc* product on the Y axis. Group 1 = normal subjects. Group 2 = patients with surgical unilateral vestibular loss. Group 3 = patients with bilateral vestibular weakness on caloric testing caused by gentamicin ototoxicity. The regression shows the line fit between remaining vestibular function and the Gain*Tc* product.

TABLE 2 | Regressions of Gain*Tc*, Gain, and *Tc* on remaining vestibular function, *R*.

Parameter	r^2	Slope	Intercept
Gain*Tc*	0.76	11.3	−0.60
Gain	0.55	1.23	0.11
Tc	0.60	0.045	0.15

*Each of these regressions can be used to estimate the remaining function based on the GainTc, Gain, or Tc. For example, using the GainTc regression, GainTc = (11.3 * R) – 0.6. More usefully, when rearranged in terms of remaining function, the equation becomes R = (GainTc/11.3) – 0.6.*

TABLE 3 | Literature values for gain and Tc.

n	Gain	*Tc*	Gain*Tc*	References
NORMAL SUBJECTS				
55	0.53	13.44	7.12	(14)
743	0.65	16.00	10.4	(13)
100	0.66	16.6	11.0	(15)
UNILATERAL VESTIBULAR LOSS				
7	0.49	6.2	3.04	(18)
43	0.38	9	3.38	(13)
11	0.49	6.2	3.04	(19)

of smaller values for the VOR time constant based on higher velocity rotational tests than those used in the present work. Honrubia et al. did not develop this concept further.

Other estimates of the Gain and *Tc* and their product can be obtained from larger studies of rotatory chair testing in patients.

Table 3 summarizes literature data, selecting out those having larger numbers of subjects, and providing gain and *Tc*-values from rotatory chair testing in normal subjects and patients with well documented unilateral vestibular loss. For normal subjects, the study of Wade et al. (13), included almost an order of magnitude more subjects than other similar studies, and computing the Gain*Tc* from their data resulted in a similar estimate for the "normal" Gain*Tc* (10.4) as ours (11.3). Average gains and time constants from smaller studies (4, 14–17), yielded values for the Gain*Tc* product ranging from 7.12 to 11.26.

With respect to studies reporting values for patients with well documented unilateral loss, all of the studies in **Table 3** result in a similar estimate for the Gain*Tc* product, between 3.03 and 3.375. This is similar to our finding of a value of 3.75 in 25 subjects.

For patients with bilateral vestibular loss, if their vestibular loss is complete, the gain would be 0 and thus the Gain*Tc* product should be 0. We know of no datasets comparable to ours where caloric responses were used to estimate total response in patients with gentamicin induced ototoxicity. There is, however, documentation of the failure of individual gain and *Tc*-values to correlate with reduction of caloric responses. Hess et al. reported a wide range of gains (0–0.8) and time constants (1–9) in 17 patients with partial bilateral vestibular loss (10).

As the ages of our unilateral and bilateral subjects were much lower than those of our normal subjects, and one might hypothesize that the effects seen were at least partially due to decline in vestibular output with age. We computed the Gain*Tc* product from several other studies of the VOR as a function of age (20, 21) in an attempt to estimate the magnitude of the effect of age on the Gain*Tc* product.

Baloh et al. reported the gains and time constants of the VOR in a study of 75 "elderly" normal people, averaging 79.6 years old, who were compared to 25 normal younger people, averaging 26.2 years old (20). Their data results in a Gain*Tc* product of 9.5 for the younger subjects, and 6.8 for the older subjects, from which it can be calculated that the slope of the Gain*Tc*/year is−0.051/year. Similarly, Paige (21) reported gain and phase data in 30 "young" (18–44) and 23 "Middle-Aged" (45–69) subjects. The Gain*Tc* products for the 0.025 Hz−50°/s stimulus, similar to our methodology, were computed to be 13.23 and 10.07 for young and middle-aged, respectively, resulting in a slope of −0.12°/year. This analysis suggests that the Gain*Tc* product declines slowly with age. From these two values, for the ages of our subjects, the amount of decrement of Gain*Tc* that would be predicted from the age differences between our bilateral (average age of 62) and normal subjects (36) is between 1.3 and 3.1°. This amount of decline in the Gain*Tc* is much smaller than the 7.5° or more deg. decline in Gain*Tc* found in the unilateral and severe bilateral vestibular groups.

As the Gain*Tc* product has the highest correlation (r^2), with remaining function, this implies that it better reflects remaining vestibular function than high-frequency VOR gain or the time constant. We suggest that the Gain*Tc* product performs better because of the following observations: As illustrated by **Table 3**, compared to normal subjects, vestibular gain is little changed by unilateral vestibular weakness or loss. However, the time constant is greatly reduced. In patients with near complete vestibular loss, the VOR time constant cannot decrease below that of the mechanics of the inner ear (about 6 s) (6), but the gain continues to decrease until it reaches 0. Thus, the Gain*Tc* product, which is sensitive to unilateral loss from decline in the time constant, and is sensitive to bilateral loss from decline in the gain, correlates better with remaining vestibular function than either the gain or the time constant, considered separately. Furthermore, as the Gain*Tc* product is a continuous variable, it could be reasonably used to follow progress over time and answer questions such as: Am I getting better or worse?

LIMITATIONS

Our "normal" group was largely composed of individuals with complaints of dizziness, but with no peripheral vestibular lesion. It is possible that these persons had undiscovered peripheral vestibular lesions, or the process that caused their symptoms affects the Gain*Tc* Product. While possible, this is unlikely, as in **Table 3** we point out that several large studies of normal subjects containing data from which the Gain*Tc* product can be computed, produce similar values to ours.

Second, participants in this study were tested in two different commercially available rotatory chairs. It is possible that there are systemic differences in the Gain*Tc* product, depending on differences in device characteristics. Again, while possible, this is unlikely as in **Table 3** we point out that studies of subjects in many other settings, including subjects with unilateral vestibular loss, resulted in similar values for the Gain*Tc* product.

Thirdly, the Gain*Tc* product is a measure of horizontal canal function alone. It does not quantify vestibular function of the vertical semicircular canals or the otolith organs. Other vestibular tests such as the VHIT or caloric test are better able to determine the side of a vestibular lesion. This is an important consideration that shows that the rotatory chair test quantifies only a subset of vestibular function. Nevertheless, the Gain*Tc* parameter, appears well suited to for quantification of bilateral vestibular weakness that affects the entire vestibular apparatus.

CONCLUSION

The Gain*Tc* product is a method of inferring remaining vestibular function of the horizontal semicircular canals. It provides an answer to the question "how much vestibular function do I have." It suffers from the variability intrinsic to other vestibular measures, but has the advantage of simplicity, as it provides a "single number" to quantify vestibular output. As it is a continuous variable, it may be suitable to monitoring progressive vestibulopathies such as those commonly encountered in ototoxicity.

AUTHOR CONTRIBUTIONS

TH accumulated the data, wrote the manuscript. MC reviewed the manuscript. NP-F contributed cases from his practice and provided critical review of the manuscript.

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REVIEW
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Psychophysical Evaluation of Sensory Reweighting in Bilateral Vestibulopathy

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Perception of spatial orientation is thought to rely on the brain's integration of visual, vestibular, proprioceptive, and somatosensory signals, as well as internal beliefs. When one of these signals breaks down, such as the vestibular signal in bilateral vestibulopathy, patients start compensating by relying more on the remaining cues. How these signals are reweighted in this integration process is difficult to establish, since they cannot be measured in isolation during natural tasks, are inherently noisy, and can be ambiguous or in conflict. Here, we review our recent work, combining experimental psychophysics with a reverse engineering approach, based on Bayesian inference principles, to quantify sensory noise levels and optimal (re)weighting at the individual subject level, in both patients with bilateral vestibular deficits and healthy controls. We show that these patients reweight the remaining sensory information, relying more on visual and other nonvestibular information than healthy controls in the perception of spatial orientation. This quantification approach could improve diagnostics and prognostics of multisensory integration deficits in vestibular patients, and contribute to an evaluation of rehabilitation therapies directed toward specific training programs.

Keywords: spatial orientation, vertical perception, multisensory integration, sensory reweighting, rod-and-frame, bilateral vestibular areflexia, psychophysics, Bayesian integration

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INTRODUCTION

Accurate perception of gravity is important for spatial orientation, the maintenance of balance, and the regulation of gait. While the vestibular sense is crucial, it is known that visual, proprioceptive, and somatosensory signals are also used and integrated to estimate the gravitational direction (1–3). In addition, cognitive processes and inflows have been suggested to contribute to deriving this estimate (4, 5). When one of these signals breaks down because of injury, disease, or aging, perception of gravity is disturbed, which can result in inability to orient correctly, reduced ability to stand or walk, and even falling (6–8).

Such sensory impairments not only have a huge impact on quality of life and productivity but also impose high costs to public health service (9, 10). In Europe, for example, more than 20% of the population will be over 65 in 2025, with a particularly rapid increase in the number of persons over 80, and many of them showing age-related functional sensory loss (11). Sensory dysfunction also affects members of the younger population, e.g., through genetic disposition [such as Usher syndrome, see Ref. (12)], as a result of accidents, or through work-related exposure to harmful sensory stimuli, and this represents a significant economic burden to society. Minimizing the

impact of sensory impairments is, therefore, important from various perspectives.

Sensory impairments, while debilitating, may be difficult to diagnose for a number of reasons. First, it is not straightforward to measure the various contributing sensory systems in isolation during natural tasks. For example, a tilt of the head is not only sensed by the vestibular organs, located in the inner ear, but also by the proprioceptors in the neck. But then, one cannot switch off the proprioceptive sense and measure just the vestibular sense in natural conditions. Second, different sensory systems have different dynamics and sometimes provide conflicting information, e.g., visual cues can conflict with vestibular cues. Third, sensory signals can be ambiguous; e.g., the otoliths cannot discriminate between gravity and other linear accelerations (13). Fourth, sensory signals are inherently noisy, which makes them unreliable to some extent by definition; in fact, their noise level is not even fixed, but may, for example, depend on the signal's strength (14, 15). Finally, if one signal deteriorates, or breaks, remaining senses can compensate for this loss; this process, called *sensory reweighting,* is useful, but masks a direct view on the origin of the sensory deficit. Sensory integration reflects the interplay of all these factors, which in turn, makes it difficult to decompose this process into its constituent elements.

Most standard vestibular tests address reflexive behaviors rather than the natural behaviors that depend on the integration of multiple sensory signals (8). For example, tests such as the head impulse test, the caloric test, or VEMP testing merely probe the vestibular system in isolation, in an open-loop manner. While these tests make important contributions to vestibular diagnosis, they lack the sensitivity and selectivity to reveal the weighting of the vestibular component in multisensory integration. Also, the Romberg test and other dynamic posturography tests are difficult to interpret when it comes to a precise quantification of how vestibular signals contribute to the sensory integration process (8).

There is a considerable potential for new diagnostics and prognostics approaches on deficits in multisensory integration (16). Such approaches should aid in tracking the quality of sensory systems across the life span or disease, addressing the risk factors, and signaling when (older) people and patients may be in need of additional care or training programs to keep living an active life. Prognostic and diagnostic markers of the underlying sensory deficits could help in developing programs that mitigate risks for these and other people.

In the present paper, we describe a novel psychophysical approach to assessing sensory reweighting in bilateral vestibular patients. This approach culminated from a series of modeling and psychophysics studies that we performed over recent years to understand the integration of the multiple sensory cues for spatial orientation (5, 17–22). Recently, all this work has been extensively reviewed by Kheradmand and Winnick (23) and we refer the reader there for an overview.

In the present paper, we focus on the use of a reverse engineering approach for assessing multisensory integration and reweighting in bilateral vestibular patients. We first provide a short summary of our approach and what it has revealed about sensory integration in healthy participants. Next, we will demonstrate the utility of this approach for clinical testing, showing that it explains major task-dependent features as well as idiosyncratic differences of bilateral vestibular patients in spatial orientation tasks.

STATISTICAL FRAMEWORK

Sense organs, for instance, those informing the brain about the position or orientation of body or body parts, have only limited precision. The same physical situation will, across different instances, lead to similar, but not identical neural firing patterns. Conversely, one particular neural firing pattern of a sense organ may, in different instances, result from resembling, but not identical physical situations. Due to the omnipresence of such sensory noise, the input–output relationship is not deterministic, but rather probabilistic in character, even in the absence of sensory ambiguities or conflicts (24).

This means that for modeling the information transfer from sensory inputs to the state estimate inferred a probabilistic approach is called for. That is, the output of an individual sensory source is not taken to be one specific state estimate, but rather a probability distribution of state estimates (often a Gaussian distribution is assumed) centered at some state, but with a certain amount of spread. This spread, the variance of the distribution, represents the sensory noise level. The statistically optimal strategy for achieving a state estimate from multiple probabilistic sensory signals is known as Bayesian integration. In this framework, uncertainty about the state is reduced by fusing overlapping sensory information, weighting each sensory signal in proportion to its reliability, i.e., inversely proportional to its noise level (25–27).

Various perceptual studies have provided evidence that the brain might perform such Bayesian multisensory integration. The approach of these studies was to first estimate the noise levels of the individual sensory sources and then use these isolated measures to predict performance in the combined condition (28). Unfortunately, such a forward approach cannot be applied when the contributing signals cannot be assessed in isolation, as in spatial orientation, which is based on visual, somatosensory, and vestibular cues, as well as cognitive processes.

In Clemens et al. (5), we, therefore, approached this problem from the opposite perspective. We assumed that the behavioral outcomes result from an optimal integration process of multiple sensory modalities and implemented an inverse probabilistic approach to infer, given this assumption, how the individual sensory modalities are weighted in. More specifically, we deduced the individual sensory noise levels by behaviorally probing two state estimates—the orientation of the body-in-space and the orientation of the head-in-space—which, under the assumption of optimal integration, weigh all available sensory signals based on their noise levels, after converting them into the task-specific reference frame.

Figure 1A illustrates the transformation and integration steps involved in computing the body-in-space and head-in-space estimates. The scheme is based on the processing of signals from three sensory systems: (1) the otoliths, detecting the orientation of the head with respect to gravity; (2) body somatosensory signals, which are sensitive to the orientation of the body-in-space; and (3) neck sensors, which signal the angle between head and

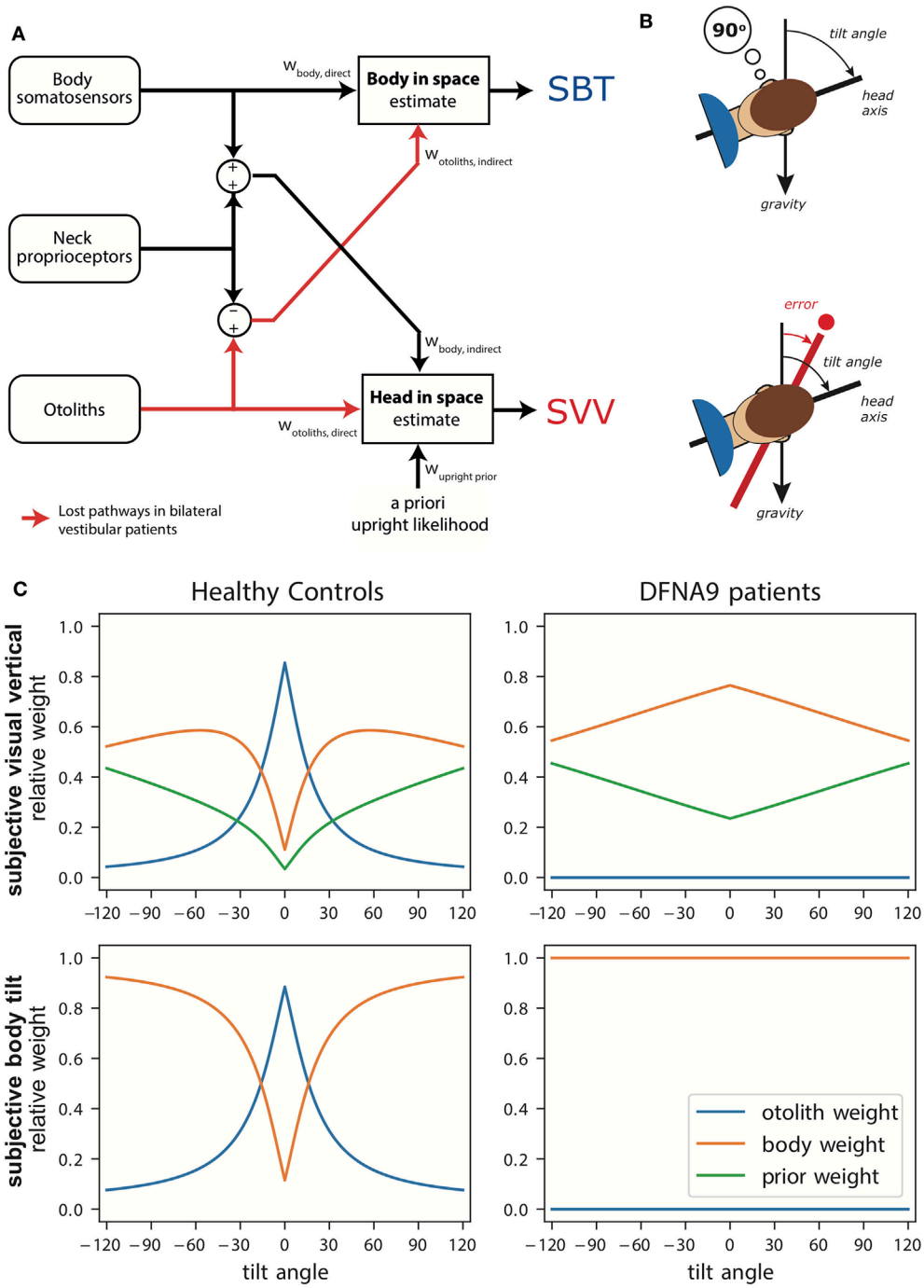

FIGURE 1 | **(A)** Schematic of the Bayesian optimal integration model by Clemens et al. (5). In the subjective body tilt (SBT) task, body somatosensors provide direct information about body orientation in space, whereas the otolith signals undergo a coordinate transformation based on neck proprioception and provide an indirect measurement of body orientation in space. Both signals are weighted ($w_{body,\ direct}$, $w_{otoliths,\ indirect}$) based on their reliability to provide an estimate of body orientation in space. Weights are always relative, summing to unity. In the subjective visual vertical (SVV) task, the otoliths provide direct information about the head-in-space and the body somatosensors provide indirect information. In addition, the brain assumes that upright head orientations are more likely based on prior experience. All three signals are weighted ($w_{otoliths,\ direct}$, $w_{body,\ indirect}$, $w_{upright,\ prior}$) in proportion to their reliability to provide a head-in-space estimate. **(B)** Schematic of the SBT and SVV task. In the SBT task, the subject is given a reference orientation (here 90°) and subsequently rotated in roll, in complete darkness, to an orientation around this reference. Subsequently, the subject is asked to indicate whether his/her current orientation is clockwise or counterclockwise relative to the given reference. In the SVV task, the subject is rotated to a roll tilt angle in complete darkness. Subsequently, a line if briefly flashed and the subject must indicate whether this line is oriented clockwise or counterclockwise relative to gravity. **(C)** Weights attributed to the signals in the Bayesian optimal integration model for healthy controls and bilateral vestibular patients for the SVV and SBT task. Note the clear difference in weighting between patients and control. Weights are derived based on sensory noise levels determined in Alberts et al. (20, 22).

body based on proprioception. All sensory signals are taken to be unbiased, but corrupted with independent Gaussian noise with a given variance.

According to the scheme, an estimate of body orientation in space can be obtained directly from body somatosensory signals, but also indirectly from the head-centered otolith signal, by subtracting the head-on-body signal derived from neck proprioception (5). Likewise, the estimate of head-in-space orientation can be obtained directly from the otoliths, but also through an indirect pathway, by combining the body somatosensory signals with neck proprioceptive information (5). Because the body-in-space and the head-in-space estimates require different coordinate system transformations, the noise levels of the direct and indirect pathways, and thus their weighting, differ. Furthermore, a loss or severe disruption of the otolith or somatosensory inputs will deteriorate both state estimates, but should not completely break down performance due to their multimodal dependence on the direct and indirect pathways (5).

In addition to the two sensory pathways, the scheme allows for the possibility that the two orientation estimates are influenced by prior beliefs about certain orientations. In particular, it has been suggested that the brain takes into account in the integration process that the head is oriented in an upright position most of our daily life (4, 17).

Thus, based on optimality principles, the model estimates the noise levels of the involved sensory systems from behavioral responses in tasks that psychometrically probe body-in-space and head-in-space orientation. These noise levels, in turn, determine the relative weight to be attributed to each sensory signal in the integration process. In the same manner, it can be computed how signals are re-evaluated, i.e., reweighted, in the integration process when one of these signals loses fidelity (i.e., becomes noisier), such as in vestibulopathy. For clarity, we note that sensory substitution is also a form of sensory reweighting in that the weight is zero for the lost sense (because it is completely unreliable). Sensory substitution is used in case of complete loss, and may even suggest that this modality was not used before the sensory loss. In this review we use sensory reweighting as the more general term, embracing sensory substitution.

MEASURING SPATIAL ORIENTATION

To test this model experimentally, it is important to use tasks with outcome measures that allow back-inferring the weights. Two important tasks that are typically used to study spatial orientations are the subjective visual vertical (SVV) and the subjective body tilt (SBT) task [**Figure 1B**, (5)]. In the SVV task, subjects have to report their perception of the orientation of a visual line relative to the gravitational vertical. Note that, to compute the SVV, the brain not only necessitates an estimate of the orientation of the head-in-space but also must compensate for ocular counterroll (OCR) and its effect on line orientation on the retina. In the SBT task, subjects must report how they perceive the orientation of their body relative to gravity or another given reference angle.

When using these tasks for evaluating sensory reweighting, special attention should be given to how responses are measured. In the literature, various studies tested the SVV and SBT task using adjustment methods [see Ref. (29) for a list of adjustment studies]. For example, (tilted) subjects have to adjust the direction of a visual line in front of them until they perceive it vertical in space. While such adjustment methods are easy and intuitively appealing, doubts about the observer's interpretation of the perceptual criterion, as well as a possible response bias, could confound the interpretation of the results (30).

This has elicited the development of more objective psychophysical approaches, such as the two-alternative forced choice (2AFC) paradigm. Using this paradigm, subjects are to make on every trial a binary decision relative to the perceptual criterion, for example, judging whether the orientation of a briefly flashed line is counterclockwise (CWW) or clockwise (CW) relative to their perceived direction of gravity. If not sure, subjects must guess. So, using 2AFC, one does not directly measure the point of subjective equality (as in adjustment tasks), but collects psychometric data to determine this point as the 50%-point of a binary choice.

Responses in the 2AFC task can then be summarized by fitting a cumulative Gaussian function. In the SBT task, the mean of the Gaussian (the 50%-point) represents the subjective perception of the reference orientation. In the SVV task, it represents the SVV compensation angle (the angle between the apparent visual vertical line and the body axis). The variance of the Gaussian, inversely related to reliability or precision, serves as a measure of the variability of the subject in the tasks. Compared to the abundant literature on SBT and SVV accuracy, data on their perceptual variability are still quite scarce, although this measure is key in assessing sensory (re)weighting.

SPATIAL ORIENTATION IN DARKNESS

We have used this psychophysical approach to test healthy human subjects using the SVV and SBT tasks, performed at tilts <120° (5). We found the SBT to be relatively unbiased across the tilt range and the SVV to show substantial biases for tilt angles beyond 60°. The SVV bias is well known in the literature (31–34) and referred to as the A-effect (35). Furthermore, in both tasks, variability became larger with tilt angle, but appeared consistently lower in the SVV.

We used the sensory integration model, described above, to fit both the SBT and SVV data simultaneously (5). To account for the bias in the SVV, the model suggests a contribution of prior knowledge to the integration process, consistent with previous suggestions that the brain has learnt that the head is typically upright in life (4). Given that the SBT is virtually unbiased suggests that this upright prior is not used in its underlying computations. To explain, one could argue that a head prior reduces variability in the SVV, which may be useful for stable visual processing, but at the expense of a bias. Consistent with a mere role of the prior in visual processing, Bortolami et al. (36) reported virtually no bias in the haptically indicated vertical. A bias is also unwarranted for body orientation perception for reasons of balance and postural control, and the brain rather chooses accuracy over precision.

The model fits also confirmed previous suggestions that otolith noise increases with tilt angle. This decreasing reliability with increasing tilt angle (37, 38) may relate to the utricle containing significantly more hair cells than the saccule (39). This arrangement may yield tilt-dependent noise because the utricle senses most effectively head tilts close to upright, whereas the saccule best detects head tilts around 90°.

The sensory noise parameters determine the optimal sensory weights in the integration process. **Figure 1C** (left panels) shows these weights in healthy subjects as a function of tilt angle. Perhaps surprisingly, the SBT estimate is not dominated by information from the body receptors in the direct pathway, but is actually mainly determined by the indirect pathway, carrying the signals of the otoliths, in the behaviorally important range near upright. Only at larger tilt angles, when the otoliths become less reliable, the body sensors (direct pathway) start to dominate. For the SVV, the pattern of otolith weights is remarkably similar, again reflecting increasing otolith noise. As the otolith contribution becomes smaller, the contributions of the prior and indirect pathway become more apparent.

Can this model, which provides a computational account of sensory weighting in healthy participants, also be applied to infer the ramifications in case of vestibular deficits? To our knowledge, there have been no studies that tested SVV and SBT within the same patients, at multiple tilt angles, and reporting quantitative values of bias and variability. This is not to ignore that already quite some important work has been done studying spatial orientation in vestibular patient groups (40–43).

We recently measured the SVV and SBT in a homogeneous group of bilateral vestibular patients, diagnosed with a DFNA9 mutation (20). DFNA9 is a progressive autosomal dominant vestibulo-cochlear disorder, in which an acidophilic mucopolysaccharide deposit is found in both the cochlea and macula, causing strangulation of the nerve endings (44, 45). Furthermore, these patients show neuroepithelial and neural degeneration in the inner ear (46). The DFNA9 mutation causes hearing impairment and bilateral vestibular function loss, but does not affect the proprioceptive or visual system. We performed several clinical tests to confirm complete loss of vestibular function, including the OCR task, VEMP measurements, caloric tests, and VOR velocity step tests (90 and 250°/s) [see Ref. (20)].

Because these patients have bilaterally lost the otolith pathway, it is conceivable that they have reweighted the contribution of the sensory modalities to the integrated percept of verticality. We, therefore, tested them in darkness to establish how body and neck sensors now contribute to the SVV and SBT computations (20). Patients and a group of age-matched controls were tested in the upright position (0°) and at 90° sideways roll tilt.

The SVV was unbiased when upright, but showed a stronger bias in the patients than controls at 90° tilt. This increased bias can be understood with the model at hand (**Figure 1C**, right panels): the sensory-derived head tilt estimate is now solely based on the indirect, body somatosensory, pathway because the otolith weight is set to zero, and thus becomes noisier. This increases the relative weight of the prior and its biasing effect becomes more prominent.

The patients' perception of body tilt (SBT) was unbiased and showed larger variability in both groups at 90°. From the perspective of the model, this increase of perceptual variability with tilt angle in the patients suggests that body somatosensory cues are also contaminated by tilt-dependent uncertainty just like the otoliths [as established in healthy controls (5, 18)]. Recently, we and other research groups found further support for tilt-dependent somatosensory uncertainty using a paradigm that dissociates the orientations of head and body (22, 47). In these experiments, a head-on-body tilt on top of whole body roll tilt was introduced while the percept of vertical was measured. In Alberts et al. (22), we found that the percept of vertical is processed in a head-in-space reference frame, with an increasing bias for larger head-in-space orientations. From the perceptual variability, we inferred that the otoliths contribute more strongly around upright while the body somatosensors make contributions when the body was tilted to larger angles.

The findings in the DFNA9 patients are consistent with previous reports. For instance, Bisdorff et al. (40) showed that bilateral vestibular patients perform quite accurately in the SBT at upright, but are substantially more variable in their responses than normal subjects. Bronstein et al. (41) reported that vestibular patients still compensate for their tilt angle when testing the SVV at 90°, but with a bias about twice as large as in healthy subjects. With our optimal integration model we are now able to explain both observations in terms of sensory reweighting.

SPATIAL ORIENTATION IN THE LIGHT

Hitherto, we have described the integration of vestibular, proprioceptive, and somatosensory information in spatial orientation. To examine this process, participants are typically tested in darkness. But obviously, spatial orientation is a crucial ability that we also need in the light. In the light, visual contextual information from the surrounding environment provides an important cue for spatial orientation, since most common orientations in a naturalistic visual scene are vertical or horizontal (48–50). The brain is known to use this panoramic information as a gravity indicator (51).

The rod-and-frame task can be used to operationalize the effect of panoramic visual cues on the perception of vertical (52). In the rod-and-frame task (**Figure 2B**), subjects have to indicate the orientation of a visual line (rod) within a square frame. Previous work has shown that, when seated upright, frames rotated relative to the gravitational vertical cause biases in the rod-and-frame task, showing a periodical modulation. Biases are about absent for upright and ±45° roll-tilted frame orientations, but increase for intermediate frame orientations (52, 53). In Vingerhoets et al. (54), we have shown that these biases increase when the head is tilted, even when the square frame is replaced by a single line in the retinal periphery.

To interpret rod-and-frame effects in terms of optimal sensory integration, a sensory integration model is needed that incorporates visual contextual information. In Vingerhoets et al. (54), we put forward such a model for the first time, structuring how the rod-and-frame effect relates to statistical properties of the various sensory signals that are involved, representing the frame effect as a distribution with four equally high modes corresponding to the orientations of the sides of the square. In Alberts et al. (21),

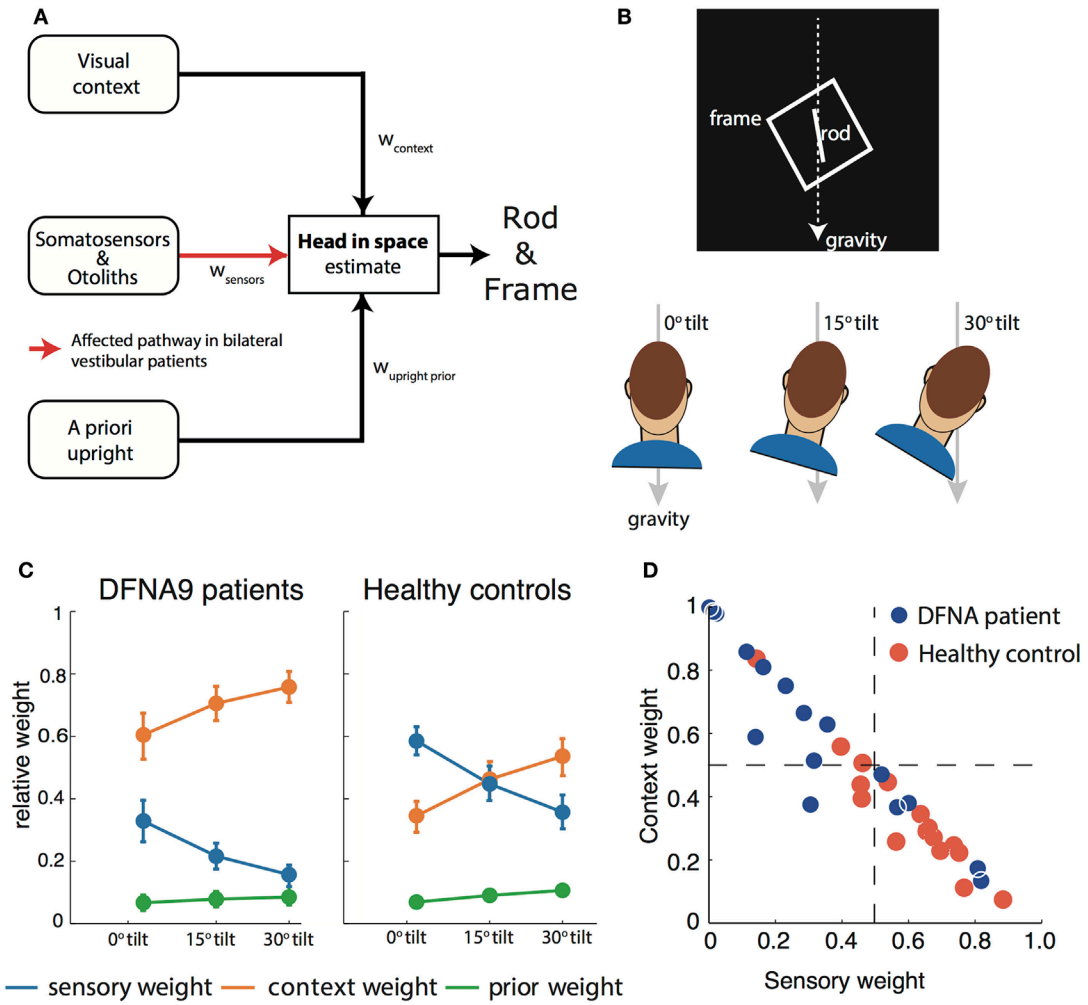

FIGURE 2 | **(A)** Schematic of the Bayesian optimal integration model as proposed in Alberts et al. (21, 55) for the rod-and-frame effect. In the rod-and-frame task, an estimate of head orientation in space is used that is derived from visual context information, sensory information from somatosensors in the body, and otoliths in the head. In addition, the brain assumes that upright positions are more likely based on prior experience. Each of these information streams is weighted into the head-in-space estimate based on its reliability. **(B)** Schematic of the rod-and-frame task. The subject views a rotated frame in which an oriented line is shortly flashed. He/she must indicate whether this line is rotated clockwise or counterclockwise relative to gravity, using a two-alternative forced choice response. Subjects performed this task under three head orientations (0°, 15°, and 30°). **(C)** Weights attributed to the various sources for bilateral vestibular patients and healthy controls. Notice that the patients rely much more (factor 2–3) on the visual contextual information than the controls. **(D)** Weighting of sensory information, lumped from somatosensors and otoliths, and contextual information of the frame to estimate the head orientation in space for the individual patients and controls.

we combined this model with the model of Clemens et al. (5), but lumping the tilt-dependent decrease in precision of the body sensors and otoliths. In addition, we replaced the original four equally high modes relative to the frame with separate modes corresponding to the vertical and horizontal axes of the frame (**Figure 2A**).

We tested this model by collecting the appropriate psychometric measures—accuracy and variability—in conditions in which we manipulated the frame reliability (by increasing its distance from the observer) and head orientation reliability (by tilting the head). We found that the rod-and-frame effect is reduced when the frame reliability is reduced, meaning that it has a weaker biasing effect, and enhanced when the head is tilted and thus the head orientation signals are reduced in precision. We further found that response variability was lowest when the frame was upright, became greater with larger frame orientations and subsequently leveling off. The sensory integration model, which involves a flexible, precision-dependent weighting of head orientation signals and panoramic visual signals (**Figure 2C**, right panel), with separate weights for horizontal and vertical panoramic cues, provided a good description of the data. Because the rod-and-frame task, in combination with the integration model, can characterize the weighting of visual and vestibular information in the estimate of verticality, we subsequently also applied it to quantify the visual compensation strategies in bilateral vestibulopathy.

SENSORY REWEIGHTING IN BILATERAL VESTIBULOPATHY

Recently, we performed a psychophysical evaluation of sensory reweighting in bilateral vestibulopathy using the rod-and-frame task (55). We compared a group of 16 DFNA9 patients to a control group in judging the orientation of a rod (clockwise or counterclockwise relative to gravity), presented within an oriented square frame, while the head was maintained in three different orientations relative to the body. We found larger biases in the patients' percept of vertical and increased variability compared to the control group.

We then fitted the model to back-infer the noise characteristics of the (remaining) signals and compute the weights from these noise characteristics. This revealed that patients had increased their visual weight by a factor of about 2–3 compared to controls, consistent with the hypothesis that, after vestibular loss, the remaining sensory cues are reweighted (**Figure 2C**).

A further strength of this psychophysical evaluation is that weights can be determined at the individual level. Most patients manifested a high visual context weight, but in two patients this weight appeared low and rather a high nonvestibular weight bore out (**Figure 2D**). Such an individualized assessment has good potential for clinical practice, allowing to develop personalized rehabilitation therapies. Healthy controls show a high combined vestibular and nonvestibular weight and are much less influenced by visual contextual cues than the patients.

Based on the findings in our patients, we could interpret the increase of their optokinetic response and their cervico-ocular reflexes (56, 57) as another reflection of the reweighting of visual signals in the remaining integration process. Furthermore, the results of our patients are in harmony with previous studies in bilateral vestibular patients reporting increased reliance on visual cues in spatial orientation tasks (41, 58–63). The added value of our approach, including the computational model, is that all the underlying noise sources could be back-inferred, addressing the increased visual reliance in terms of sensory reweighting and computing the specific sensory weights.

We consider it likely that the reweighting of nonvestibular and visual cues in our patients amounts to sensory substitution in the brain, since our patients showed complete vestibular loss in vestibular diagnostic tests. Of course, increasing the reliance on a visual indicator of what is upright causes a larger bias when the frame axes are not aligned with the gravitational horizontal and vertical. In natural situations, however, this hardly ever happens, which may explain why we found a compensation strategy that enhanced reliance on the visual cues.

The neural correlate of multisensory integration and sensory reweighting remains a matter of speculation. The vestibular nuclei (VN) are the first stage of sensory integration and reweighting for spatial orientation, where neurons are not only tuned to vestibular input, but also to visual, proprioceptive, and motor inputs (3, 64). The VN are structurally and functionally linked to the posterior-temporal junction [TPJ (65)], where the parieto-insular vestibular cortex is situated. Recent brain stimulation studies have implicated the TPJ in estimating the visual vertical (66–68). Other imaging and TMS studies have identified the superior parietal lobule (SPL) for the integration of visual contextual information in the perceived gravity reference frame, mediated by reciprocal inhibitory connections between the early visual areas and the TPJ (67, 69, 70). Thus, if the representation of the gravitational vertical (based on vestibular and nonvestibular signals) is less reliable, there will be more inhibition of the visual contextual representation. This would suggest that visual contextual information drives the SPL more strongly in patients than healthy controls.

VESTIBULAR REHABILITATION

Using simple tasks, such as the SVV, SBT, and the Rod-and-Frame task, embedded in a psychometric test paradigm, we quantified sensory (re)weighting (or sensory substitution because of complete sensory loss) at the single subject level. Note that we mostly used these tasks in static, sustained conditions [but see Ref. (19)], i.e., when the rotation signals in the canals have died away and the only stimulation to the otoliths is gravity. Assessment of canal contributions in sensory reweighting requires dynamic tasks and measurements, which is outside the scope of this paper.

In particular, the rod-and-frame task appears an effective tool for an individualized assessment of visual–vestibular–somatosensory integration and reweighting. If made clinic-ready, such a task could contribute to prognosticate, diagnose, and evaluate clinical treatment in multisensory integration processes that underlie spatial orientation, postural balance, and regulation of gait. Before reaching this stage, however, various aspects need to be optimized, from stimulus design to data recording, test duration, and data-analysis. One way to proceed is by incorporating modern adaptive psychometric procedures, which could improve efficiency in parameter estimation, both in terms of number of trials needed and the quality of the estimates (71, 72).

To date, most vestibular rehabilitation programs consist of exercises that aim to improve postural stability and visual acuity and decrease complaints of dizziness, visual vertigo, and oscillopsia. For balance training (73), our results may suggest (but this needs to be tested) that patients with a larger visual weight will profit more from using the visual context as a vestibular replacement, whereas patients with low visual weight may gain more from somatosensory training. This weight distribution may change with time, i.e., when the rehabilitation has been effective or when disease progresses.

The presented approach, based on inverse probabilistic modeling, could make vestibular rehabilitation programs more specific and better tailored to the need of the end user or patient, providing information to track the recovery, decline, or disease.

AUTHOR CONTRIBUTIONS

WPM wrote the first draft of the manuscript. WPM drafted and LS created the figures. All authors were involved in editing the final version of the manuscript.

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Hierarchical Cluster Analysis of Semicircular Canal and Otolith Deficits in Bilateral Vestibulopathy

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Background: Gait imbalance and oscillopsia are frequent complaints of bilateral vestibular loss (BLV). Video-head-impulse testing (vHIT) of all six semicircular canals (SCCs) has demonstrated varying involvement of the different canals. Sparing of anterior-canal function has been linked to aminoglycoside-related vestibulopathy and Menière's disease. We hypothesized that utricular and saccular impairment [assessed by vestibular-evoked myogenic potentials (VEMPs)] may be disease-specific also, possibly facilitating the differential diagnosis.

Methods: We searched our vHIT database (n = 3,271) for patients with bilaterally impaired SCC function who also received ocular VEMPs (oVEMPs) and cervical VEMPs (cVEMPs) and identified 101 patients. oVEMP/cVEMP latencies above the 95th percentile and peak-to-peak amplitudes below the 5th percentile of normal were considered abnormal. Frequency of impairment of vestibular end organs (horizontal/anterior/posterior SCC, utriculus/sacculus) was analyzed with hierarchical cluster analysis and correlated with the underlying etiology.

Results: Rates of utricular and saccular loss of function were similar (87.1 vs. 78.2%, p = 0.136, Fisher's exact test). oVEMP abnormalities were found more frequent in aminoglycoside-related bilateral vestibular loss (BVL) compared with Menière's disease (91.7 vs. 54.6%, p = 0.039). Hierarchical cluster analysis indicated distinct patterns of vestibular end-organ impairment, showing that the results for the same end-organs on both sides are more similar than to other end-organs. Relative sparing of anterior-canal function was reflected in late merging with the other end-organs, emphasizing their distinct state. An anatomically corresponding pattern of SCC/otolith hypofunction was present in 60.4% (oVEMPs vs. horizontal SCCs), 34.7% (oVEMPs vs. anterior SCCs), and 48.5% (cVEMPs vs. posterior SCCs) of cases. Average (±1 SD) number of damaged sensors was 6.8 ± 2.2 out of 10. Significantly ($p < 0.001$) more sensors were impaired in patients with aminoglycoside-related BVL (8.1 ± 1.2) or inner-ear infections (8.7 ± 1.8) compared with Menière-related BVL (5.5 ± 1.5).

Discussion: Hierarchical cluster analysis may help differentiate characteristic patterns of BVL. With a prevalence of ≈80%, utricular and/or saccular impairment is frequent in BVL.

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The extent of SCC and otolith impairment was disease-dependent, showing most extensive damage in BVL related to inner-ear infection and aminoglycoside-exposure and more selective impairment in Menière's disease. Specifically, assessing utricular function may help in the distinction between aminoglycoside-related BVL and bilateral Menière's disease.

Keywords: vestibulo-ocular reflex, video-head-impulse testing, Menière's disease, aminoglycoside-related ototoxicity, vestibular-evoked myogenic potentials

INTRODUCTION

Key complaints in patients with bilateral loss of peripheral-vestibular function [bilateral vestibular loss (BVL)] are unsteadiness of gait (worse in the dark and on uneven surfaces), postural imbalance, blurred vision (i.e., "oscillopsia") during head movements due to an insufficient angular vestibulo-ocular reflex (aVOR) and impaired spatial orientation (1–6). We previously characterized the distribution of affected semicircular canals (SCCs) in a cohort of 109 patients with BVL due to various causes and described disease-specific patterns of SCC hypofunction (7). Whereas for BVL related to infectious inner-ear disorders, cerebellar ataxia–neuropathy–vestibular areflexia syndrome (CANVAS) and bilateral hearing-loss horizontal, anterior and posterior SCCs were equally affected, we found significant sparing of the anterior SCCs in patients with aminoglycoside-related BVL, bilateral Menière's disease and idiopathic BVL. While our previous study provided detailed information on SCC function, it did not assess the functional integrity of the otolith organs (i.e., the utriculus and sacculus). Previous studies have indicated impairment of the otolith organs as well in BVL, using eccentric rotation (8) or inter-aural linear head motion (9). These paradigms, however, are limited in their applicability, as they allow testing of utricular function only and provide information on bilateral utricular function only in case of inter-aural accelerations. More detailed and targeted testing of utricular and saccular function became available with the introduction of vestibular-evoked myogenic potentials (VEMPs) (10, 11). Compared with loss of function of the horizontal SCCs, saccular impairment has previously been reported to be less frequent, with unilaterally absent responses on cervical VEMPs (cVEMPs) in 4/84 cases only and no cases with bilaterally absent responses (12). In another study, response amplitudes in BVL patients were below the 5th percentile of values in healthy normal subjects in 64% [ocular VEMPs (oVEMPs)] and 61% (cVEMPs), respectively (13). In their study, utricular function differed significantly depending on the underlying cause of BVL, being worst for aminoglycoside-related vestibulopathy and best for Menière's disease.

In analogy to the observed disease-specific pattern of SCC function and following-up on previous studies restricted to the assessment of horizontal SCC function, we hypothesized that the pattern of utricular and saccular dysfunction in BVL may be disease-specific and associated with different SCCs. Based on the results published by Agrawal and coworkers (13), we predicted worst utricular function in aminoglycoside-related vestibulopathy. Furthermore, there is currently no convincing explanation for the disease-specific patterns of SCC hypofunction in BVL. Possibly, peripheral-vestibular hypofunction in BLV follows the anatomy of the vestibular nerve or the vestibular artery. Alternatively, other—yet poorly understood—mechanisms affecting SCC and otolith hair cell function such as local inflammation, toxins [see, e.g., Ref. (14)] or disruption of the endolymphatic membrane may lead to BLV. In the first case, we predict (a) simultaneous normal or impaired functioning of the anterior and horizontal canal and the utriculus (being supported by the superior branch of vestibular nerve/artery) and (b) normal or impaired functioning of the posterior SCC and the sacculus (being linked to the inferior branch of vestibular nerve/artery) (15). In the latter case (i.e., damage to the hair cells), no such correlation is expected. To address these predictions in patients with BVL, we analyzed results from video-head-impulse testing (vHIT) of all six SCCs and VEMPs of both the utriculus (termed oVEMPs) and the sacculus (termed cVEMPs) with hierarchical cluster analysis and correlated the pattern of SCC, utricular and saccular hypofunction with the underlying cause of BVL.

MATERIALS AND METHODS

This study was carried out in accordance with the recommendations of the Cantonal Ethics Committee Zurich and in accordance with the Declaration of Helsinki. As this was a retrospective database analysis, retrieval of informed written consent from all involved patients was not feasible. The protocol was approved by the Cantonal Ethics Committee Zurich and exempt for retrieval of written informed consent was granted (study protocol 2013-0468). We retrospectively screened our vHIT database for patients with a diagnosis of BVL, i.e., that demonstrated vestibular loss in at least one SCC on each side, that have also received otolith testing. This search was last updated in March 2016 and included the entire time period after introducing testing of both the horizontal and vertical SCCs at our clinic in October 2012.

vHIT Recording Procedure

The standard procedure used for testing individual SCCs by vHIT at our clinic requires 20 valid head impulses for each canal [see Ref. (16) for a detailed description], with SCCs tested in pairs according to the planes of stimulation (horizontal canals, RALP plane for right anterior and left posterior canal, LARP plane for left anterior and right posterior canal). For video-oculography, commercially available video-head-impulse testing goggles (Otometrics, Taastrup, Denmark) with an infrared camera recording the right eye was used. Horizontal and vertical eye position was measured at a frequency of 250 Hz, and angular head

velocity was determined by three orthogonal mini-gyroscopes. For further analysis, eye and head velocity values were calculated.

VEMP Recording Procedure

We reviewed otolith function as assessed by cVEMPs (saccular testing, air- or bone-conducted stimulation) and oVEMPs (utricular testing, bone-conducted stimulation). Calibrated headphones (Telephonics TDH-39P; Telephonics Corp., Farmingdale, NY, USA) were used to apply air-conducted sound stimuli (500 Hz, 6 ms tone bursts at 90–100 dB normal hearing level, total of 200 bursts) monaurally to the right and left ears for cVEMPs. The procedure was identical to the one described by Blanquet and colleagues (17): "During stimulation, subjects were asked to sit and turn their head as much as possible to the side to tense their sternocleidomastoid muscle (SCM). EMG activity was recorded (Viking V system; Nicolet Biomedical, Madison, WI, USA) from the upper half of the SCM ipsilateral to the side of acoustic stimulation. A reference electrode was placed on the upper part of the sternum. The background SCM contraction was monitored online and measured over the 20-ms prestimulus interval (using root-mean-square EMG amplitude). Signals of 200 air-conducted cVEMP stimuli were averaged, as previously reported by Poretti et al. (18). Note that in case of inconclusive or negative air-conducted cVEMPs, bone-conducted cVEMPs were obtained and judgment was based on the findings from the latter. Vibrations (unshaped 500 Hz bursts resulting in inter-aural accelerations of about 0.1 g, duration 4 ms, 200 stimuli in total) were applied using a Minishaker (Model 4810, Brüel & Kjaer, P/L, Naerum, Denmark) placed over the hairline near Fz, as previously described by Weber et al. (19). Again, responses from the contralateral SCM were recorded. To improve reproducibility of measurements and to reduce noise from asymmetric muscle tension in individuals, response amplitudes were normalized. This procedure is based on the assumption that there is a linear relationship between the level of muscle contraction and the response amplitude. This was demonstrated for moderate to strong muscle contractions (20) and confirmed by Rosengren more recently (21). Reported values for air- and bone-conducted cVEMPS will therefore be unitless." Only responses obtained at the highest stimulus intensity applied were considered. If more than one measurement was obtained at this intensity, we calculated the average.

"Bone-conducted oVEMPs (unshaped 500 Hz bursts resulting in inter-aural accelerations of about 0.1 g, duration 4 ms, 200 stimuli in total) were applied by the same Minishaker, placed again over the hairline near Fz. Stimuli were recorded with surface electrodes placed beneath the eyes during up-gaze," as described by Blanquet and colleagues (17). Further details can be found here (10, 11).

Patient Identification and Data Analysis

Previously, we have reported on patterns of SCC hypofunction in patients with vHIT-confirmed BVL (7). If serial vHITs were obtained in individual patients and concomitant VEMPs were available only from one session, all results were selected from this session. We re-analyzed aVOR gains in all patients using Otosuite Version 3.0 (Otometrics, Taastrup, Denmark) and used custom-written MATLAB (R2017b, The MathWorks, Natick, MA, USA) routines for the quantification of corrective saccades. This provided cumulative overt saccade amplitudes [for detailed analysis, see Ref. (7)]. Vestibular hypofunction was defined as a reduction in VOR gain and/or the occurrence of compensatory saccades. For a diagnosis of BVL, hypofunction of at least one canal on either side was required; importantly, these two canals could be coplanar or not. For gains, cutoff values of 0.8 (for the horizontal canals) and 0.7 (for the vertical canals) have been proposed by the manufacturer of the video-goggles (GN otometrics) to distinguish normal from reduced aVOR function. Recently proposed cutoff values suggest that cumulative saccade amplitudes above 0.7–0.8°/trial indicate loss of function of the canal tested (7, 22). Here, we adhered to the cutoff value (0.73°/trial) proposed by Tarnutzer et al. (7), as the same statistical approach was used. The underlying cause of BVL—if identified—was retrieved from the patients' clinical files. Files were screened for exposure to vestibulotoxic drugs such as aminoglycosides and to CNS infections. We followed the AAO-HNS 1995 guidelines for diagnosing MD (23). A diagnosis of bilateral sensorineural hearing loss (SNHL) required documented hearing impairment as assessed by pure tone audiogram based on CPT-AMA guidelines (24) with a CPT value > 20% on both sides and exclusion for other causes. Diagnostic criteria for CANVAS were based on the definition provided by Szmulewicz et al. (25). MR imaging was required to confirm vestibular schwannoma or central causes. The diagnosis of vestibular neuritis was based on clinical grounds (defined as a single episode with acute-onset, prolonged vertigo or dizziness and spontaneous nystagmus) as documented in the patient's medical records and—if available—on vestibular testing in the acute stage (26).

Two experienced neurootologists (Alexander A. Tarnutzer and Konrad P. Weber) independently reviewed all vHIT traces. Interrater agreement for individual canal function (normal vs. pathological) was 0.85 (Cohen's kappa) (27). Traces were evaluated for reduced aVOR gain, increased corrective saccades or a combination of both (7). Discordant ratings were resolved by discussion among the two reviewers.

For assessing the integrity of the utriculus and sacculus, three different VEMP parameters were included: peak-to-peak amplitudes, amplitude asymmetry ratio (left vs. right side) and latencies. Left to right amplitude asymmetries of more than 30% were considered abnormal for oVEMPs and cVEMPs. This was based both on normative values obtained with the same setup and derived cutoff values (defined as mean + 2 SD) and the range of cutoff values typically proposed in the literature (10). Regarding response latencies and peak-to-peak amplitudes, values were compared with those recorded from 26 healthy human subjects (aged 38.4 ± 15.8 years; 11 females) with the same setup. For latency, values above the 95th percentile of values in the controls were considered abnormal, while for amplitudes, values below the 5th percentile of normal values were defined as abnormal (for details see **Table 1**).

Individual patterns of SCC and otolith hypofunction were analyzed and compared for different underlying disorders. MATLAB and SPSS 23 (IBM, Armonk, NY, USA) were used for statistical analyses. Fisher's exact test with Bonferroni correction for multiple tests was applied to determine significant differences in the frequency of specific conditions (such as impaired vs. normal peripheral-vestibular function). Analysis of gain values

TABLE 1 | Diagnostic criteria for impairment of the semicircular canals (SCCs) and the otolith organs.

SCCs	Method: vHIT Parameters: 1. Gain 2. Catch-up saccades Definition of impairment (at least one): • Reduced gains (horizontal canals <0.8; vertical canals <0.7) • Overt/covert catch-up saccades
Utriculus	Method: bone-conducted oVEMPs Parameters: 1. Peak-to-peak amplitude (n10–p15) 2. Amplitude asymmetry (L/R) 3. Response latencies (n10, p15) Definition of impairment (at least one) 1. Amplitude < 5.8 μV 2. Amplitude asymmetry > 30% 3. Response latencies > 95th percentile of normal: a. n10 > 13.8 ms b. p15 > 18.7 ms
Sacculus	Method: air-conducted/bone-conducted cVEMPs Parameters: 4. Peak-to-peak amplitude (p13–n23) 5. Amplitude asymmetry (L/R) 6. Response latencies (p13, n23) Definition of impairment (at least one) 1. Amplitude < 0.8[a] 2. Amplitude asymmetry > 30% 3. Response latencies > 95th percentile of normal: a. p13 > 17.3 ms b. n23 > 30.3 ms

[a]Peak-to-peak amplitudes for air- and bone-conducted cVEMPs were normalized for sternocleidomastoid muscle contraction level. Therefore, these values are unitless. cVEMPs, cervical vestibular-evoked myogenic potentials; L, left; oVEMPs, ocular vestibular-evoked myogenic potentials; R, right; vHIT, video-head-impulse testing.

TABLE 2 | Epidemiological findings of the 101 patients with BVL and both SCC and otolith testing available.

Disease	Cases (%)
Unclear	54 (53.4)
Vestibulotoxic drugs[c]	12 (11.8)
Menière's disease	11 (10.9)
Infectious	7 (6.9)
Bilateral SNHL	3 (3.0)
CANVAS	2 (2.0)
Autoimmune[a]	3 (3.0)
Head trauma	2 (2.0)
Bilateral schwannoma	4 (4.0)
Central causes[b]	2 (2.0)
Schwannoma + VN[d]	1 (1.0)
Total	101 (100)

BVL, bilateral vestibular loss; CANVAS, cerebellar ataxia, neuropathy, vestibular areflexia syndrome; SCC, semicircular canal; SNHL, sensorineural hearing loss; VN, vestibular neuritis.
[a]One case of possible Cogan's syndrome, one case with Wegener granulomatosis, one case with unknown autoimmune-related disorder.
[b]MRI-confirmed cavernoma in the left brachium pontis with possible involvement of the vestibular nuclei in one case, cerebellar ataxia with bilateral vestibulopathy (but no signs of ganglionopathy or polyneuropathy) in the other case.
[c]This includes the following aminoglycosides: gentamicin (n = 9), tobramicin (n = 2). In one case, the type of aminoglycoside remained unclear.
[d]Sequential occurrence of vestibular schwannoma on one side and vestibular neuritis on the other side (n = 1).

and cumulative saccade amplitudes was based on non-parametric analysis of variance (Kruskal–Wallis ANOVA) with Tukey–Kramer correction for multiple tests. The level of significance for all statistical tests was $p = 0.05$. We applied a generalized linear model (SPSS) to analyze effects of the underlying disorders on the extent of peripheral-vestibular impairment. Fisher's least significant difference method was used to correct for multiple comparisons when performing pairwise comparisons between the different diagnoses.

For visualization of coherent patterns in large data sets the cluster heat map has been very useful and became one of the most popular graphical illustrations in biological sciences (28). We implemented this approach to our data analysis to identify patterns of vestibular impairment in patients with bilateral vestibulopathy of diverse origin. For each sensor and subject, the functional state (based on the overall rating) was retrieved (intact vs. deficient). We applied hierarchical clustering using the clustergram function (MATLAB) to obtain heat maps with dendrograms of the entire data set [see Ref. (29)]. The heat map was clustered by Euclidean distance, i.e., the geometric distance of the single (raw) data points in the multidimensional space. The data were standardized along the data columns, i.e., for the individual results from single subjects. This means that values are transformed such that the mean is 0 and the SD is 1 in the specified dimension (i.e., each column—reflecting the results from a single subject—in our analysis). This standardized value will then be depicted in a range of colors between 2.5 (dark blue) to −2.5 (dark red) as indicated by the legend. Note, however, that for individual patients, only one intensity of blue and red (being more or less dark/light) are used as only two functional states (1 = intact, 0 = deficient) are possible. The intensity of the colors depends on the calculated SD when performing the standardization. If all 10 sensors had the same functional state (i.e., were deficient) in a single patient, resulting values after standardization in these cases will be 0 and by definition coded by white color. Cluster dendrograms in our data set indicate those patients (x-axis) and vestibular sensors (y-axis) that are the least different, as these groups cluster together first. More distinct clusters will group later.

RESULTS

From the 3,271 patients stored in the vHIT database, 142 patients with suspected BVL were identified and their vHIT recordings were reviewed independently by two reviewers (Alexander A. Tarnutzer and Konrad P. Weber). Eventually, 101 patients with confirmed BVL who also had received quantitative testing of both the utricles and the saccules were included (38 females and 63 males, 61.9 ± 16.8 years old, mean age ± 1 SD). Findings of 68 of those 101 patients were previously reported in a study restricted to video-head-impulse testing (7). A diagnosis of the underlying cause of BVL could be identified in 47/101 cases (46.6%), with vestibulotoxic drugs (12/101, 11.8%), Menière's disease (11/101,

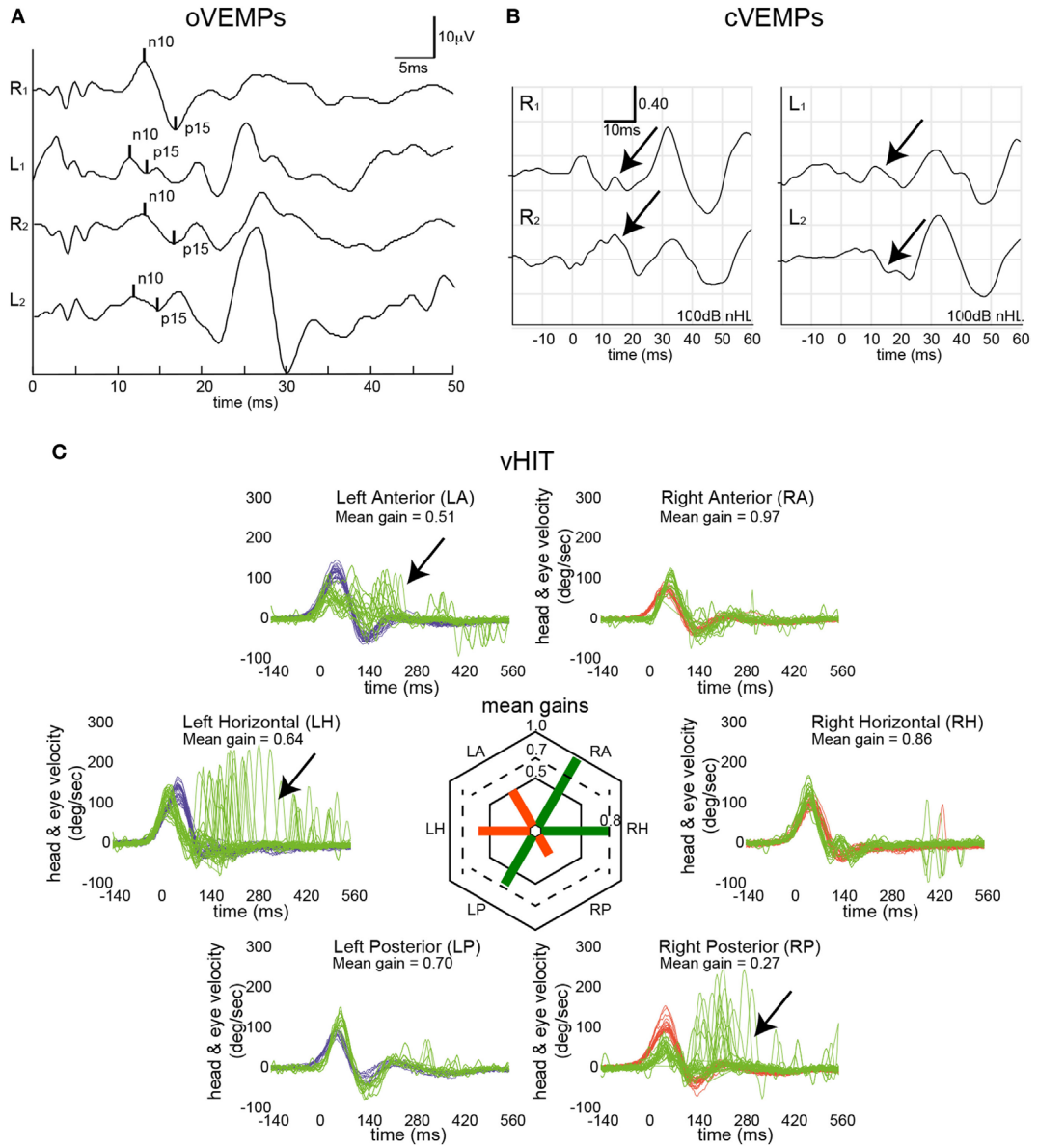

FIGURE 1 | Vestibular mapping in a single patient with bilateral Menière's disease. Otolith testing indicated left-sided utricular impairment [ocular vestibular-evoked myogenic potentials (oVEMPs) **(A)**] based on two repetitions with an average asymmetry ratio of 67% (cutoff ≤ 30%) and a reduced peak-to-peak amplitude (3.64 µV, 5th percentile = 5.8 µV), while n10 and p15 latencies were within normal range. Bone-conducted cervical vestibular-evoked myogenic potentials (cVEMPs) **(B)** were bilaterally absent (as indicated by the black arrows). In panel **(C)**, eye velocity traces (in green) and head velocity traces (in blue for head turns to the left and in red for head turns to the right) are plotted against time for each semicircular canal (20 trials per canal recorded). Note that eye velocity traces were inverted for better visualization and comparison with the head velocity traces. Catch-up saccades identified by OtosuiteV 3.0 are presented in dark red. vHIT demonstrated loss of function (as indicated by the black arrows) in the left horizontal and left anterior canal and the right posterior canal.

10.9%), and infections involving the inner ear (7/101, 6.9%) being the most frequent disorders (see **Table 2** for details).

Single subject data are shown in **Figure 1** for a patient with bilateral Menière's disease. While on the left side the horizontal and the anterior canal were impaired, it was the posterior canal on the right side that demonstrated reduced gain and correction saccades. In addition, oVEMPs indicated impaired utricular function on the left side, while cVEMPs suggested bilateral saccular loss of function.

Distribution of Affected SCCs, Gains and Cumulative Saccade Amplitudes

Different aspects of peripheral-vestibular loss are illustrated in this section. This includes statistical analysis of the frequency of SCCs rated as having peripheral-vestibular hypofunction, distribution of gain values and cumulative saccade amplitudes (see **Figure 2**; **Table 3**). Similar as in our previous publication (7), no significant ($p > 0.05$, Fisher's exact test) left/right differences were found regarding

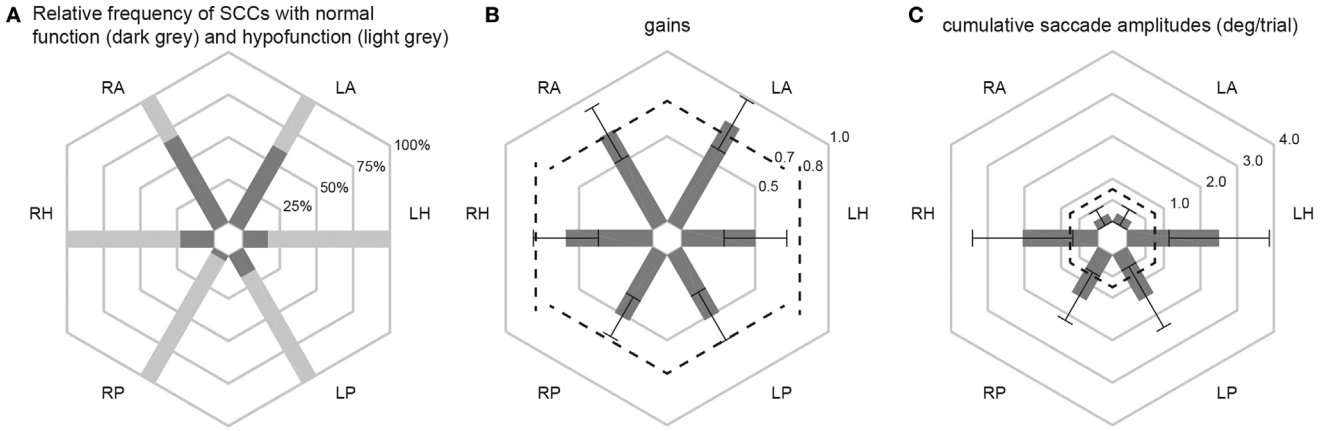

FIGURE 2 | In panel **(A)**, the percentage of patients with normal function (dark gray shaded areas) and with hypofunction (light gray shaded areas) for the different semicircular canals (SCCs) are illustrated in a hexplot. Median (±1 median absolute deviation) gains **(B)** and cumulative saccadic amplitudes **(C)** of all patients ($n = 101$) are shown separately. Gain values (from 0 to 1) and cumulative saccadic amplitudes (°/trial, from 0 to 4) are provided along the different hexagons. Cutoff values for reduced gains (<0.8 for the horizontal canals, <0.7 for the vertical canals) and for abnormally increased cumulative saccade amplitudes (>0.73°/trial) are indicated by dashed lines.

the frequency of SCCs rated as deficient. Therefore, trials from the left and right side were pooled for further analyses. This was also true for the distribution of gains and cumulative saccade amplitudes.

Overall, fractions of SCCs rated as having peripheral-vestibular hypofunction were significantly ($p < 0.001$) larger for the horizontal and posterior SCCs than for the anterior SCCs. Likewise, compared with the posterior and horizontal SCCs, anterior SCCs showed significantly ($p < 0.001$) higher median gains and significantly ($p < 0.001$) smaller cumulative saccade amplitudes. In agreement with our previous publication, which included subpopulations with at least five samples studied with greater detail, rates of affected SCCs were not significantly different ($p > 0.05$) for infectious inner-ear disorders. At the same time, we noted significantly higher rates of impairment for the horizontal and posterior canals compared with the anterior canals in patients with aminoglycoside-induced BVL, Menière's disease and idiopathic causes (see **Table 3** for specific p-values).

In 12 patients (11.9%), vHIT demonstrated bilaterally normal horizontal canal function. In 10 out of those 12 patients, the posterior canals were bilaterally impaired, with SCC impairments being restricted to the posterior canals in 8/12. In these patients, cVEMPs were more frequently abnormal than oVEMPs (75%; bilateral in 4 and unilateral in 5) vs. 50% (6/12; bilateral in 2, unilateral in 4). Underlying diagnoses in these patients were BVL of unclear origin ($n = 6$), bilateral Menière's disease ($n = 4$), bilateral SNHL ($n = 1$), and bilateral schwannoma ($n = 1$).

oVEMPs—Response Latencies and Amplitudes

Median [±1 median absolute deviation (MAD)] latencies in oVEMPs were calculated for the n10 and p15 response and peak-to-peak amplitude (n10–p15) was determined, with values from both sides pooled for calculation, as they did not differ significantly ($p > 0.05$, t-test). oVEMP responses were unilaterally ($n = 15$) or bilaterally ($n = 33$) absent in 48 patients. In those with preserved oVEMP responses, n10 latencies were above the 95th percentile of latencies in healthy controls in 22 patients (unilateral = 15, bilateral = 7). Overall, abnormal (i.e., either delayed or absent) n10 responses (unilateral or bilateral) were found in 66.3% (67/101) of all patients. Likewise, in those with preserved oVEMP responses, p15 latencies were above the 95th percentile of latencies in healthy controls in 12 patients (unilateral = 10, bilateral = 2). Overall, abnormal (i.e., either delayed or absent) p15 responses (unilateral or bilateral) were found in 58.4% (59/101) of all patients (see **Table 4** for details).

In those patients with preserved oVEMP responses, amplitudes were below the 5th percentile of responses in healthy controls in 34 (unilateral = 27, bilateral = 7). Overall, amplitudes were (unilateral or bilateral) abnormal (i.e., either below the 5th percentile or absent) in 76.2% (77/101) of all patients. Rates of reduced amplitudes in our patients were significantly higher than rates of increased n10 ($p = 0.010$) or p15 ($p < 0.001$) latencies. The distribution of amplitudes and oVEMP latencies is illustrated in **Figure 3** both for the entire study population and the most frequent diagnoses. Overall, rates of abnormally increased latencies (n10, p15) and reduced amplitudes were highest for those patients with aminoglycoside-related BVL and those with a history of inner-ear infections, whereas they were lower for Menière's disease and in those cases with BVL of unclear origin (**Table 4**). The peak-to-peak oVEMP amplitude asymmetry ratio (left side vs. right side) was calculated in patients that had preserved responses on at least one side ($n = 68$). Significant asymmetry ratios (i.e., >30%) were identified in 35 patients.

The number of parameters showing impairment (n10 latency, p15 latency, peak-to-peak amplitude, amplitude asymmetry) differed significantly among the subgroups (df = 4, chi-square = 15.777, $p = 0.003$; generalized linear model). Pairwise comparisons demonstrated higher average numbers of parameters affected in patients with BVD related to inner-ear-infections or

TABLE 3 | SCC function—overall rating, gains and saccade amplitudes.[a]

Group	Fraction of SCCs with rated hypofunction (%)				Median gains (1 MAD)				Median cumulative saccade amplitudes (1 MAD) (°/trial)			
	Hor	Ant	Post	Stats	Hor	Ant	Post	Stats	Hor	Ant	Post	Stats
All (n = 101)	162/202 (80.2%)	72/202 (35.6%)	181/202 (89.6%)	H vs. A: $p < 0.001$* H vs. P: $p = 0.036$* P vs. A: $p < 0.001$*	0.56 (0.23)	0.76 (0.21)	0.52 (0.17)	H vs. A: $p < 0.001$* H vs. P: $p = 0.052$ P vs. A: $p < 0.001$*	2.29 (1.50)	0.25 (0.25)	1.44 (0.82)	H vs. A: $p < 0.001$* H vs. P: $p = 0.002$* P vs. A: $p < 0.001$*
Unclear (n = 54)	86/108 (79.6%)	33/108 (30.6%)	96/108 (88.9%)	H vs. A: $p < 0.001$* H vs. P: $p = 0.275$ A vs. P: $p < 0.001$*	0.59 (0.21)	0.78 (0.19)	0.54 (0.15)	H vs. A: $p < 0.001$* H vs. P: $p = 0.124$ P vs. A: $p < 0.001$*	2.04 (1.31)	0.21 (0.21)	1.24 (0.85)	H vs. A: $p < 0.001$* H vs. P: $p = 0.019$* P vs. A: $p < 0.001$*
Vestibulotox. drugs (n = 12)	22/24 (91.7%)	8/24 (33.3%)	24/24 (100%)	H vs. A: $p < 0.001$* H vs. P: $p = 0.578$ A vs. P: $p < 0.001$*	0.45 (0.17)	0.75 (0.14)	0.42 (0.10)	H vs. A: $p = 0.018$* H vs. P: $p = 0.993$ P vs. A: $p = 0.013$*	2.85 (1.10)	0.38 (0.30)	1.85 (0.43)	H vs. A: $p < 0.001$* H vs. P: $p = 0.546$ P vs. A: $p = 0.003$*
Menière's disease (n = 11)	13/22 (59.1%)	3/22 (13.6%)	17/22 (77.3%)	H vs. A: $p = 0.012$* H vs. P: $p = 0.332$ A vs. P: $p < 0.001$*	0.77 (0.12)	0.99 (0.11)	0.61 (0.11)	H vs. A: $p = 0.011$* H vs. P: $p = 0.235$ P vs. A: $p < 0.001$*	1.37 (1.05)	0.01 (0.01)	1.16 (0.87)	H vs. A: $p < 0.000$* H vs. P: $p = 0.489$ P vs. A: $p = 0.001$*
Infectious (n = 7)	13/14 (92.9%)	10/14 (71.4%)	14/14 (100%)	H vs. A: $p = 0.328$ H vs. P: $p = 1.000$ A vs. P: $p = 0.105$	0.32 (0.14)	0.44 (0.26)	0.26 (0.08)	H vs. A: $p = 0.381$ H vs. P: $p = 0.915$ P vs. A: $p = 0.196$	4.24 (0.88)	1.74 (0.72)	2.81 (1.31)	H vs. A: $p = 0.009$* H vs. P: $p = 0.185$ P vs. A: $p = 0.452$

A/Ant, anterior; H/Hor, horizontal; MAD, median absolute deviation; P/Post, posterior; SCC, semicircular canal.

**Indicate statistically significant i.e. ($p < 0.05$) differences.*

[a]*Since statistical analysis showed no effects of laterality ($p > 0.05$), results from left and right sides were pooled for further analyses.*

status post aminoglycoside treatment compared with those with Menière's disease, various causes and unclear origin ($p \leq 0.042$).

When pooling the different parameters indicating utricular hypofunction, abnormalities were noted in 88/101 patients (bilateral = 57, unilateral = 31). Among the different subgroups with specific diagnoses (i.e., BVL related to inner-ear infections, aminoglycosides, Menière's disease, unclear causes), utricular impairment (both sides pooled) was significantly more frequent in aminoglycoside-related BVL compared with bilateral Menière's disease (91.7 vs. 54.6%, $p = 0.039$, Fisher's exact test, Bonferroni-corrected for multiple comparisons). Among the other subgroups, no significant differences were found.

cVEMPs—Response Latencies and Amplitudes

Median (±1 MAD) latencies were determined for the p13 and the n23 responses and peak-to-peak amplitudes (p13–n23) were calculated. Again, values from both sides were pooled, as they did not differ significantly ($p > 0.05$, t-test). cVEMP responses were unilaterally ($n = 14$) or bilaterally ($n = 24$) absent in 38 patients. In those patients with preserved cVEMP responses, p13 latencies were above the 95th percentile of latencies in healthy controls in 11 (unilateral = 8, bilateral = 3). Overall, abnormal (i.e., either delayed or absent) p13 responses (unilateral or bilateral) were found in 47.5% (48/101) of all patients. Likewise, in those patients with preserved cVEMP responses, n23 latencies were above the 95th percentile of latencies in healthy controls in 4 (unilateral = 4, bilateral = 0). Overall, abnormal (i.e., either delayed or absent) n23 responses (unilateral or bilateral) were found in 41.6% (42/101) of all patients (see **Table 5** for details).

In those patients with preserved cVEMP responses, amplitudes were below the 5th percentile of responses in healthy controls in 46 (unilateral = 31, bilateral = 15). Overall, amplitudes were (unilateral or bilateral) abnormal (i.e., either below the 5th percentile or absent) in 73.3% (74/101) of all patients. Rates of reduced amplitudes in our patients were significantly higher than rates of increased p13 ($p < 0.001$) or n23 ($p < 0.001$) latencies. The distribution of amplitudes and cVEMP latencies are illustrated in **Figure 4**. Overall, rates of abnormally increased latencies (p13, n23) and reduced amplitudes were highest for those patients with aminoglycoside-related BVL and those with a history of inner-ear infections, whereas they were lower for those with BVL of unclear origin (see **Table 5**). The peak-to-peak amplitude asymmetry ratio was calculated in patients that had preserved oVEMP responses on at least one side ($n = 78$). Significant asymmetry ratios (i.e., >30%) were identified in 26 patients.

The number of parameters showing impairment (p13 latency, n23 latency, peak-to-peak amplitude, amplitude asymmetry) differed significantly among the subgroups (df = 4, chi-square = 20.174, $p < 0.001$). Pairwise comparisons demonstrated higher average numbers of parameters affected in those patients with BVD related to inner-ear-infections compared with those with Menière's disease, various causes and unclear origin ($p \leq 0.035$).

Abnormalities in absolute amplitudes, amplitude asymmetries or latencies for cVEMPs could be found in 79/101 patients (bilateral = 50, unilateral = 29). Comparing the frequency of cVEMP

TABLE 4 | Ocular vestibular-evoked myogenic potential amplitudes and latencies.

	Peak-to-peak amplitude[a]			n10 Latency[a]			p15 Latency[a]		
	<5th % unilateral (%)[b]	<5th % bilateral (%)[b]	<5th % total (%)[b]	>95th % unilateral (%)[c]	>95th % bilateral (%)[c]	>95th % total (%)[c]	>95th % unilateral (%)[c]	>95th % bilateral (%)[c]	>95th % total (%)[c]
Unclear (n = 54)	17/54 (31.5)	20/54 (37.0)	37/54 (68.5)	13/54 (24.1)	22/54 (40.7)	35/54 (64.8)	13/54 (24.1)	17/54 (31.5)	30/54 (55.6)
Vestibulotoxic drugs (n = 12)	2/11 (26.7)	9/12 (75.0)	11/12 (91.7)	2/12 (26.7)	9/12 (75.0)	11/12 (91.7)	3/12 (25)	8/12 (66.7)	11/12 (91.7)
Menière's disease (n = 11)	2/11 (18.2)	4/11 (36.4)	6/11 (54.6)	3/11 (27.3)	3/11 (27.3)	6/11 (54.6)	1/11 (9.1)	2/11 (18.2)	3/11 (27.3)
Infectious (n = 7)	2/7 (28.6)	5/7 (71.4)	7/7 (100.0)	1/7 (14.3)	5/7 (71.4)	6/7 (85.7)	1/7 (14.3)	5/7 (71.4)	6/7 (85.7)
All (n = 101)	32/101 (31.6)	45/101 (44.6)	77/101 (76.2)	24/101 (23.7)	43/101 (42.6)	67/101 (66.3)	23/101 (22.8)	36/101 (35.6)	59/101 (58.4)

[a]*Since statistical analysis showed no effects of laterality ($p > 0.05$), results from left and right sides were pooled for further analyses. This includes those patients with preserved but abnormal (i.e., with increased latency or decreased amplitude) responses and those with absent responses.*

[b]*Significant reductions in peak-to-peak amplitude were defined as amplitudes below the 5th percentile of peak-to-peak amplitudes in the healthy controls (5th percentile = 5.8 μV).*

[c]*Significant increases in latency were defined as latencies above the 95th percentile of latency-values in the healthy controls (n10 = 13.8 ms; p15 = 18.7 ms).*

impairment (both sides pooled) among the different subgroups with specific diagnoses, we found a significantly higher rate in aminoglycoside-related BVL compared with those cases with BVL of unclear origin (87.5 vs. 50.0%, $p = 0.004$). Among the other subgroups, no significant differences were found.

Individual Patterns of Utricular and Saccular Impairment

The distribution of VEMP patterns in all patients is illustrated in **Table 6**, showing various combinations of unilateral or bilateral utricular and/or saccular hypofunction. Most frequently, oVEMPs and cVEMPs were bilaterally (31%) or unilaterally (12%) abnormal, or bilaterally abnormal oVEMPs were accompanied by unilaterally abnormal cVEMPs (16%). Overall, rates of utricular and saccular loss of function (unilateral or bilateral) in the study population ($n = 101$) were not significantly different (87.1 vs. 78.2%, $p = 0.136$). Noteworthy, the lower rates of otolith (saccular or utricular) hypofunction compared with SCC hypofunction (in 100% of cases) were a consequence of the inclusion criteria (bilateral SCC hypofunction) applied here.

Comparison Between Otolith Function and SCC Function

We compared overall otolith function (VEMPs) and SCC function (vHIT), looking at joint probabilities. This analysis was driven by the question whether the patterns of vestibular (SCC and/or otolith) impairment in BVL match the anatomy of the vascular supply and the innervation of the vestibular organs or rather reflect local damage to the vestibular hair cells. Central to this question is the fact that vascular supply and innervation are provided by two separate branches of the vestibular artery and nerve, respectively. While the superior branch of the vestibular nerve and artery supports the anterior and horizontal SCC and the utriculus, the inferior branch is linked to the posterior SCC and the sacculus. In each patient, we categorized anterior, posterior and horizontal SCC function and oVEMPs/cVEMP as "bilaterally normal," "unilaterally reduced," or "bilaterally reduced." We then correlated otolith and SSC function according to the anatomy as described above (i.e., oVEMPs vs. anterior SCC function, oVEMPs vs. horizontal SCC function, cVEMPs vs. posterior SCC function). This segregation showed that a corresponding pattern of SCC and otolith hypofunction was present in 60.4% (oVEMPs and horizontal SCCs), 34.7% (oVEMPs and anterior SCCs), and 48.5% (cVEMPs and posterior SCCs) of cases (see **Table 7** for details). Specifically, utricular and SCC function were corresponding (i.e., either both normal or both abnormal) with a significantly higher rate for the horizontal canal compared with the anterior canal ($p < 0.001$).

Noteworthy, in those 83 patients with bilateral hypofunction of the posterior SCCs, saccular function was preserved bilaterally ($n = 20$) or unilaterally ($n = 20$) in 40, showing a discrepancy between canal and otolith function despite common innervation/vascular supply by the inferior branch of the vestibular nerve/vestibular artery. Discrepancies between SCC and otolith function showed distinct patterns: bilaterally ($n = 4$) or unilaterally ($n = 19$) preserved utricular function was noted in 73 patients with bilateral hypofunction of the horizontal canals, while bilaterally ($n = 26$) or unilaterally ($n = 16$) impaired utricular function was noted in 53 patients with bilaterally normal function of the anterior canals. While we found no cases with bilaterally normal oVEMPs and bilateral hypofunction of the anterior canals, we identified 42 patients with unilaterally or bilaterally abnormal oVEMPs and bilaterally normal function of the anterior SCCs, showing a dissociation between anterior-canal function and utricular function. For the horizontal SCCs, we observed six cases with (unilaterally) impaired oVEMPs and bilaterally normal canal function, while oVEMPs were bilaterally normal in seven patients with bilateral ($n = 4$) or unilateral ($n = 3$) hypofunction of the horizontal SCCs, suggesting minor discrepancy only between these two parameters. Segregating this analysis for the previously specified disorders, we found the rate of corresponding canal and otolith function to vary between underlying disorders and pairs of canal/otolith function—for details see **Table 8**.

The average (±1 SD) number of damaged sensors (from 2 in case of isolated involvement of 2 canals to 10 in case of complete bilateral vestibular loss) in the entire study population was 6.8 ± 2.0. We noted a significant main effect of the underlying diagnosis (df = 4, chi-square = 26.650, $p < 0.001$; a generalized linear model used as data was normally distributed). Pairwise comparisons demonstrated

significantly ($p \leq 0.001$) higher numbers of affected sensors for patients with BVD related to infectious disorders than for those with BVD linked to Menière's disease and unclear causes. Compared with patients with BVD related to Menière's disease, patients with aminoglycoside-related BVD showed involvement of significantly more sensors ($p < 0.001$) (see **Figure 5** for detailed statistics).

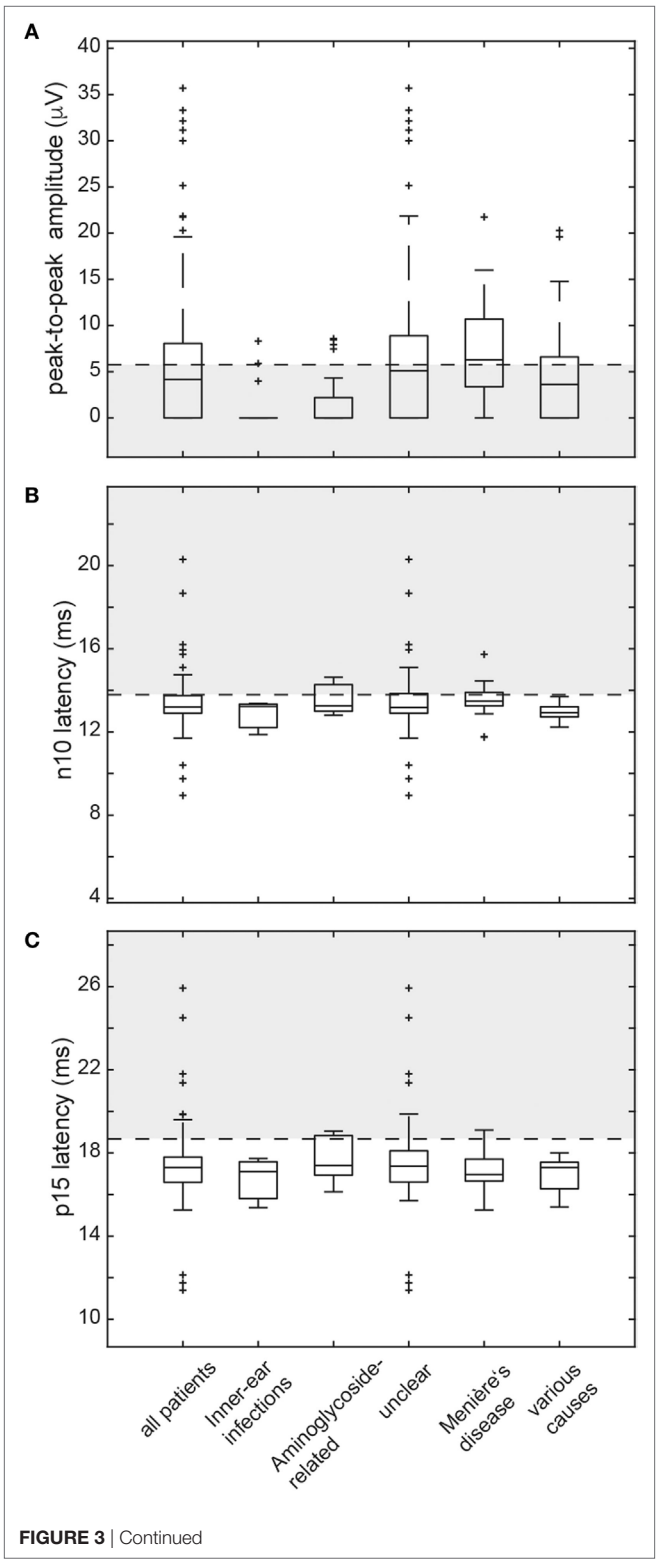

FIGURE 3 | Continued

FIGURE 3 | Box and whisker plots illustrating both peak-to-peak amplitudes (μV) and latencies (ms) for ocular vestibular-evoked myogenic potentials (oVEMPs) in all patients. For peak-to-peak (n10–p15) amplitudes **(A)**, a horizontal dashed line refers to the lower limit of normal (i.e., the 5th percentile of amplitudes measured in the healthy controls). The gray shaded area below indicates significantly reduced amplitudes. For both n10 latencies **(B)** and p15 latencies **(C)**, the upper limit of normal (i.e., the 95th percentile of latency values in the healthy controls) is indicated by a horizontal dashed line. The gray shaded area above refers to significantly increased latencies. The box has lines at the lower quartile, the median, and the upper quartile values. Whiskers extend from each end of the box to 1.5 times the interquartile range from the ends of the box. Outliers (black "+" sign) are data with values beyond the ends of the whiskers. Note that subjects with absent oVEMP responses are not shown on this figure.

Hierarchical Cluster Analysis

Cluster analysis resulted in a heat map with the different vestibular end organs ($n = 10$ in total) and patients ($n = 101$) assessed separately (**Figure 6**). The dendrogram illustrating the clustering of the vestibular sensors (at the left border of the figure) indicated that identical sensors on the left side and the right side merged first (this was true for all three pairs of canals (anterior, posterior, horizontal) and the saccular organs). Only the two utricular organs merged later. Mergers between the different vestibular end organs occurred first for the posterior canals and the horizontal canals (that already had merged with the left utriculus) and then with the right utriculus. At the next higher level of merger, the saccular organs were added, whereas the anterior canals were added last. The top dendrogram [showing the clustering of the patients (columns)] indicated five clusters with at least 15 nodes (marked with black bars). The distinguishing feature in node A ($n = 17$, 8/17 diagnosed as "unclear") was the state of the saccular organs (being spared whereas all other sensors were impaired), whereas in node B ($n = 15$, 11/15 rated as "unclear") it was the state of the saccular organs and the posterior SCCs (both being impaired, whereas all other sensors were relatively spared). This pattern (node B) is consistent with the innervation/vascular supply by the inferior branch of the vestibular nerve. In contrast, for node C, the state of the anterior canals and the saccular organs were the distinguishing features (both remaining intact), whereas for node D it was the residual functioning of the anterior canals that mattered. While most patients belonging to node C remain undiagnosed ("unclear" in 16/19), a significant fraction of patients in node D received a diagnosis of aminoglycoside-related bilateral vestibulopathy (6/16). In node F ($n = 16$), patterns were variable, whereas for some patients only a single anterior canal was outstanding (i.e., being functionally intact), others showed a more balanced pattern with grouping of, e.g., the anterior canals, the posterior canals and the utricular organs. In a smaller node (node E, $n = 11$) with no distinguishing features on the heat map (i.e., white (= 0) on the color bar) all patients with impairment of all 10 vestibular end organs were included. In this cluster, diagnoses as infectious inner-ear disease ($n = 3$), bilateral SNHL ($n = 1$) and autoimmune disorder ($n = 1$) were overrepresented.

TABLE 5 | cVEMP amplitudes and latencies.

	Peak-to-peak amplitude[a]			p13 Latency[a]			n23 Latency[a]		
	<5th % unilateral (%)[b]	<5th % bilateral (%)[b]	<5th % total (%)[b]	>95th % unilateral (%)[c]	>95th % bilateral (%)[c]	>95th % total (%)[c]	>95th % unilateral (%)[c]	>95th % bilateral (%)[c]	>95th % total (%)[c]
Unclear (n = 54)	19/54 (35.2)	17/54 (31.5)	36/54 (66.7)	8/54 (14.7)	10/54 (18.5)	18/54 (33.3)	5/54 (9.3)	8/54 (14.8)	13/54 (24.1)
Vestibulotoxic drugs (n = 12)	1/12 (8.5)	10/12 (83.3)	11/12 (91.7)	3/12 (25.0)	5/12 (41.7)	8/12 (66.7)	3/12 (25.0)	5/12 (41.7)	8/12 (66.7)
Menière's disease (n = 11)	2/11 (17.7)	6/11 (54.6)	8/11 (72.3)	2/11 (18.2)	4/11 (36.4)	6/11 (54.6)	2/11 (18.2)	3/11 (27.3)	5/11 (45.5)
Infectious (n = 7)	1/7 (14.3)	5/7 (71.4)	6/7 (85.7)	2/7 (28.6)	5/7 (71.4)	7/7 (100.0)	1/7 (14.3)	5/7 (71.4)	6/7 (85.7)
All (n = 101)	25/101 (24.8)	49/101 (48.5)	74/101 (73.3)	20/101 (19.8)	28/101 (27.7)	48/101 (47.5)	18/101 (17.8)	24/101 (23.8)	42/101 (41.6)

[a]*Since statistical analysis showed no effects of laterality ($p > 0.05$), results from left and right sides were pooled for further analyses.*

[b]*Significant reductions in peak-to-peak amplitude were defined as amplitudes below the 5th percentile of peak-to-peak amplitudes in the healthy controls (5th percentile = 0.8). Note that peak-to-peak amplitudes for air- and bone-conducted cervical vestibular-evoked myogenic potentials (cVEMPs) were normalized for sternocleidomastoid muscle contraction level. Therefore, these values are unitless.*

[c]*Significant increases in latency were defined as latencies above the 95th percentile of latency values in the healthy controls (n13 = 17.3 ms; p23 = 30.3 ms).*

DISCUSSION

Bilateral vestibular loss of function is often subtle initially and when eventually diagnosed remains of unknown origin in 20–50% of all cases (7, 30–33). Previously, we provided a detailed characterization of horizontal and vertical canal function in BVL, reporting disease-specific patterns of SCC hypofunction which may help in the differential diagnosis and allow more specific treatment (7). Particularly, we described relative sparing of anterior-canal function in aminoglycoside-related BVL and bilateral Menière's disease, while in BVL secondary to inner-ear infections or early hearing loss all SCCs were affected with similar frequency. Here we provide a detailed peripheral-vestibular mapping with hierarchical clustering of quantitative canal and otolith testing in 101 BVL patients asking which pathomechanisms best reflect the patterns of vestibular end-organ damage observed and whether these patterns are disease-specific. The combination of SCC and otolith damage observed in our BVL patients was variable and matched a vascular/neuronal pattern only in about half the cases, limiting the role of this pathomechanism for the development of the pattern of peripheral-vestibular hypofunction in BVL. Rather, the observed dissociation of horizontal and anterior-canal function in the presence of utricular hypofunction suggest that damage to the specific vestibular sensors (i.e., the hair cells) plays an important role.

The Value of Hierarchical Cluster Analysis in Pattern Recognition in BVL

The implementation of hierarchical cluster analysis in the assessment of SCC and otolith damage in BVL patients proved very useful and confirmed and extended our observations from previous work (7). Specifically, hierarchical cluster analysis indicated that identical sensors on the left side and the right side merged first (with the exception of the utricular organs). This observation suggests that in patients with bilateral vestibulopathy the individual vestibular end organs are typically in a similar condition in both labyrinths. The observation that the anterior canals merged latest suggests that the condition of the anterior canals is a distinguishing feature in our patients. Furthermore, cluster analysis revealed several nodes with different patterns of vestibular end-organ impairment, ranging from isolated impairment of the posterior canals to sparing of the anterior canals and/or the saccular organs to loss of function of all vestibular end organs. The cluster analysis therefore further emphasizes the broad spectrum of SCC and otolith impairment in patients with BVL. At the same time, certain diagnoses were enriched in single nodes. Most consistent was the accumulation of patients with aminoglycoside-related vestibulotoxicity in the node with anterior-canal sparing, supporting our findings from the statistical analysis.

Otolith Function—Correlations and Comparison With the Literature

Since we included only patients with bilateral SCC hypofunction, the lower rate of utricular/saccular hypofunction compared with SCC hypofunction is likely due to a selection bias. With utricular (87.1%) and saccular (78.2%) hypofunction occurring at similar frequencies, our findings emphasize the frequent involvement of the otolith organs and confirm a previous report that stated comparable rates of utricular (64%) and saccular (61%) deficits (13). Whereas rates of impairment were somewhat larger in our case series compared with Agrawal and colleagues, this was most likely due to differences in the methodology: besides response amplitudes [as applied by Agrawal et al. (13)], we took latencies and asymmetry ratios into account and assessed vertical canal function also. Therefore, bilateral horizontal SCC hypofunction was not a prerequisite, as in studies that relied on caloric irrigation for diagnosing BVL. In another study, using bilateral horizontal SCC hypofunction as the inclusion criteria, cVEMPs amplitudes were abnormal (bilateral: $n = 51$, unilateral: $n = 8$) in 70.2% of patients (12), which is in a similar range as the 76.7% reported here in those 73 patients with bilateral horizontal SCC hypofunction. Nonetheless, Zingler and coworkers proposed relative sparing of saccular function, as compared with 40 patients with bilaterally absent response on caloric irrigation, cVEMPs were unilaterally absent only in four patients and bilaterally absent in none (12). In our study, cVEMPs were absent in 30 cases (bilateral = 20; unilateral = 10), representing a clearly

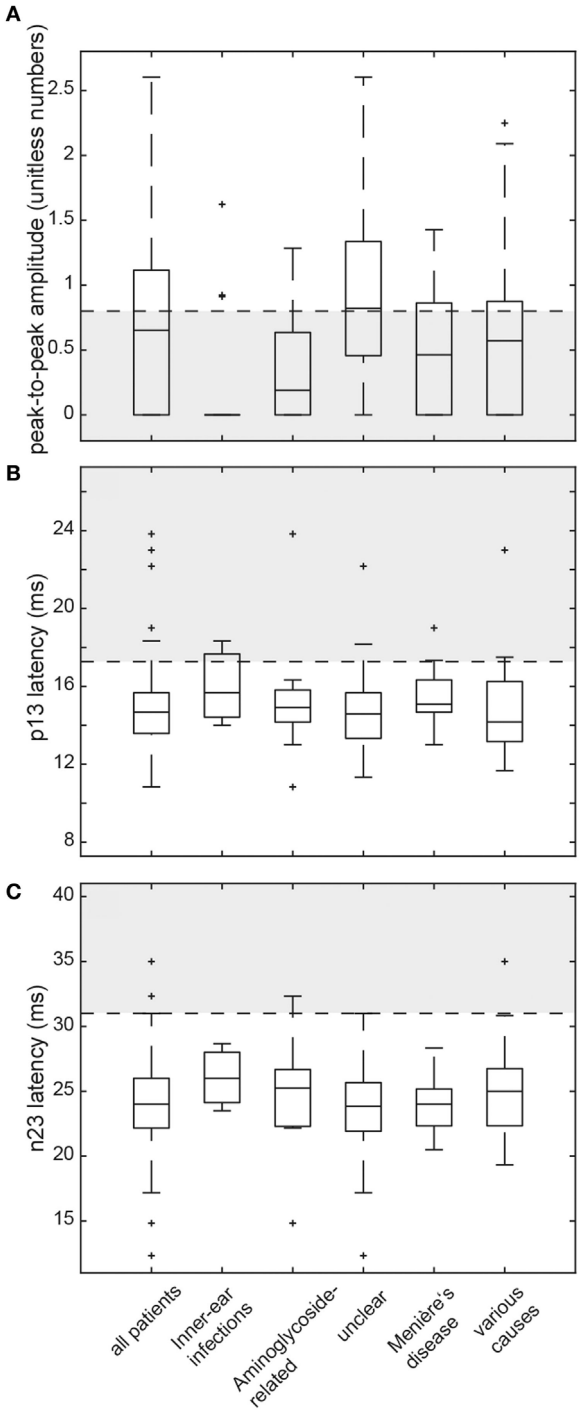

FIGURE 4 | Box and whisker plots illustrating both peak-to-peak amplitudes (unitless numbers) and latencies (ms) for cervical vestibular-evoked myogenic potentials (cVEMPs) in all patients. For peak-to-peak (p13–n23) amplitudes **(A)**, a horizontal dashed line refers to the lower limit or normal (i.e., the 5th percentile of amplitudes measured in the healthy controls). The gray shaded area below indicates significantly reduced amplitudes. For both p13 latencies **(B)** and n23 latencies **(C)**, the upper limit of normal (i.e., the 95th percentile of latency values in the healthy controls) is indicated by a horizontal dashed line. The gray shaded area above refers to significantly increased latencies. For a detailed explanation of the boxes and whiskers, see figure legend of **Figure 3**. Note that subjects with absent cVEMP responses are not shown on this figure.

TABLE 6 | Distribution of utricular and saccular function in the bilateral vestibular loss patients (n = 101).

Combination	Fraction (%)
Ocular vestibular-evoked myogenic potentials (oVEMPs) and cervical vestibular-evoked myogenic potentials (cVEMPs) bilaterally abnormal	31
oVEMPs bilaterally abnormal, cVEMPs unilaterally abnormal,	16
cVEMPs and oVEMPs unilaterally abnormal	12
cVEMPs bilaterally abnormal, oVEMPs unilaterally abnormal	11
cVEMPs bilaterally normal, oVEMPs bilaterally abnormal	10
cVEMPs bilaterally abnormal, oVEMPs bilaterally normal	8
cVEMPs bilaterally normal, oVEMPs unilaterally abnormal	8
cVEMPs and oVEMPs bilaterally normal	4
cVEMPs unilaterally abnormal, oVEMPs bilaterally normal	<1

TABLE 7 | Comparison of semicircular canal (SCC) and otolith function according to the vestibular anatomy—percentage of cases that match in function for various disorders.

Disorders	Hor SCCs vs. utriculus	Ant SCCs vs. utriculus	Post SCC vs. sacculus
Unknown cause (n = 54)	32/54 (59.3%)	18/54 (33.3%)	16/54 (29.6%)
Vestibulotoxic drugs (n = 12)	8/12 (66.7%)	3/12 (25.0%)	10/12 (83.3%)
Menière's disease (n = 11)	6/11 (54.5%)	4/11 (36.4%)	6/11 (54.5%)
Various causes (n = 17)	9/17 (52.9%)	2/17 (11.8%)	9/17 (52.9%)
Infection-related bilateral vestibular loss (n = 7)	6/7 (85.7%)	6/7 (85.7%)	5/7 (71.4%)
All pooled (n = 101)	61/101 (60.4%)	35/101 (34.7%)	49/101 (48.5%)

higher frequency of absent saccular function than proposed by Zingler and colleagues. Sparing of saccular function was also reported in a series of five patients with BVL on caloric irrigation but preserved cVEMPs (34). However, the true rate of saccular impairment in BVL remains to be determined, as requiring bilateral (horizontal) SCC hypofunction as inclusion criterion results in a selection bias.

Rates of abnormal utricular function were disease-dependent, showing significantly larger proportions of impairment in those disorders that resulted in the most extensive SCC damage, i.e., BVL related to inner-ear infections and aminoglycoside-toxicity. Specifically, rates of abnormal oVEMPs were higher in patients with aminoglycoside-related BVL compared with patients with bilateral Menière's disease (91.7 vs. 54.6%, $p = 0.039$), while no such difference was found for cVEMPs. Therefore, oVEMPs may be helpful in the distinction between BVL related to aminoglycoside-toxicity and Menière's disease. This is consistent with findings from Ref. (13). Noteworthy, a pattern of bilaterally impaired utricular function and bilaterally preserved anterior-canal function was noted only in 5/12 patients diagnosed with aminoglycoside-related bilateral vestibulopathy (sensitivity = 41.7%, specificity = 76.4%). This underlines that also for these patients, the pattern of impairment can be variable, with, e.g., only one anterior canal spared or only one utricle affected.

Furthermore, bilaterally impaired utricular function was a very good predictor for bilateral loss of function of the horizontal canals, as in 50 out of 58 cases with bilateral utricular impairment bilateral horizontal canal hypofunction was present as well.

TABLE 8 | All bilateral vestibular loss (BVL) cases with vHIT, ocular vestibular-evoked myogenic potentials (oVEMPs) and cervical vestibular-evoked myogenic potentials (cVEMPs) (n = 101).

		Hor semicircular canal (SCC) function				Ant SCC function				Post SCC function		
		Normal	Unilat red.	Bilat red.		Normal	Unilat red.	Bilat red.		Normal	Unilat red.	Bilat red.
All groups pooled[a]												
oVEMPs	Normal B	6	3	4	oVEMPs	11	2	0	cVEMPs	0	3	20
	Abnormal U	4	5 (2)	19		16	7	7		2	6	20
	Abnormal B	2	6	50		26	15	17		2	5	43
Subgroup analyses[a]												
BVL of unknown cause (n =54)												
oVEMPs	Normal B	4	3	2	oVEMPs	8	1		cVEMPs		3	15
	Abnormal U	2	2 (1)	10		10	2 (1)	2			2 (3)	14
	Abnormal B		4	26		14	8	8		2	1	14
Aminoglycoside-induced vestibulotoxicity (n = 12)												
oVEMPs	Normal B				oVEMPs				cVEMPs			1
	Abnormal U			2		1	1					1
	Abnormal B		2	8		5	3	2				10
Menière's disease (n = 11)												
oVEMPs	Normal B	2		1	oVEMPs	3			cVEMPs			2
	Abnormal U	1	1	2		2	1	1		1	1	
	Abnormal B	1		3		4					2	5
Infectious inner-ear disorders (n = 7)												
oVEMPs	Normal B				oVEMPs				cVEMPs			
	Abnormal U		1	1		1	1					2
	Abnormal B			5				5				5
Various disorders (n = 17)												
oVEMPs	Normal B			1	oVEMPs		1		cVEMPs			2
	Abnormal U	1	1 (1)	4		2	0 (1)	4		1		3
	Abnormal B	1		8		3	4	2			2	9

[a]*All patients with corresponding impairment of both sensors compared are reported in the grey-shaded areas. Note that values in brackets indicate cases with unilateral impairment on non-corresponding sides (e.g., left-sided utricular hypofunction and right-sided horizontal canal impairment).*

Likewise, bilateral impairment of saccular function predicted with high probability bilateral loss of function of the posterior canals (bilateral posterior-canal hypofunction was found in 43 out of 50 cases with bilateral saccular impairment). Bilateral anterior-canal hypofunction, on the other hand, was found in only 17/58 cases with bilateral utricular loss of function, making the utricles a poor predictor for anterior-canal function.

Correlating SCC and Otolith Function in the Entire Study Population and in Disease-Specific Subgroups

Complete bilateral loss of peripheral-vestibular function (i.e., hypofunction of all six SCCs, both utricles and saccules) was present in 11 out of 101 patients (10.9%). Much more frequently, loss of function was restricted to a part of all vestibular end organs. Specifically, we found no patients with bilaterally normal oVEMPs and bilateral hypofunction of the anterior canals. In contrast, we identified 42 cases with unilaterally or bilaterally abnormal oVEMPs and bilaterally normal function of the anterior SCCs. This shows that anterior-canal hypofunction is usually accompanied by abnormal oVEMPs, while loss of utricular function may be isolated, i.e., not reflected in anterior-canal hypofunction. For the horizontal SCCs, we observed only six cases with (unilaterally) abnormal oVEMPs and bilaterally normal horizontal canal function, while oVEMPs were bilaterally normal in seven patients with bilateral or unilateral hypofunction of the horizontal SCCs. This indicates that utricular hypofunction and hypofunction of the horizontal SCCs are frequently linked—a pattern that is also demonstrated in the dendrogram (**Figure 6**). For the posterior SCCs, we observed only four cases with (unilaterally) abnormal cVEMPs and bilaterally normal canal function, while cVEMPs were bilaterally normal in 23 patients with bilateral (n = 20) or unilateral (n = 3) hypofunction of the posterior SCCs. This suggests that posterior-canal hypofunction can be isolated, while cVEMP abnormalities are usually accompanied by posterior-canal hypofunction.

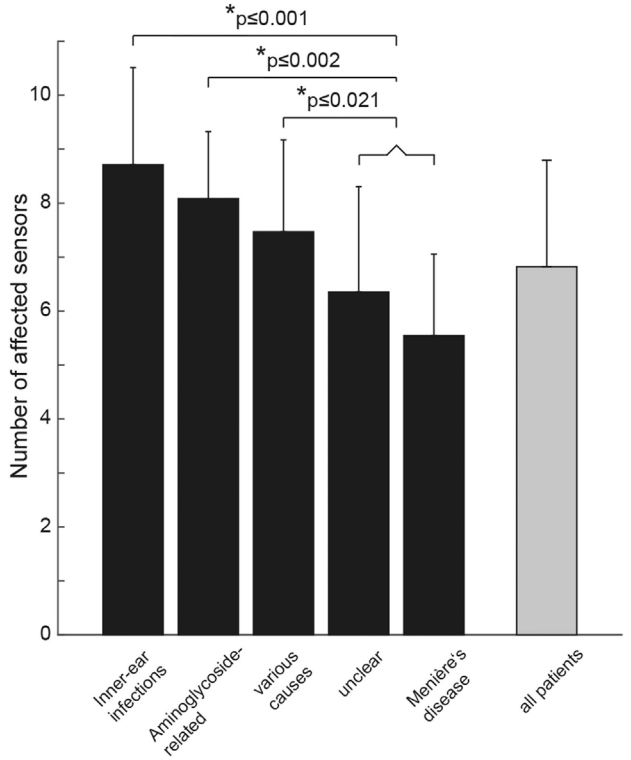

FIGURE 5 | Bar plot illustrating the mean (±1 SD) number of affected vestibular sensors (for each side: anterior/posterior/horizontal semicircular canal, utriculus, sacculus) separately for the different subgroups (in black) and for all patients pooled (in gray). "Various" includes patients with trauma ($n = 2$), bilateral sensorineural hearing loss ($n = 3$), bilateral schwannoma ($n = 4$), combined schwannoma and vestibular neuropathy ($n = 1$), cerebellar ataxia, neuropathy, vestibular areflexia syndrome ($n = 2$), autoimmune ($n = 3$), and central causes ($n = 2$). Statistically significant differences (SPSS: generalized linear model) are indicated by an asterisk (*).

Consistent patterns between (1) posterior SCC and saccular function, (2) horizontal SCC and utricular function, and (3) anterior SCC and utricular function were noted with rates of 49, 60, and 35%, respectively, only. This finding shows that canal and otolith function in BVL is often dissociated. Noteworthy, the pattern varied for different disorders, most likely linked to the underlying pathomechanisms. For disorders with diffuse peripheral-vestibular damage, such as infectious inner-ear disease, rates of concomitance were 72% or higher, while in other disorders such as Menière's disease rates were between 36 and 55% for the different combinations. Similarly, in the largest subgroup (idiopathic BVL), rates were between 30 and 59%. These fairly low percentages speak against combined damage according to the vascular supply or the innervation of the vestibular organs as a common cause in BVL. Rather, the patterns observed in our study favor other, likely local mechanisms affecting the hair cells of the distinct vestibular end organs including inflammation/infection, toxins, and endolymphatic hydrops. Sparing of certain vestibular end organs (as the anterior canals) may point to varying susceptibility to these mechanisms.

In a subgroup of patients ($n = 12$), the horizontal canals were bilaterally spared when assessed by vHIT, whereas both posterior canals were abnormal in 10 out of these patients and the anterior canals were impaired in only four cases. This pattern may suggest a sequential loss of function of the different SCCs, with posterior-canal function showing impairment first, as discussed also by the authors in a previous publication (35). Furthermore, these 12 patients had higher rates of abnormal cVEMPs than oVEMPs (75 vs. 50%), suggesting a predominantly inferior vestibular branch/artery involvement. Interestingly, this pattern was mostly associated with BVL of unclear origin and Menière's disease. To determine whether these patients would have been diagnosed as having BVL when testing the horizontal canals only by use of caloric irrigation, we retrieved results on caloric irrigation as well in these 12 cases. For diagnosing bilateral hypofunction on caloric irrigation, a nystagmus with a mean peak slow-phase velocity of <5°/s for cold- and warm-water irrigation on both sides was required (31). Noteworthy, only two of those 12 patients met criteria for BVL on caloric irrigation, whereas 6 demonstrated unilateral hypofunction only and four had bilaterally normal responses. Therefore, 10 of those patients would have been missed when using caloric irrigation only for diagnosing BVL. Previously, the combination of bilaterally absent cVEMPs and bilaterally normal response on caloric irrigation has been reported in three patients with BVL of unclear origin selected from a large sample of 1,025 patients presenting to a specialized dizzy clinic (36). Furthermore, Fujimoto and colleagues reported dissociated BVL (e.g., abnormal caloric irrigation on one side and impaired cVEMPs on the other side) in 20.3% of their BVL patients (37), again emphasizing the varying combination of involvement of the different vestibular sensors.

Overall, the extent of SCC and otolith damage (as reflected by the number of vestibular sensors affected) was disease-dependent, showing significantly higher rates for BVL related to inner-ear infections and aminoglycoside-toxicity than for Menière's disease. This further stresses out differences in the underlying pathomechanisms leading to BVL and available residual vestibular function. The importance of otolith testing was previously emphasized by others as well: Agrawal and coworkers have reported that otolith dysfunction had a greater association with functional impairment (as assessed by the dizziness handicap inventory) compared with SCC function (13) and Lempert and colleagues have demonstrated a functional role of the otolith-ocular reflex in visual stabilization during high frequency linear head motion (9). Thus, loss of otolith function may be reflected in more severe symptoms and therefore, from a therapeutic perspective, physical therapy and balance training should especially be enforced in those patients with aminoglycoside-related BVL and infectious inner-ear disorders.

Limitations

Our study design was retrospective and patient selection depended on a single test (vHIT). Therefore, these patients did not receive a standardized clinical neuro-otologic examination and there were no prospectively defined diagnostic criteria for specific disorders. For Menière's disease, guidelines according to the AAO-HNS

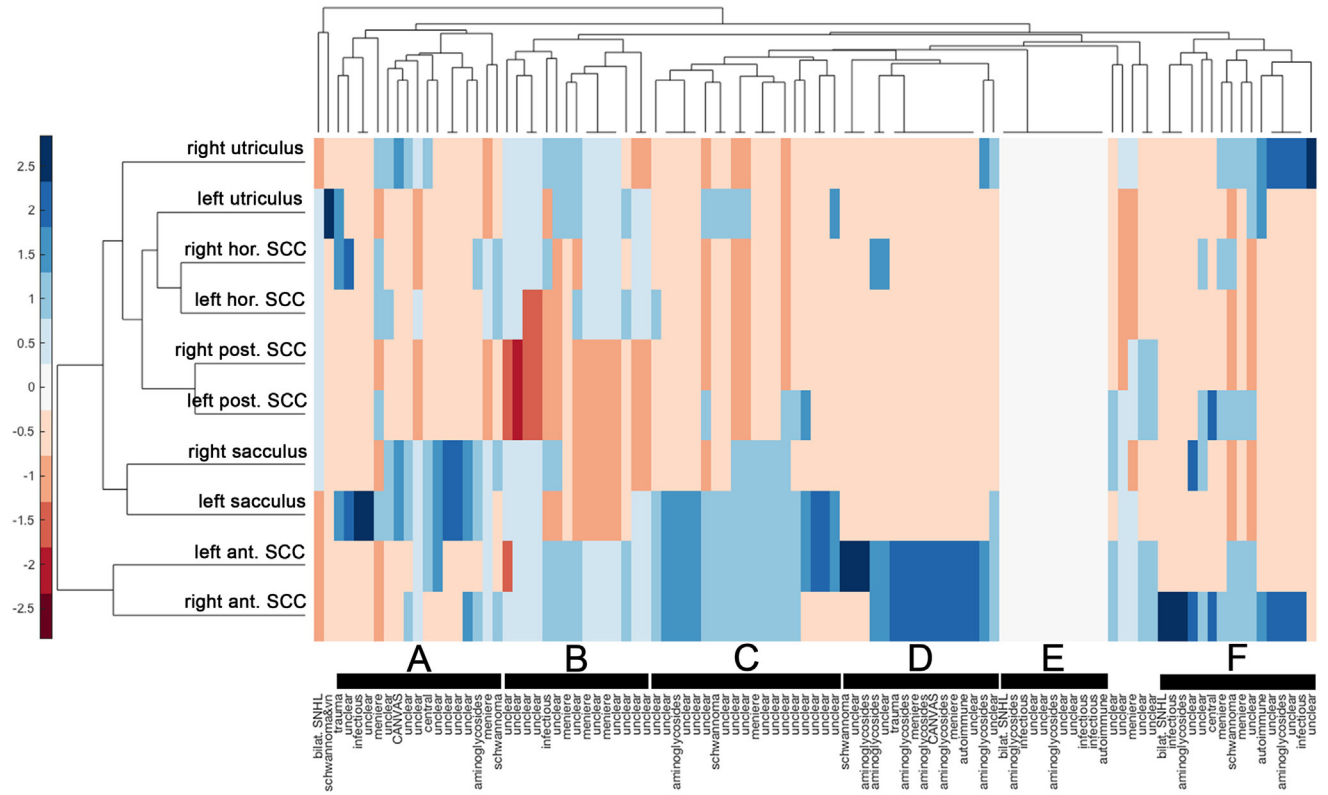

FIGURE 6 | Hierarchical cluster analysis based on the overall rating (intact vs. impaired) of each vestibular end organ. A heat map indicates the functional state [from intact (=blue) to deficient (=red)] for each vestibular end organ (n = 10) and patient (n = 101). The heat map was clustered by Euclidean distance. The data were standardized along the columns of data, i.e., for the individual results from single subjects, resulting in a range of colors between 2.5 (blue) to −2.5 (red) as indicated by the legend on the left side. Diagnosis in each patient is provided along the x-axis. Cluster dendrograms indicate those patients (x-axis) and vestibular end organs (y-axis) that are the least different, as these groups cluster together first. Cluster analysis identified 5 clusters with at least 15 patients (nodes A, B, C, D, and F) and one smaller cluster (node E), which are all marked with black bars.

from 1995 were used and MR imaging was mandatory for cases with vestibular schwannoma. The diagnosis of aminoglycoside-related vestibulopathy and BVL due to inner-ear infection was based on the patient's medical files. Furthermore, in half of our patients the underlying cause of disease could not be identified. This is within the range of 20–51% of cases with an idiopathic origin reported previously (30, 31, 33, 38). Noteworthy, as bilateral SCC hypofunction was a prerequisite for inclusion, we may have missed patients with isolated bilateral loss of saccular function (36).

While for the vHIT gain values have been shown to remain stable in healthy human subjects until very high age (no significant changes until ages 80–89 years) (39), significantly higher rates of absent responses were observed at advanced age for ocular (≥80 years) and cervical (≥70 years) VEMPs (40). The same authors noted decreases in peak-to-peak response amplitude in cVEMPs and oVEMPs with age and an increase in n10 latency (oVEMPs) by 0.12 ms per decade, while no such increase was noted for p13 latencies (cVEMPs) (40). With regards to our study, 24 patients were aged between 70 and 80 years, and 14 patients were aged more than 80 years. We therefore cannot exclude that some abnormalities in our very old patients were physiological and that we therefore may have overestimated the extent of otolith damage in these patients. Noteworthy, diagnosis of BVL did not depend solely on otolith function in our study but required bilaterally abnormal SCC function as well.

Currently, there is ongoing controversy about the diagnostic criteria for BVL. While recently proposed diagnostic criteria by the classification committee of the Bárány Society propose impairment of both horizontal SCCs (6), we have also included patients that presented with bilateral impairment of the vertical canals only or suffered from a combination of horizontal and vertical canal impairment. While this may result in an overall less affected patient population, this reflects a real-life scenario, with only few patients showing completely abolished vestibular function bilaterally.

CONCLUSION

Detailed peripheral-vestibular mapping with hierarchical clustering in BVL revealed a patchy loss of function of the SCCs and the otolith organs in the majority of cases, which could be segregated in six nodes with distinct patterns of SCC and otolith impairment. Our findings therefore confirm and extend the previous notion of variable and at least partially disease-specific loss of SCC function in BVL. Utricular and saccular

impairment was frequent and occurred in similar fractions. Overall, bilaterally impaired utricular function was a very good predictor for bilaterally deficient horizontal canals and bilateral saccular impairment predicted bilateral posterior-canal damage with high probability. In contrast, bilateral utricular hypofunction was a poor predictor of anterior-canal dysfunction. The extent of SCC and otolith impairment was disease-dependent, showing most extensive damage in BVL related to inner-ear infection and aminoglycoside exposure and more selective impairment in other groups such as BVL secondary to Menière's disease. Specifically, assessing utricular function may help in the distinction between aminoglycoside-related BVL and bilateral Menière's disease. Based on these disease-specific patterns of SCC and otolith function in BVL, we promote complete peripheral-vestibular mapping, since this may be useful in the differential diagnosis and eventually treatment decisions in BVL of presumably unknown origin.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Cantonal Ethics Committee Zurich and in accordance with the Declaration of Helsinki. As this was a retrospective database analysis, retrieval of informed written consent from all involved patients was not feasible. The protocol was approved by the Cantonal Ethics Committee Zurich and exempt for retrieval of written informed consent was granted (study protocol 2013-0468).

AUTHOR CONTRIBUTIONS

AT drafted the manuscript, analyzed the data, and conceived of the study. CB helped in the data analysis and interpretation. EB performed the data collection. KW was involved in the design of the study, participated in the data analysis and the statistical analysis, and critically reviewed and edited the manuscript. All the authors read, revised, and approved the final version of the manuscript.

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A Tool to Quantify the Functional Impact of Oscillopsia

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Background: Individuals with bilateral vestibular hypofunction (BVH) often report symptoms of oscillopsia during walking. Existing assessments of oscillopsia are limited to descriptions of severity and symptom frequency, neither of which provides a description of functional limitations attributed to oscillopsia. A novel questionnaire, the Oscillopsia Functional Impact scale (OFI) was developed to describe the impact of oscillopsia on daily life activities. Questions on the OFI ask how often individuals are able to execute specific activities considered to depend on gaze stability in an effort to link functional mobility impairments to oscillopsia for individuals with vestibular loss.

Methods: Subjective reports of oscillopsia and balance confidence were recorded for 21 individuals with BVH and 48 healthy controls. Spearman correlation coefficients were calculated to determine the relationship between the OFI and oscillopsia visual analog scale (OS VAS), oscillopsia severity questionnaire (OSQ), and Activities-Specific Balance Confidence scale to demonstrate face validity. Chronbach's α was calculated to determine internal validity for the items of the OFI. A one-way MANOVA was conducted with planned *post hoc* paired *t*-tests for group differences on all oscillopsia questionnaires using a corrected $\alpha = 0.0125$.

Results: The OFI was highly correlated with measures of oscillopsia severity (OS VAS; $r = 0.69$, $p < 0.001$) and frequency (OSQ; $r = 0.84$, $p < 0.001$) and also with the Activities-Specific Balance Confidence scale ($r = -0.84$, $p < 0.001$). Cronbach's α for the OFI was 0.97. Individuals with BVH scored worse on all measures of oscillopsia and balance confidence compared to healthy individuals (p's < 0.001).

Conclusion: The OFI appears to capture the construct of oscillopsia in the context of functional mobility. Combining with oscillopsia metrics that quantify severity and frequency allows for a more complete characterization of the impact of oscillopsia on an individual's daily behavior. The OFI discriminated individuals with BVH from healthy individuals.

Keywords: oscillospia, vestibular loss, activity and participation restriction, balance, mobility

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INTRODUCTION

During locomotion, the ability to see clearly in order to avoid or interact with objects or to facilitate use of optic flow for balance and heading is essential (1, 2). The primary purpose of the vestibulo-ocular reflex (VOR) may be to stabilize gaze during locomotion, when frequencies of head movement far exceed the capabilities of other eye movement systems (3, 4). Gaze instability during walking

has been directly attributed to loss of function of the VOR (5–9). Impaired gaze stabilization makes navigation and obstacle avoidance during walking more challenging, which may contribute to gait variability in individuals with bilateral vestibular hypofunction (BVH) (10). After VOR failure, a commonly reported complaint was that stationary environmental objects appear to "jump" during walking (6). Oscillopsia has also been reported in individuals with intact saccular function further indicating that oscillopsia symptoms may depend on angular VOR capabilities (11). However, complaints of oscillopsia are not consistent across all individuals with a diagnosis of BVH (12).

Current physiological vestibular function tests do not adequately characterize oscillopsia or the daily life impairments experienced by individuals with BVH. Oscillopsia has been studied using visual analog scales of symptom severity (5, 13) or symptom frequency (9, 14). However, oscillopsia severity and frequency do not consistently relate to physiological (i.e., VOR) or perceptual assessments of vestibular function like dynamic visual acuity (DVA) (5, 9, 12, 15–17). This disconnect between diagnostic testing and subjective quality of life may represent a limitation in the ability of existing questionnaires or diagnostic tests to adequately capture the functional impact of oscillopsia symptoms on daily life. Combining physiological assessments of gaze stability by simultaneous measurement of the VOR and other oculomotor responses and reading capability using tests such as the HITD will help to close the gap between physiology and function (18), but may not fully account for reported symptoms of oscillopsia. Recently, the presence of oscillopsia symptoms in individuals with BVH was found to correlate with their performance on a suppression head impulse test (SHIMP) (19). There are no self-report symptom scales that specifically characterize the impact of oscillopsia symptoms on the ability to execute daily life activities. This suggests that subjective measures that are linked to functional daily life tasks are needed to more completely describe the relationship between vestibular pathology and oscillopsia and the impact of both on an individual.

The two most common subjective measures of oscillopsia are the oscillopsia visual analog scale [OS VAS (13)] and an oscillopsia severity questionnaire [OSQ (9)]. The OS VAS describes oscillopsia symptom severity and the OSQ describes symptom frequency but is not specific to head motion-induced oscillopsia. Although very important in characterizing disease state, symptom severity and frequency may not adequately characterize the ability to execute daily life activities, which could explain the inconsistent relationship between VOR gain, DVA scores, and oscillopsia symptoms. The existing scales do not adequately characterize how oscillopsia impacts daily function from an activity or participation perspective as described by the International Classification of Functioning, Disability, and Health (ICF) (20). The ICF model includes four domains: (1) body functions; (2) body structures; (3) activities and participation; and (4) environmental factors. The WHO defines activities as "the execution of a task or action by an individual" and participation as "involvement in a life situation" (20). The OS VAS and OSQ would both address the Body Functions domain of the ICF as would diagnostic measures of vestibular function like VOR gain and caloric responses. Imaging and postoperative anatomical status would provide information in the domain of Body Structures. There are currently no *oscillopsia specific* measures, which address the ICF domain of Activities and Participation (15). Oscillopsia has been reported to diminish quality of life *via* activity restriction (21, 22); therefore, development of a valid scale that can identify the impact of oscillopsia on the ability to perform or participate in specific activities is greatly needed.

A new questionnaire, the Oscillopsia Functional Impact (OFI) scale (see Supplementary Material) was developed to more completely characterize the impact of oscillopsia on daily life. The OFI was designed to characterize the impact of oscillopsia during functional mobility and other tasks with implicit visual acuity or visual attention components for individuals with vestibular loss. We investigated whether the OFI had face validity based on existing scales related to oscillopsia and balance ability and whether the OFI could discriminate between healthy individuals and individuals with vestibular hypofunction.

MATERIALS AND METHODS

Subjects

Sixty nine individuals (33 males, 36 females) participated in this experiment after providing informed consent. A diagnosis of BVH was made based on weak (<10°/s combined per ear) or absent caloric responses and/or bilaterally pathologic head impulse tests (23, 24). Healthy individuals did not have a history of vertigo, dizziness, or balance problems. 48 healthy individuals and 21 individuals with BVH participated in the study. This study was carried out in accordance with the recommendations of the institutional review boards at Johns Hopkins School of Medicine and the University of Maryland, and all subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review boards at Johns Hopkins School of Medicine and the University of Maryland.

Procedures

Each subject completed several questionnaires including: (1) the Activity-Specific Balance Confidence scale (ABC) (25); (2) the oscillopsia visual analog scale (OS VAS) (13); (3) the oscillopsia severity questionnaire (OSQ) (9); and (4) the Oscillopsia Functional Impact (OFI) scale developed for this experiment. Questions on the OFI were designed to identify the degree to which oscillopsia interferes with execution of daily activities based on subjective complaints reported by patients seen by John P. Carey and Eric R. Anson in their respective clinical practice. The OFI was modeled after a scale designed to characterize symptoms of autophony for individuals with superior canal dehiscence (26) and is scored out of a total of 215 points with a maximum score of 5 for each question with "n/a" scored as a 0. Individuals were instructed to use the following scale to answer each question on the OFI: Not at all, A little of the time, Some of the time, A good deal of the time, Almost all the time, I have given up this activity because of symptoms, Don't know, as I just don't do this activity. Questions 12, 13, 14, 15, 16, 21, 22, 23, and 24 were phrased negatively and are scored in reverse order.

Data Analysis

Cronbach's α was calculated to determine internal consistency for the OFI scores. To determine face validity, Spearman's correlation coefficients were calculated to determine the relationships between OFI total scores, OS VAS scores, OSC scores, and ABC scores. A *t*-test was used to determine whether there was a difference in age between groups. A one-way MANOVA was conducted with planned *post hoc t*-tests for group differences on all questionnaires. Significance was tested at $\alpha = 0.05$ for Cronbach's α and Spearman's correlation and a Bonferroni corrected $\alpha = 0.0125$ was used for *post hoc t*-tests.

RESULTS

One healthy individual declined to provide his age. The mean age for the rest of the healthy individuals was 44.1 [range (19–75); SD = 18.1] and the mean age for the individuals with BVH was 60.84 [range (35–80); SD = 13.0]. The control group was significantly younger than the BVH group ($t = -3.8086$, $p = 0.002$).

Cronbach's α for OFI scores was 0.97 demonstrating high internal consistency for the individual items of the OFI. The OFI scores were highly correlated with the other subjective measures of oscillopsia and balance confidence, see **Table 1**. The MANOVA was highly significant for between group differences on the distribution of scores on all questionnaires [$F(4, 64) = 36.5$, $p < 0.001$]. Subsequent *post hoc* group comparisons are as follows. Individuals with BVH reported greater oscillopsia severity [$t(2, 67) = 11.69$, $p < 0.001$], higher oscillopsia frequency [$t(2, 67) = 9.91$, $p < 0.001$], greater impact of oscillopsia on activity performance [$t(2, 67) = 9.62$, $p < 0.001$], and lower balance confidence [$t(2, 67) = -10.31$, $p < 0.001$] compared to healthy individuals. Group average scores and 95% confidence intervals for each of the questionnaires are presented in **Table 2**.

Because the control group was significantly younger than the individuals with BVH, we performed a sensitivity analysis by repeating the MANOVA excluding all subjects under 60 years old. The overall sample was reduced to 16 healthy controls and 12 individuals with BVH. The statistical results were the same. The MANOVA was highly significant for between group differences on the distribution of scores on all questionnaires [$F(4, 23) = 17.6$, $p < 0.001$]. Subsequent *post hoc* group comparisons are as follows. Individuals with BVH reported greater oscillopsia severity [$t(2, 26) = 8.04$, $p < 0.001$], higher oscillopsia frequency [$t(2, 26) = 5.89$, $p < 0.001$], greater impact of oscillopsia on activity performance [$t(2, 26) = 5.68$, $p < 0.001$], and lower balance confidence [$t(2, 67) = -8.01$, $p < 0.001$] compared to healthy individuals.

DISCUSSION

Overall, the OFI demonstrated high internal consistency as well as excellent face validity based on high correlations with other measures of oscillopsia and also the ABC scale. Scores on the OFI and OS VAS and OSQ were all positively correlated indicating that oscillopsia related activity restriction, oscillopsia severity, and oscillopsia frequency all increase together. The strong relationship between the OFI and the ABC scale indicates that the OFI captured limitations in execution of daily life activities for the individuals with vestibular loss. OFI scores appear to capture activity restriction due to oscillopsia symptoms; however, the cause of the activity restriction remains to be determined. The individuals with BVH may be limited in their ability to perform the specific tasks due to oscillopsia from gaze instability. However, individuals with BVH often also present with gait and balance impairments that may contribute to changes in activity independent of oscillopsia. Additionally, cognitive or emotional factors may result in self-imposed participation restriction, with limited involvement in life situations. Future work is needed to determine whether oscillopsia independently contributes to limitations in task performance or participation in daily life.

Individuals with BVH reported more severe oscillopsia (OS VAS), more frequent episodes of oscillopsia (OSQ), and greater functional impairment (OFI) compared to healthy individuals, even when the sample was restricted to individuals 60 years and older. The present results extend those prior results regarding symptom frequency (OSQ) to symptom severity (OS VAS) and activity restriction (OFI). The average OSQ score for individuals with BVH in this cohort was only 2.6 which is lower than that reported previously (9). The difference in OSQ scores for individuals with BVH between studies highlights the variable nature of subjective reports across diagnoses of BVH. Some individuals in this cohort may have greater tolerance for

TABLE 1 | Spearman correlation coefficients between subjective rating scales of oscillopsia and balance confidence.

	OS VAS	OSC	ABC scale
OFI total	0.69* $p < 0.001$	0.84* $p < 0.001$	−0.84* $p < 0.001$
OS VAS		0.77* $p < 0.001$	−0.69* $p < 0.001$
OSC			−0.84* $p < 0.001$

*Significant correlations are indicated with an *.*
ABC scale, Activity-Specific Balance Confidence scale; OFI, Oscillopsia Functional Impact scale; OSC, Oscillopsia Severity scale; OS VAS, Oscillopsia Visual Analog Scale.

TABLE 2 | Between group differences on subjective measures of oscillopsia and balance.

Group	OFI total	OSC	OS VAS	ABC scale
Healthy	12.0 (1.6) [8.8–15.3]	1.2 (0.04) [1.10–1.26]	0.1 (0.03) [0.03–0.16]	96.0 (0.67) [94.7–97.4]
BVH	65.9 (7.7)* [49.8–81.9]	2.7 (0.22)* [2.3–3.2]	5.0 (0.63)* [3.6–6.3]	67.4 (4.0)* [59.2–75.6]

*Average (SEM) [95% CI] scores are presented and significant differences from healthy individuals are indicated by an *, all $p < 0.001$.*
ABC scale, Activity-Specific Balance Confidence scale; BVH, bilateral vestibular hypofunction; OFI, Oscillopsia Functional Impact scale; OSC, Oscillopsia Severity scale; OS VAS, Oscillopsia Visual Analog Scale.

oscillopsia, more residual vestibular function, or more completely developed adaptive anticipatory behavior following the vestibular loss.

Inconsistent oscillopsia complaints have been attributed to learned anticipatory mechanisms (27), which would include feed-forward saccades that occur during head motion (28). It is also possible that due to limitations in vestibular diagnostic testing, individuals diagnosed with BVH may have substantial residual vestibular function (11, 23). Tolerance for perceived retinal image motion has also been proposed as an explanation for the discordance between oscillopsia symptoms (whether severity, frequency, or participation based) and VOR gain or DVA (14). Recently, using a SHIMP paradigm allowed identification of two distinct saccadic responses in individuals with vestibular loss (19). A subset of individuals with vestibular loss demonstrated consistent covert saccades that would be compensatory for a deficient VOR, and subsequent saccades to shift gaze back to the visual target, which had moved. This suggests that a pre-planned covert saccade may result in more optimal gaze stability; however, the impact on oscillopsia symptoms remains to be investigated.

Activity restriction, as measured by the OFI, may depend on multiple factors. Individuals with vestibular loss are known to have balance impairments attributable to the vestibular pathology (29, 30). Reduced vestibular afference will impact both the VOR and vestibulo-spinal reflex pathways. It is possible that scores on some of the items in the OFI are impacted by changes in balance rather than gaze instability and resulting oscillopsia symptoms. In an effort to minimize this confound, the OFI items related to balancing behaviors are also tied to the presence of oscillopsia symptoms or a gaze target task. Additionally, belief (or fear) that secondary symptoms (i.e., falls, dizziness, oscillopsia, anxiety/depression) will result in negative effects (injury, embarrassment) may contribute to activity restriction in ways not identified here (31, 32). Many of the context-based questions involve dual tasking (like walking and texting or reading) and brain fog or mental fatigue could result in activity restriction more related to cognitive or attentional resources and less related to oscillopsia (33). Future studies should investigate this in cohorts of individuals with chronic brain fog and non-vestibular oscillopsia.

Limitations

The OFI as described here is lengthy and a shorter version would enhance clinical utility. Some of the questions may characterize similar constructs, and future work is needed to examine whether a shorter version of the OFI would have similar validity and discriminatory ability while characterizing the impact of unstable vision on activity restriction. The results presented here may not generalize to less severe presentations BVH such as may occur with aging. Test retest reliability and change over time will need to be established to enhance clinical utility.

CONCLUSION

The OFI captures the construct of oscillopsia in the context of mobility and activity restriction. Combining the OFI with existing oscillopsia metrics that quantify severity and frequency allows for a more complete characterization of the impact of oscillopsia symptoms.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the institutional review boards at Johns Hopkins School of Medicine and the University of Maryland and all subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review boards at Johns Hopkins School of Medicine and the University of Maryland.

AUTHOR NOTES

Recruitment of additional subjects at the request of the reviewers necessitated the addition of an additional author YG who collected and analyzed data for those subjects.

AUTHOR CONTRIBUTIONS

EA and JC developed the OFI. EA, TK, JJ, and JC conceived of and designed the study. EA and YG collected these data. EA drafted the manuscript. TK, JC, JJ, and YG critically edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2018.00142/full#supplementary-material.

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A Novel Saccadic Strategy Revealed by Suppression Head Impulse Testing of Patients with Bilateral Vestibular Loss

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Objective: We examined the eye movement response patterns of a group of patients with bilateral vestibular loss (BVL) during suppression head impulse testing. Some showed a new saccadic strategy that may have potential for explaining how patients use saccades to recover from vestibular loss.

Methods: Eight patients with severe BVL [vestibulo-ocular reflex (VOR) gains less than 0.35 and absent otolithic function] were tested. All patients were given the Dizziness Handicap Inventory and questioned about oscillopsia during abrupt head movements. Two paradigms of video head impulse testing of the horizontal VOR were used: (1) the classical head impulse paradigm [called head impulse test (HIMPs)]—fixating an earth-fixed target during the head impulse and (2) the new complementary test paradigm—fixating a head-fixed target during the head impulse (called SHIMPs). The VOR gain of HIMPs was quantified by two algorithms.

Results: During SHIMPs testing, some BVL patients consistently generated an inappropriate covert compensatory saccade during the head impulse that required a corresponding large anti-compensatory saccade at the end of the head impulse in order to obey the instructions to maintain gaze on the head-fixed target. By contrast, other BVL patients did not generate this inappropriate covert saccade and did not exhibit a corresponding anti-compensatory saccade. The latencies of the covert saccade in SHIMPs and HIMPs were similar.

Conclusion: The pattern of covert saccades during SHIMPs appears to be related to the reduction of oscillopsia during abrupt head movements. BVL patients who did not report oscillopsia showed this unusual saccadic pattern, whereas BVL patients who reported oscillopsia did not show this pattern. This inappropriate covert SHIMPs saccade may be an objective indicator of how some patients with vestibular loss have learned to trigger covert saccades during head movements in everyday life.

Keywords: bilateral vestibular loss, dizziness handicap inventory, horizontal vestibulo-ocular reflex, suppression head impulse test, video head impulse test

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Abbreviations: BVL, bilateral vestibular loss; DHI, the Dizziness Handicap Inventory; HIMP, conventional head impulse test paradigm; HVOR, horizontal vestibulo-ocular reflex; SHIMP, suppression head impulse paradigm; VEMPs, vestibular-evoked myogenic potentials; vHIT, video head impulse test; VOR, vestibulo-ocular reflex; WBB, the Nintendo Wii Balance Board.

INTRODUCTION

Bilateral vestibular loss (BVL) patients are often severely handicapped during head movements in their daily life. Profound dysfunction of bilateral semicircular canals usually causes unstable gaze, oscillopsia, and postural imbalance (1). The prevalence of BVL is very low – in the US population it is 28 per 100,000 (2) and the origin is usually difficult to define. Causative factors include ototoxic aminoglycosides, Menière's disease, Meningitis, systemic autoimmune diseases, Cogan's syndrome, and positive family history for inner ear diseases, etc (3). In particular, patients often complain of oscillopsia when turning the head rapidly in the horizontal plane, although surprisingly some do not complain of oscillopsia during such rapid head movements.

The conventional video head impulse test (vHIT) [now called head impulse test (HIMP) (4, 5)] quantifies the gain of the vestibulo-ocular reflex (VOR) function (6). In HIMPs, subjects are instructed to maintain gaze on an earth-fixed target during brief, abrupt, unpredictable, horizontal head turns to the left or right. In healthy subjects, the compensatory horizontal slow phase eye velocity matches head velocity, so the gain of the horizontal VOR (HVOR) is around 1.0 (7) and so overt or covert compensatory saccades are only small or are absent (7). By contrast, BVL patients show significantly lower HVOR gain for both horizontal directions and always generate large compensatory covert and/or overt saccades to regain the earth-fixed fixation target (8). In this study, we use the standard terminology (9): a "compensatory" saccade is one which is opposite to the direction of head turn whereas an "anti-compensatory" saccade is one which is in the same direction as the direction of head turn.

Recently, a variant of the HIMPs test has been introduced, called the suppression head impulse paradigm (SHIMPs) (4). It measures VOR and follows the same procedure as HIMPs with one exception: there is no earth-fixed fixation target, instead the patient is instructed to follow the movement of a head-fixed laser spot on the wall during the passive head impulses (see **Figure 1**). Although slow phase VOR gain is similar in both paradigms, the saccadic performance is very different. The result in SHIMPs is complementary to HIMPs—now healthy subjects generate large anti-compensatory saccades at the end of the head impulse, whereas most patients with BVL usually have very small or absent anti-compensatory saccades. The reason for the anti-compensatory saccade is that in healthy subjects at the onset of the head turn (and for about the first 80 ms) the VOR acts to drive the eyes opposite to head turn and so off the moving target, consequently requiring a large anti-compensatory saccade to regain the target at the end of the head turn (4). The presence and size of this anti-compensatory saccade is an indicator of the level of vestibular function (10). In patients with bilateral VOR deficit, the VOR is minimally functional so the patient's eyes usually remain on the moving fixation target during the head turn and at the end of the head impulse there is no detectable anti-compensatory saccade. This is in sharp contrast with the performance of the healthy subject (10).

SHIMP testing is now in routine clinical use at Hospital Salpetriere and has been used on many hundreds of patients. In the course of this testing, it has been found that some patients with BVL show, in the SHIMPs paradigm, a saccadic strategy different from the usual strategy described above. Despite the absence of semicircular canal function, some BVL patients consistently generate a compensatory covert saccade during the head turn in the SHIMPs paradigm, even though it is inappropriate because it takes the eyes off target. Thus, these patients must make a large anti-compensatory saccade at the end of the head turn, similar to that produced by healthy subjects, to regain the fixation target. So in these rare cases clinicians cannot rely on the size of the anti-compensatory saccade alone to indicate vestibular loss (10)—they need to inspect the eye movement records and to check the VOR gain as well.

While covert compensatory saccades are well known in patients with unilateral vestibular loss (11–14), their cause has not been established (15). The covert saccades in this group

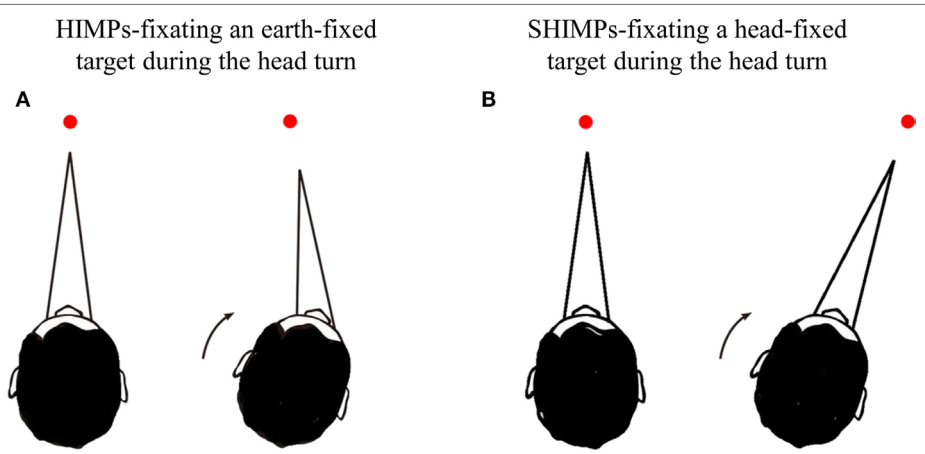

FIGURE 1 | Schematic diagram showing the procedures for head impulse test (HIMP) and SHIMP tests. **(A)** In HIMPs, subjects were instructed to fixate on an earth-fixed laser dot on the wall at 90 cm distance in front of the patient. The clinician applied 20 horizontal head impulses to each side with unpredictable timing and direction. **(B)** In SHIMPs, patients were instructed to fixate a laser spot target projected on the wall at 90 cm distance in front of them from a head-mounted laser. This spot moved with the head and subjects were instructed to stare at the spot. Ten serial impulses were delivered to left and right side, respectively.

of BVL patients are of special interest, since they cannot be triggered by vestibular input, and the patients appear not to be able to suppress them in accordance with the instructions. By contrast, in the SHIMPs paradigm, patients with unilateral vestibular loss do suppress covert saccades [see **Figure 3** of MacDougall et al. (4)].

Interestingly, this new saccadic strategy seems to be related to the subjective experience of oscillopsia of these BVL patients in everyday life—despite their BVL, these patients do not report being troubled by oscillopsia. This novel saccadic strategy is of special interest since it has been suggested that saccades play a major role in recovery after vestibular loss (16–19), and this new SHIMPs paradigm may be a new way of exploring how patients with BVL trigger covert saccades.

MATERIALS AND METHODS

Overview

Eight BVL patients (seven men and one woman; mean age 56 ± 16; min–max: 34–77) with complete bilateral peripheral vestibular deficit were recruited in this study based on the diagnostic criteria by the Classification Committee of the Bárány Society (20). The inclusion criteria were that they demonstrated the following symptoms: postural imbalance, unsteadiness of gait, movement-induced blurred vision (oscillopsia) during walking or most quick head/body movement, and worsening of postural imbalance or unsteadiness of gait in darkness and/or on uneven ground (20). To establish their loss of vestibular function we measured: (1) horizontal semicircular canal function by the video HIMPs, the suppression head impulse paradigm (SHIMPs), the caloric test; (2) otolith function by cervical and ocular vestibular-evoked myogenic potentials (VEMPs) (21, 22); (3) postural stability by the EquiTest, and the Nintendo Wii balance Board (WBB) (23).

Bilateral vestibular loss patients were identified by severe loss of semicircular canal function—they exhibited no responses to caloric testing of both left and right sides with either warm or cold water irrigation function (cold 30°C and warm 44°C water irrigation). Their SPV VOR gain on HIMPs testing was less than 0.35. Both sides were affected about equally—the VOR gain asymmetry between left and right was 2.03 ± 1.33. All eight patients had absent cervical vestibular-evoked myogenic potentials (cVEMPs): no detectable p13-n23 cervical potentials and no detectable ocular vestibular-evoked myogenic potentials (oVEMPs): no n1-p1 ocular potentials were detected on either side in response to short tone bursts of air-conducted sound at 500 Hz at 102 dB SPL (24). All of them fell on condition 5 in Equitest and were unable to maintain balance in the WBB test on foam with eyes closed or on foam at VR0.1 condition (23). We were able to determine the cause of the bilateral loss in four patients (for patients 1,5,7 (**Table 1**) it was the result of systemic gentamicin; for patient 6 it was genetic).

All subjects were informed of the vestibular tests and gave written informed consent. The Clinical Research Ethics Committee approved this work, which was registered at ANSM (ID RCB 2014-A00222-45).

TABLE 1 | Vestibular function test in eight bilateral vestibular loss (BVL) patients.

				Head impulse test (HIMPs)								SHIMPs							
				Vestibulo-ocular reflex (VOR) gain (area)		VOR gain (slope)		Covert saccade		Overt saccade		Peak velocity of anti-compensatory saccade (°/s)		% of anti-compensatory saccades		Latency of anti-compensatory saccade (ms)		Peak velocity of inappropriate saccade (°/s)		Latency of inappropriate saccade (ms)	
#	Age	Gender	Dizziness handicap inventory	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1	47	M	48	0.03	0.01	0.10	0.01	N	N	Y	Y	31.77	9.37	13	4	N/A	N/A	N/A	N/A	N/A	N/A
2	62	M	56	0.30	0.20	0.19	0.12	Y	Y	Y	Y	64.85	31.63	23	14	N/A	N/A	N/A	N/A	N/A	N/A
3	77	M	12	0.17	0.28	0.17	0.19	Y	Y	N	N	0	66.76	0	30	N/A	N/A	N/A	N/A	N/A	N/A
4	34	F	70	0.32	0.33	0.11	0.10	N	N	Y	Y	0	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A
5	69	M	52	0.21	0.17	0.27	0.22	Y	Y	N	N	178.74	55.79	65	25	300	N/A	205.80	N/A	110	N/A
6	57	M	56	0.09	0.02	0.05	0.00	Y	Y	N	N	199.43	0	75	0	260	N/A	220.29	N/A	130	N/A
7	69	M	28	0.14	0.10	0.14	0.18	Y	Y	Y	Y	193.94	80.89	76	33	290	N/A	203.64	N/A	90	N/A
8	36	M	26	0.27	0.09	0.06	0.05	N	N	Y	Y	170.46	104.92	70	45	240	280	183.36	167.27	130	190
Average latency of anti-compensatory saccade in #5–8 (ms)																		270 ± 20			
Average latency of inappropriate saccade in #5–8 (ms)																		130 ± 40			

Patients 1–4 showed low VOR gain (both area and slope) on HIMPs and small SHIMP anti-compensatory saccades. In one side or both sides of patients 5–8, VOR area gain and VOR slope gain remained low, but the appearance of covert saccades led to large SHIMP anti-compensatory saccades. Red highlights: BVL patients who performed covert saccades in SHIMPs.

Dizziness Handicap Inventory (DHI) and Complaints of Oscillopsia

In this study, the life quality and complaints of all BVL patients were assessed by the DHI and by an additional question on oscillopsia. The DHI is a self-assessment inventory, including 25 questions to evaluate self-perceived activity limitation and restriction resulting from dizziness (25). To specifically evaluate whether patients complained of oscillopsia, special focus was given to question 11 in the DHI questionnaire "Do quick movements of your head increase your problem?" and we also asked specifically "when you turn rapidly your head horizontally, is your visual scene blurry?"

Video Head Impulse Test

The function of the horizontal semicircular canals was assessed by using horizontal video-HIT (OtosuiteV®, GN Otometrics, Denmark) (6) (**Figure 1A**). Subjects were instructed to fixate an earth-fixed laser dot on the wall at 90 cm distance in front of them. The clinician applied 20 brief, rapid, horizontal head turns (head impulses) to each side with unpredictable timing and direction. The amplitude of the head rotation was about 18–20°, and the peak head velocity of the impulse was about 180–220°/s, and of the acceleration between 4,500 and 7,500°/s^2. Eye velocity and head velocity were recorded for each head turn. Two methods of calculating VOR gain from the slow phase eye velocity were used—(1) the area under the desaccaded eye velocity curve divided by the area under the head velocity curve (8). (2) The slope of the function relating eye velocity to head velocity based on a linear regression method as described before (26). The linear regression was calculated in MATLAB R2016a using linear polynomial curve fitting (polyfit) of the eye velocity from the start of the head movement to the peak head velocity, and the slope of this function was used as the second index of VOR gain. Covert saccades were identified as starting before the moment when the head velocity had returned to 0°/s, and overt saccades were identified as the ones starting after the return to 0°/s head velocity within a maximum latency from the start of head rotation of 500 ms. The trials with VOR slope linearity less than 98% and/or overshoot of head velocity of more than 50°/s were excluded from the analysis.

Suppression Head Impulse Paradigm (SHIMPs)

The SHIMPs testing procedure was exactly the same as for HIMPs with one exception. Participants were instructed to fixate a head-fixed target—a laser spot projected on the wall at 90 cm distance in front of them projected by a head-mounted laser (4) (**Figure 1B**). This spot moved with the head, and during testing it appeared to subjects that they were looking at a dot which unexpectedly jumped around. Ten impulses were delivered to left and right sides, respectively. To avoid anticipation, the head turn always started from center. Eye velocity and head velocity were recorded in each head rotation.

Eye Movement Data

An algorithm was developed in MATLAB R2016a (The MathWorks, Inc., USA) to process ASCII data files supplied by ICS impulse (GN Otometrics, Denmark) (10). The algorithm implements saccade detection using a minimal velocity (50–200 /s) and a maximum head-peak to eye-peak duration (600 ms). Only saccades with peak velocities above 200 /s were considered as valid anti-compensatory saccades in our algorithm. The latency of anti-compensatory saccades was defined as the time interval between the onset of the head impulse and the onset of the anti-compensatory saccade response (10).

Cervical and Ocular VEMPs

Cervical and ocular VEMPs were measured in response to 500 Hz air-conducted sound of 7 ms duration and 1 ms rise time and 102 dB SPL using a Nicolet Viking four apparatus (Nicolet Biomedical Inc., WI, USA) (27). cVEMPs predominantly evaluate the function of sacculo-spinal pathways (28). The function of utriculo-ocular pathways is mainly assessed by oVEMPs (29).

EquiTest

Equilibrium was evaluated by the Sensory Organization Test in NeuroCom® Balance Manager™ System (NeuroCom® International Inc., USA) (30). Subjects were instructed to stand upright with eyes closed. The support base moved adaptively following the subject's movement. The function of somatosensory, visual, and vestibular systems was scored according to the change of the body center of pressure.

Wii Balance Board

Subjects were instructed to maintain balance on the WBB (Nintendo, Japan) with or without a foam rubber mat (Airex AG, Sins, Switzerland, 41 cm × 50 cm × 6 cm) with eyes open and then with eyes closed for 25 s. The moving trajectory of the subject was recorded by a custom app installed in iPod Touch called "VR BalanceRite" (31).

Statistical Analysis

The average horizontal slow phase eye velocity VOR gain for each side was calculated as the sum of the VOR gains for each trial divided by the number of trials. Average peak anti-compensatory saccade velocity and average peak covert saccade velocity in SHIMPs were calculated as the sum of saccade velocity from the acceptable trials divided by the number of trials. When no anti-compensatory saccade was detected in a particular trial, the peak anti-compensatory saccade velocity was considered as zero.

RESULTS

DHI Questionnaire and Complaints of Oscillopsia

The total DHI scores in these patients varied considerably (min–max: 12–70) (**Table 1**), indicating very different levels of quality of life and compensation of their vestibular deficits between individuals. In particular, some patients complained that they had blurring vision during abrupt horizontal head turns, whereas others did not complain of this. All of our patients had difficulties walking in the dark.

HIMP and SHIMPs

In HIMPs, healthy subjects showed high VOR gain (more than 0.8) and completed the test with only very small compensatory saccades. A typical example of results from a healthy subject [data from our previous study (10)] shows the amplitude of slow phase eye velocity is about equal to that of head velocity (**Figure 2A**), which means that healthy subjects maintain their gaze very well on the earth-fixed target. By contrast, in SHIMPs, after each rapid head impulse, the healthy subject generated a large anti-compensatory saccade that was in the *same* direction as the head turn, in order to return their gaze to the head-fixed target due to healthy HVOR (**Figure 2B**). This anti-compensatory saccade was necessitated because, during the head turn, the VOR drove the eyes off the target as explained above.

In HIMPs BVL patients had low VOR area gain (min–max: 0.01–0.33) for both left and right sides (**Table 1**). The value of the VOR slope gain was also relatively low in BVL patients (min–max: 0–0.27). BVL patients either made only covert saccades ($n = 3$), or only overt saccades ($n = 3$), or a mixture of both covert and overt saccades ($n = 2$). Covert and/or overt catch-up saccades were needed to regain the earth-fixed target after the rapid head turn (**Figures 3A,C**).

In SHIMPs, the eye movements of most BVL patients followed the head-fixed target during the whole duration of the head turn, from the beginning to the end, because their reduced or absent HVOR did not drive their eyes off the target (**Figure 3B**). All BVL patients showed low slow phase eye velocity VOR gains in SHIMPs, similar to their VOR gain in HIMPs (**Figure 4**). Consequently, BVL patients did not usually perform anti-compensatory saccades (**Table 1**). However, in SHIMPs, some BVL patients consistently made inappropriate covert saccades during the head turn which necessitated large anti-compensatory saccades at the end of the head impulse (**Figure 3D**).

Covert saccades in the HIMPs paradigm are compensatory for head turn, and act to return gaze to an earth-fixed target and so reduce gaze error at the end of the head impulse. In the SHIMPs paradigm, the covert saccade in BVL patients is also compensatory for head turn, but it acts to *remove* gaze from the head-fixed target, and so acts to *increase* gaze error. That is why we called it "inappropriate." The covert saccade in the SHIMPs paradigm drives the eyes off the target and so necessitates a large corrective saccade (an anti-compensatory saccade) at the end of the head turn to overcome the large gaze error and return the eyes to the target. Covert saccades in HIMPs and SHIMPs are, thus, totally different—one reduces gaze error, the other increases gaze error.

The average latency of the inappropriate covert saccade was 130 ± 40 ms (min–max: 90–190 ms) from the beginning of head turn and in almost every case was followed by a large anti-compensatory saccade. The amplitude of the inappropriate covert saccade ranged from 167 to 220°/s. The amplitude of the corresponding anti-compensatory saccade was from 205 to 382°/s and its average latency was 270 ± 20 ms (min–max: 240–300 ms), which was consistent with the size of anti-compensatory saccades in healthy people published previously (10). This strategy can be seen in detail for head turns to both left side (**Figure 5A**) and right side (**Figure 5B**) in some patients. For comparison, sample responses of a patient who did not make inappropriate covert saccades are shown in **Figures 5C,D**.

DISCUSSION

By using this new SHIMPs test paradigm, we have been able to show that some BVL patients untroubled by oscillopsia during

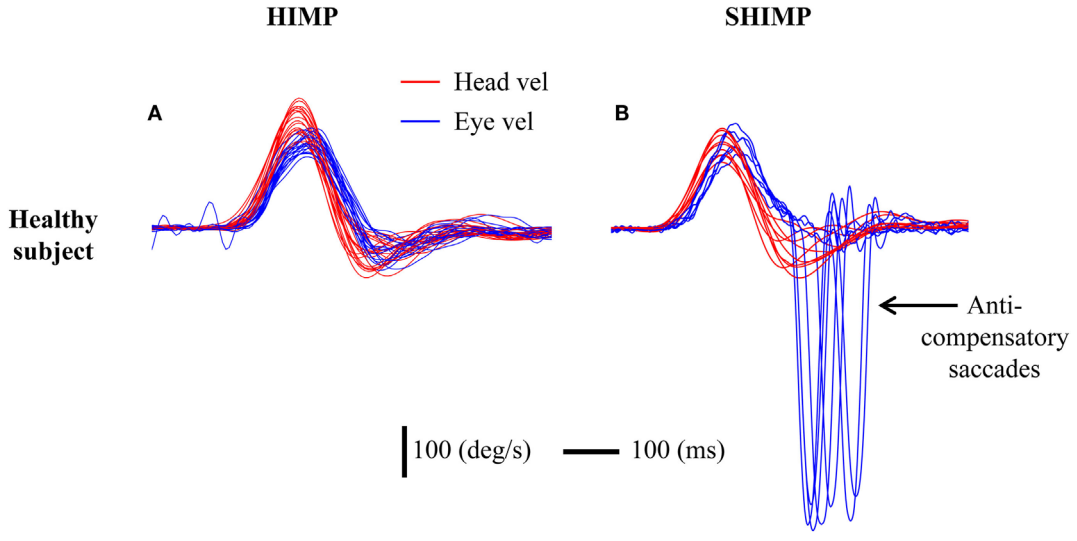

FIGURE 2 | Typical responses in head impulse test (HIMP) and SHIMP procedures in a healthy subject. The figure shows superimposed eye (blue) and head (red) velocity traces for many trials. The subject shows high vestibulo-ocular reflex (VOR) slope gain in both HIMPs and SHIMPs (gains close to 1.0). **(A)** During HIMPs, there are no compensatory saccades. **(B)** In SHIMPs, although the VOR gain was close to 1.0, the subject made no covert saccades but made large anti-compensatory saccades on every trial in order to regain the target. In this and the following figures, the conventions are eye velocity is inverted to facilitate comparison with the head velocity. Red curve: head velocity; blue curve: eye velocity; vertical bar: 100°/s; horizontal bar: 100 ms.

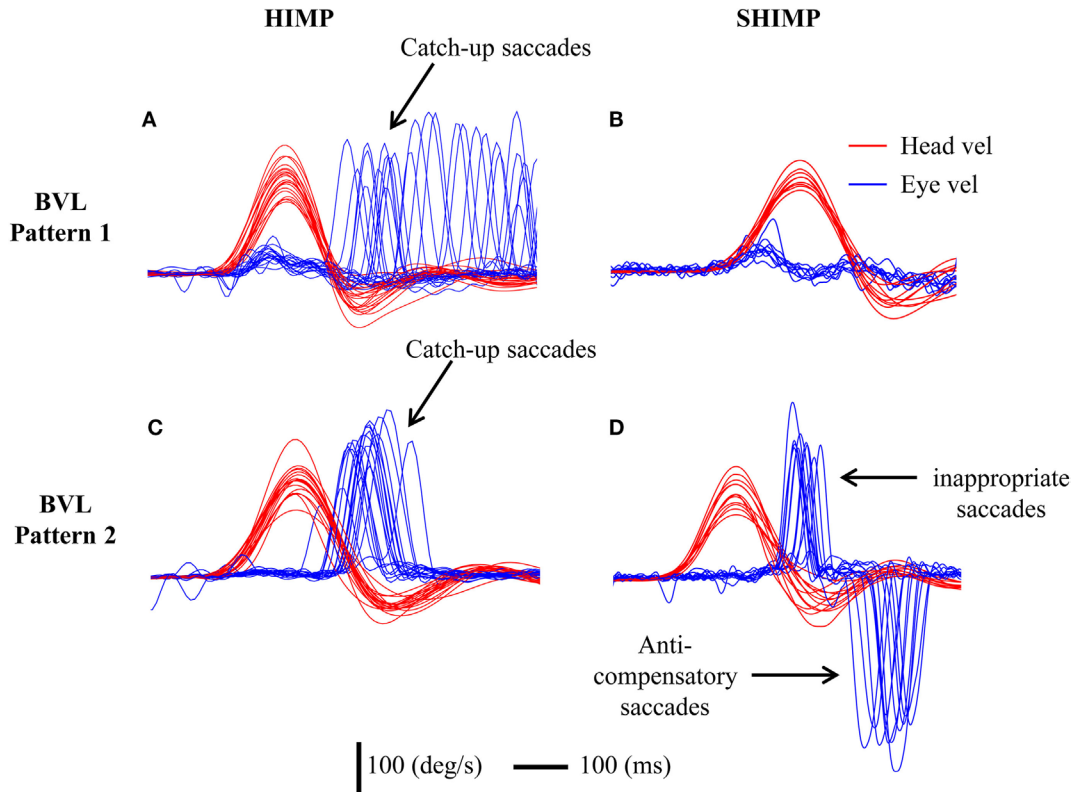

FIGURE 3 | To show the different saccadic patterns in head impulse test (HIMP) and SHIMP procedures in two bilateral vestibular loss (BVL) patients. Eye velocity has been inverted to facilitate comparison with head velocity. Both patients show low vestibulo-ocular reflex (VOR) gains during head impulses. **(A)** A BVL patient with low VOR gain and mainly overt catch-up saccades in HIMPs who **(B)** did not perform any anti-compensatory saccades in SHIMPs. **(C)** A different BVL patient with low HIMP gain and clustered early overt catch-up saccades in HIMPs who **(D)** made covert saccades in SHIMPs followed by large anti-compensatory saccades on every trial because of the covert saccades in SHIMPs.

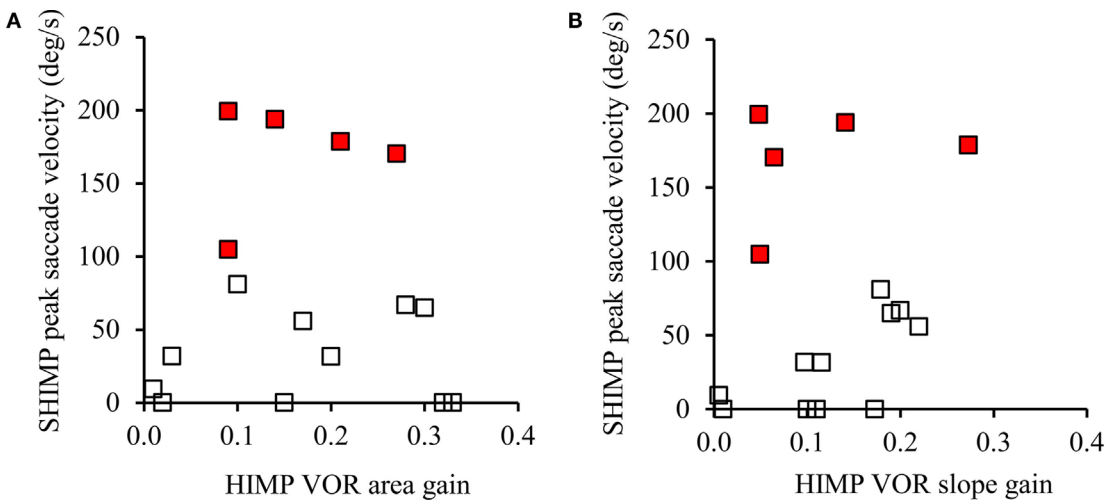

FIGURE 4 | The relation between vestibulo-ocular reflex (VOR) gain and average peak anti-compensatory eye velocity (°/s) in the SHIMPs paradigm as a function of VOR area gain **(A)** and VOR slope gain **(B)** in eight bilateral vestibular loss (BVL) patients (left and right sides). Some patients had low head impulse test (HIMP) gain/HIMP slope and low peak saccade velocity (open squares): these patients performed small or no anti-compensatory saccades in SHIMPs. On the other hand, other BVL patients (red squares) showed low VOR gain by either measure, but had large anti-compensatory saccades in SHIMPs because of earlier covert saccades.

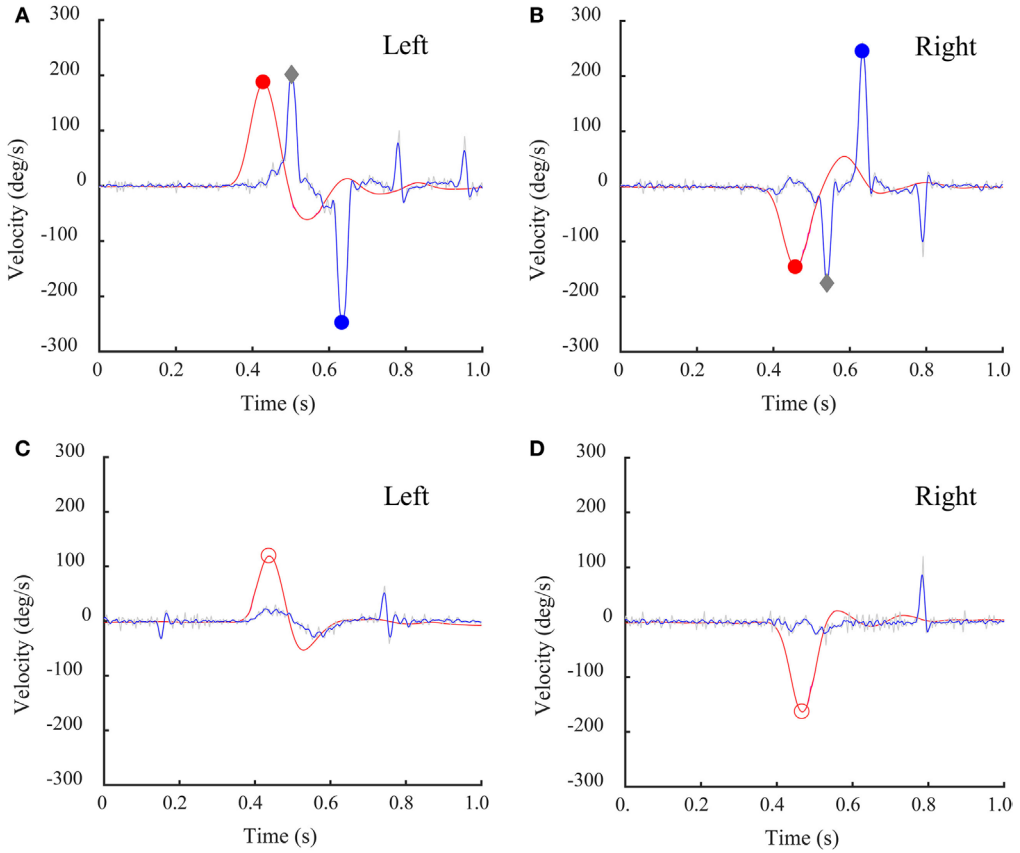

FIGURE 5 | Individual time series records of a bilateral vestibular loss (BVL) patient's SHIMP results with a covert saccade and corresponding SHIMP anti-compensatory saccades. Eye velocity has been inverted to facilitate comparison with head velocity. **(A,B)** This BVL patient, with low head impulse test (HIMP) gain, made a covert saccade followed by a large anti-compensatory saccade for both left **(A)** and right **(B)** rotation. Gray diamonds: peak saccade velocity of covert saccades. **(C,D)** This BVL patient with low HIMP gain did not make a covert saccade and did not make a corresponding anti-compensatory saccade for head turns to either side. Red circles: peak head velocity; blue circles: peak saccade velocity.

rapid head movements in everyday life, consistently make inappropriate covert saccades during rapid head movements. The inappropriate covert saccades so clearly revealed by the SHIMPs paradigm suggest that the BVL patients may, almost automatically, generate a compensatory covert saccade during any abrupt head movement. In the SHIMPs protocol the apparently automatic covert saccade is inappropriate—in the usual HIMPs paradigm such a covert saccade would be appropriate because it would be acting to compensate for the head turn to keep the eyes on the target, but in SHIMPs the covert saccade is opposite to the instructed task, because it takes the eyes *off* the target. We have only been able to show this apparently automatic covert saccade by testing a select group of patients with complete BVL in the new SHIMPs paradigm.

What we report here is that during a head impulse these BVL patients make a covert *compensatory* saccade (i.e., a saccade opposite to the direction of head turn), so it is exactly the opposite of the covert *anti-compensatory* eye movement during the head impulse (i.e., a saccade in the direction of head turn) reported by Heuberger et al. (32). (Please see **Figure 1** of their paper.) Skilled clinicians carrying out head impulse testing (Dr. de Waele and Dr. Manzari) report that only patients who do not understand the instructions or who are trying to falsify the head impulse test, make the covert anti-compensatory saccades during the head impulse which Heuberger et al. (32) reported and showed in their **Figure 1**. Eyelid artifact in video recording can also generate an apparent anti-compensatory saccadic eye movement during a head impulse [Figure 8 of Halmagyi et al. (5)].

The fact that some BVL patients made large anti-compensatory saccades at the end of the head impulse on left, right, or both sides in SHIMPs testing raises an issue in diagnosis. If the VOR gain had not been checked, it might be thought that these patients had normal vestibular function, since the presence and amplitude of such anti-compensatory saccades at the end of the head impulse is similar to the response of healthy subjects. However, inspection of the eye velocity record shows that, unlike healthy subjects, the BVL patients had very low VOR gain and the anti-compensatory saccade was preceded by an inappropriate compensatory covert saccade during the head impulse. The presence of this inappropriate covert saccade underscores the importance of the universal instruction for vHIT testing—always look at the eye movement records first. Compared to other BVL patients who made small or no anti-compensatory saccades in SHIMPs, these BVL patients

had few complaints of oscillopsia, which indicated a better adaptation in everyday life.

The two methods of calculating VOR gain (area vs slope) were used here since in the SHIMPs paradigm, it is difficult to properly desaccade the eye velocity data and so VOR gain can be in error. However, in this study, across trials and across subjects this was not a factor in these results.

There are only a small number of BVL patients—because patients with severe BVL are not common. Further not all BVL patients showed the inappropriate covert saccades, but the point of this paper is to show the existence of this new consistent saccadic strategy in some BVL patients, and the evidence from four patients shows clearly that the phenomenon exists.

What triggers the inappropriate covert saccades? Covert saccades in HIMPs have a short latency, occurring in the first 200 ms (min–max: 90–190 ms) after the onset of head rotation (14). They might be triggered by neck proprioceptors that are activated during head movement. There is evidence for a cervico-ocular response at around this latency in a human patient with total surgical bilateral loss (33) (**Figure 2**). However, we cannot eliminate vision as a possible trigger (34). In everyday life, vestibular loss induces discrepancies between head movement and compensatory eye movements and the resulting retinal smear may trigger the covert saccade revealed by the SHIMPs paradigm. Cognitive processing is not likely to be the cause because the covert saccade is so early.

We did not find a direct correlation between the DHI total score and the presence or absence of covert saccades in SHIMPs in our BVL patients. However, four BVL patients with very low VOR gain in both HIMPs and SHIMPs (0–0.33) and inappropriate covert saccades in SHIMPS reported to our specific questions that their visual scene did not become blurry when the head was rapidly turned horizontally. By contrast, four other BVL patients without covert saccades strategy reported that their visual scene *did* become blurry during rapid head turns. Those associations suggest that questions about horizontal oscillopsia may be useful to evaluate the performance of BVL patients.

It had been thought that as the process of vestibular compensation takes place, VOR gain improves and allows recovery of stable retinal images during head movement, reviewed in Ref. (35, 36). Evidence shows that this is not true for head impulses: 1 year after surgical unilateral vestibular loss, the VOR gain of a group of patients was unchanged compared to the VOR gain immediately after their surgical loss (37). Instead saccades would appear to be the vehicle for recovery (38), since the pattern of corrective saccades does change during recovery (16–19). This will affect subjective experience because visual perception is reduced before, during, and after a saccade by a neural process known as saccadic suppression (19, 39, 40). So the visual experience of oscillopsia produced by retinal smear during a head movement due to an inadequate VOR will be reduced. A covert saccade during a head movement would appear to be an effective way of eliminating the subjective experience of oscillopsia, and paradigms training subjects to make covert saccades should be used for rehabilitation of patients with vestibular loss. These suggestions are in accord with the recent evidence showing progressive clustering of saccades in patients recovering from vestibular loss (18). For the reasons above, we suggest the occurrence of such a cluster of covert saccades will be accompanied by a reduction in reports of oscillopsia and improved patient experience. These same covert saccades, while acting to reduce or eliminate retinal smear due to an inadequate VOR will, because of saccadic suppression (19, 39, 40) also reduce the detectability of visual stimuli (such as letters in dynamic visual acuity tests), presented around the time of the covert saccades. Because of this saccadic suppression by covert saccades, measuring dynamic visual acuity during head impulses (41, 42) does not index purely vestibular function.

CONCLUSION

SHIMPs are a novel paradigm for studying vestibulo-ocular performance. It gives more precise information on the gain of HVOR compared to HIMPs because, for most patients, the evaluation of the gain is not affected by covert saccades. The subject's task in SHIMPs is natural and intuitive—the person simply has to follow a moving dot during passive head movements, instead of the rather awkward and unnatural task for the usual HIMPs paradigm of maintaining gaze on an earth-fixed target during passive head movement. The presence of covert saccades is worth further exploration since it would appear to be a rehabilitation strategy, and the anti-compensatory saccade may be an objective indicator of rehabilitation showing how well patients are learning to generate a covert saccade during head movements. A compensatory covert saccade apparently independent of vestibular input is a very useful response for minimizing vestibular loss, and the SHIMP paradigm has laid this strategy bare. It could not be detected with the standard HIMPs paradigm.

ETHICS STATEMENT

All subjects were informed of the vestibular tests and gave written informed consent. The Clinical Research Ethics Committee approved this work, which was registered at ANSM (ID RCB 2014-A00222-45).

AUTHOR CONTRIBUTIONS

CW initiated the study, tested the patients, and wrote most of the paper; QS assisted in testing and wrote some of the paper; CM wrote the computer algorithms for acquiring, displaying, and quantifying the data; IC wrote some of the paper. All authors approved the final version.

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Vestibular-Evoked Myogenic Potentials in Bilateral Vestibulopathy

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Bilateral vestibulopathy (BVP) is a chronic condition in which patients have a reduction or absence of vestibular function in both ears. BVP is characterized by bilateral reduction of horizontal canal responses; however, there is increasing evidence that otolith function can also be affected. Cervical and ocular vestibular-evoked myogenic potentials (cVEMPs/oVEMPs) are relatively new tests of otolith function that can be used to test the saccule and utricle of both ears independently. Studies to date show that cVEMPs and oVEMPs are often small or absent in BVP but are in the normal range in a significant proportion of patients. The variability in otolith function is partly due to the heterogeneous nature of BVP but is also due to false negative and positive responses that occur because of the large range of normal VEMP amplitudes. Due to their variability, VEMPs are not part of the diagnosis of BVP; however, they are helpful complementary tests that can provide information about the extent of disease within the labyrinth. This article is a review of the use of VEMPs in BVP, summarizing the available data on VEMP abnormalities in patients and discussing the limitations of VEMPs in diagnosing bilateral loss of otolith function.

Keywords: vestibular-evoked myogenic potential, otolith, gentamicin, aminoglycoside, bilateral vestibulopathy, Meniere's disease, vestibular

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Bilateral vestibulopathy (BVP) is a rare and chronic condition resulting from a loss or reduction of vestibular function in both ears (1, 2). As vestibular function is critical for maintaining balance and holding gaze steady during movement, absence of vestibular function causes disabling unsteadiness and oscillopsia (3). The unsteadiness becomes worse in the dark and when walking on uneven ground due to reduction in vision and proprioception, which are key contributors to balance in these situations. In contrast, patients are typically free of symptoms when they sit with their head still. BVP can also have effects on cognition, including visuospatial ability. Patients with BVP sometimes have no other neurological deficits or hearing loss, apart from presbycusis. BVP has many causes, such as exposure to ototoxic drugs (e.g., aminoglycosides), infections (e.g., meningitis), autoimmune disease, genetic disorders (e.g., Usher syndrome or DFNA9), and Meniere's disease, while a significant number of cases are idiopathic (1, 4, 5).

Demonstration of vestibular loss has historically been sought by a caloric or rotational chair test, both of which assess the horizontal angular vestibulo-ocular reflex (VOR) (6, 7). More recently, video systems for recording the head impulse test (vHIT) have become more widely available, allowing measurement of the VOR from all three canals in both ears (8). These are all tests of semicircular canal function, and all but the vHIT of the posterior canal are tests of the superior vestibular nerve. Indeed BVP is characterized by bilateral reduction of horizontal canal responses. There is, however, increasing evidence that otolith function can also be affected in BVP. For example, in 1997 Lempert et al. (9)

showed that some patients with BVP had abnormal otolith-ocular reflex gain, symmetry and/or latency, and concomitant deficits in dynamic visual acuity during lateral translations, suggesting abnormalities of the otolith organs.

In recent years, vestibular-evoked myogenic potentials (VEMPs) have become a widespread test of otolith function (10). Cervical VEMPs (cVEMPs) are short-latency inhibitory reflexes recorded from the sternocleidomastoid (SCM) muscle, while ocular VEMPs (oVEMPs) are excitatory reflexes recorded from the inferior oblique extraocular muscles. VEMPs are considered tests of otolith function because the brief bursts of air-conducted (AC) sound or bone-conducted (BC) skull vibration used to produce them have been shown to preferentially activate irregularly firing otolith afferents in both rats and guinea pigs (11, 12). The cVEMP produced by an AC sound stimulus is a test of the saccule as this organ has the lowest threshold to AC sound stimulation and because the projection to the SCM muscle in humans (an ipsilateral inhibition) matches the projection shown in animal studies (13, 14). Likewise, the oVEMP produced by either stimulus is thought to be predominantly utricular because the contralateral excitatory projection to the inferior oblique muscle in humans matches that seen in animals (14, 15). For both reflexes, studies in patients with vestibular neuritis, who have relatively selective lesions of the superior or (rarely) inferior vestibular nerves, support an origin in the inferior (cVEMP) and superior nerves (oVEMP) (16). VEMPs are particularly useful in BVP as they remain abnormal after central vestibular compensation has occurred and can test the ears independently, unlike tests of subjective visual vertical or horizontal, which reveal only unilateral otolith abnormalities in the acute phase of disease.

CHARACTERISTICS OF cVEMPs AND oVEMPs IN BVP

Cervical VEMP abnormalities in BVP were first reported by Matsuzaki and Murofushi (17), who tested three patients who had absent ice water caloric responses bilaterally. They found that cVEMPs were absent in five of the six ears, suggesting that the saccule and inferior vestibular nerve were also affected by the disease. A further two patients reported by the same group had unilateral cVEMP abnormalities using both AC sound and galvanic vestibular stimulation (18). In 2003, Brantberg (19) described a family with presumed early-onset vestibulopathy, in which a father and two sons had attenuated caloric responses and the father additionally had absent AC cVEMPs. Brantberg hypothesized that the vestibulopathy affected the canals before the otoliths but did not extend to the cochlea. However, in a subsequent article, Brantberg and Löfqvist (20) presented a series of five patients with symptoms of unsteadiness and oscillopsia and absent caloric responses who were diagnosed with idiopathic BVP. They found that, although one patient had asymmetric amplitudes, all five patients had well-formed cVEMPs bilaterally, suggesting that saccular function may be largely spared in BVP.

Several early oVEMP studies reported absent BC oVEMPs in small series of patients, suggesting possible utricular involvement in BVP (21–23). However, these patients were recruited because they were known to have absent cVEMPs as well as absent caloric responses (to demonstrate the vestibular dependence of oVEMPs) and may not be representative of BVP patients in general. Chiarovano et al. (24) recorded oVEMPs in response to AC sound stimulation in a wide variety of patients and reported absent oVEMPs in nine patients with BVP due to aminoglycoside ototoxicity.

Two relatively large studies have now shown that cVEMPs and oVEMPs can indeed be small or absent in BVP, but in fact fall in the normal range for a significant proportion of patients. Zingler et al. (25) recorded AC cVEMPs in 84 patients with complete or partial BVP and found that cVEMPs were significantly smaller in the patients than controls (by approximately 35%). However, there were only four patients with an absent cVEMP unilaterally and no patients with absent responses bilaterally. In contrast, all 40 patients had absent caloric responses bilaterally. Agrawal et al. (26) recorded both AC cVEMPs and BC oVEMPs in 34 patients with BVP. VEMPs were considered abnormal if they were absent or the amplitude was below the fifth percentile of the normal control group. Using this criterion, 61% of patients had abnormal cVEMPs and 64% had abnormal oVEMPs. However, as the control group was much younger than the patient group, and VEMPs tend to decline with age (the AC cVEMP more than the BC oVEMP), this might be an overestimate of the rate of abnormalities. The number of patients with absent responses was not reported. Caloric slow phase velocity SPV was not correlated with cVEMP amplitude in either of the above studies, however, it was correlated with oVEMP amplitude ($r = 0.51$) (26), consistent with the caloric and oVEMP both being tests of superior vestibular nerve function.

CONCORDANCE OF OTOLITH AND CANAL FUNCTION IN BVP OF DIFFERENT ETIOLOGIES

Zingler et al. (25) found no differences among patients with different etiology or clinical course (progressive or sequential) of BVP. In contrast, Agrawal et al. (26) compared patients with BVP due to aminoglycoside toxicity, MD, and mixed origins. They found that patients with aminoglycoside toxicity tended to have the smallest responses on both the caloric and VEMP tests, though the difference between etiologies only reached significance for the oVEMP when comparing aminoglycoside toxicity and MD. It thus appears that systemic aminoglycoside toxicity has relatively severe effects across all vestibular organs (24, 26). This is not surprising, as studies of topical application of gentamicin for the treatment of intractable Meniere's disease have shown significant deterioration of cVEMPs (27–29). BVP caused by bilateral Meniere's disease is also likely to be associated with significant bilateral saccular abnormalities (26), as unilateral MD is associated with specific AC cVEMP abnormalities (30). However, caution is required when considering MD together with other causes of BVP. MD has a characteristic pattern of vestibular and auditory deficits, with significant levels of cVEMP abnormality, and inclusion of patients with MD may inflate the rate of cVEMP abnormalities compared to other causes of BVP.

A surprising frequency of preserved VEMPs has also been reported in patients with BVP combined with cerebellar

atrophy. Marti et al. (31, 32) described five patients with cerebellar atrophy and bilateral vestibulopathy (CABV), now renamed cerebellar atrophy, neuropathy, and vestibular areflexia syndrome (CANVAS), who had preserved AC cVEMPs and ocular counter-roll responses. In a later study of 31 patients with CANVAS, only 7 had absent AC cVEMPs, while 17 had impaired caloric responses and all had a bilaterally positive bedside HIT (33). Finally, a recent case report described a patient with CANVAS with preserved AC cVEMPs and oVEMPs, but absent caloric and rotation responses and absent vHIT responses in all six canal planes (34).

The dissociation of canal and otolith function is even more obvious in patients with bilateral vestibular loss due to large vestibular aqueduct syndrome. A recent article showed that many patients had bilateral canal paresis on caloric testing, but augmented AC cVEMPs and oVEMPs, with enlarged amplitudes and lowered thresholds compared to controls (35). However, the patients in this study were 7–27 years of age and these findings of canal hypofunction-otolith hyperfunction may not be applicable to older patients with LVAS.

POSSIBLE CAUSES OF THE LOWER PREVALENCE OF OTOLITH DYSFUNCTION IN BVP

One reason for the canal-otolith dissociation in BVP relates to the diagnostic criteria. By definition, all of the patients have profoundly abnormal or absent horizontal semicircular canal function bilaterally as measured by the caloric and/or HIT. It is therefore to be expected that horizontal canal dysfunction is universal in BVP, while all other end organs may have lesser degrees of dysfunction (see **Figure 1** for example). The Barany society has recently published a consensus document on the diagnostic criteria for BVP (6). To receive a diagnosis, patients must have a chronic clinical syndrome consisting of unsteadiness when standing or walking, combined with oscillopsia during head or body movements and/or worsening of unsteadiness in the dark or on uneven ground. They must also have bilaterally reduced or absent angular VOR function documented by vHIT, caloric, or rotational testing. VEMPs, and other tests of otolith function, remain peripheral to the diagnosis of BVP as they are not reliably abnormal (6).

A potential problem with the exclusion of otolith function from the diagnosis of BVP is that patients who may present with disease affecting predominantly the otolith organs would be missed. In fact, several studies have proposed a rare type of BVP, which affects the inferior vestibular nerve and causes abnormal cVEMPs, but spares the superior vestibular nerve (36–38). However, the patients in these studies were identified retrospectively from large databases by their abnormal AC cVEMP results and not by their presenting symptoms. It is currently not known whether isolated bilateral otolith dysfunction causes significant disability. Given that cVEMPs are known to be absent occasionally in normal subjects (more so with increasing age), this type of study design makes it difficult to distinguish the effects of disease from a false positive (abnormal) test result. It is possible that these cases simply represent the false positive rate expected for the cVEMP test. Further studies are therefore needed to confirm the existence of an isolated otolithic BVP, ideally using additional tests to confirm the otolith loss [such as eccentric rotation or measurement of the ocular tilt reflex (31)].

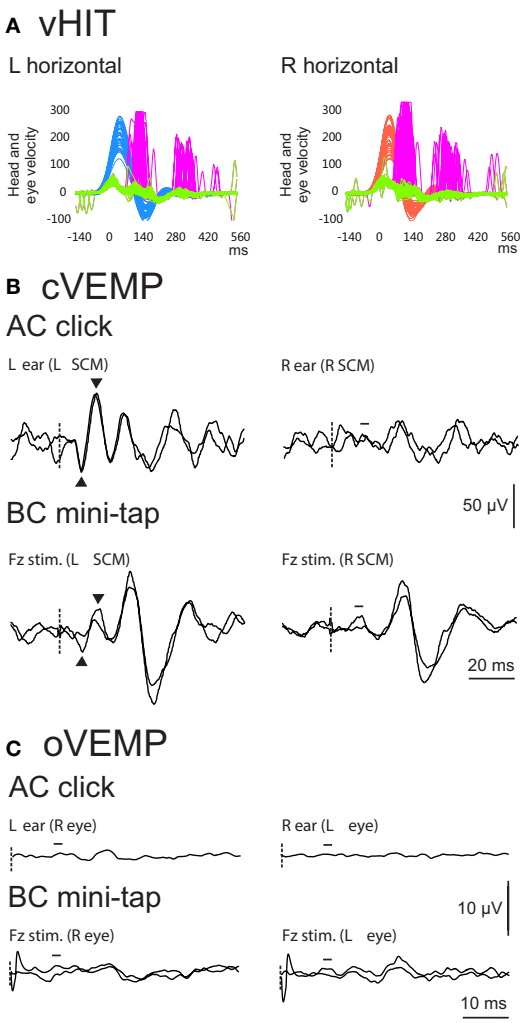

FIGURE 1 | Example vHIT **(A)**, cervical vestibular evoked myogenic potential (cVEMP) **(B)** and ocular VEMP (oVEMP) **(C)** results from a 54-year-old male patient with idiopathic bilateral vestibulopathy (BVP). For cVEMPs and oVEMPs, stimulus onset is indicated by the dashed line. vHIT results show reduced horizontal vestibulo-ocular reflex (VOR) gain [shown by the gap between the green (eye) and blue (head) traces on the left, and green and red traces on the right] and the presence of catch-up saccades (purple traces) on both sides. VOR gain on the left was 0.39 and on the right was 0.17, indicating that the patient met the test criteria for a diagnosis of BVP (gain less than 0.6) (6). cVEMPs evoked by air-conducted (AC) sound were clearly present on the left but absent on the right. cVEMPs evoked by bone-conducted (BC) mini-taps were present on one trial on the left only but were not readily reproducible. oVEMPs evoked by both AC and BC stimulation were absent bilaterally. The results in this patient highlight the mixed results often seen with VEMP testing in BVP.

The variability of otolith function in BVP is very likely to depend on the cause of BVP, as mentioned above. Bilateral loss of vestibular function is the final outcome of a range of diseases with variable course and duration, including exposure to ototoxic

drugs, neurodegenerative disease (CANVAS), and congenital malformations (LVAS). As it is a rare condition and VEMPs are relatively new tests, there are few studies comparing sufficient numbers of patients with different etiologies. Alternately, factors relating to the VEMP test itself may also affect the rate of otolith abnormalities found in BVP.

Due to the large range of normal VEMP amplitudes false negative responses may occur, i.e., responses fall in the normal range, but may be smaller than they would be without the effects of BVP. Unlike the vHIT, in which the obtained VOR gain is compared to an ideal of 1.0 (39), there is no objective target amplitude for VEMPs. While unilaterally reduced amplitudes are easy to detect by comparison with the opposite side, bilaterally reduced amplitudes can usually be detected only in group comparisons and not in individual patients. This can be seen in studies of BPV, in which average patient amplitudes are smaller than control values (25, 26), suggesting a degree of otolith dysfunction. VEMP amplitude is determined not only by the effect of the stimulus on the otolith organs but also by measurement of a synchronous change in motor activity in the target muscle. It is not known how much residual otolith activity is required to produce a synchronous motor discharge or how much otolith function can be lost before a VEMP falls below the 5% normal limit.

False positive (abnormal) responses can also occur for several reasons. There is a well-documented effect of age on reflex amplitudes, which is greater for the AC cVEMP than BC oVEMP (40–44). For the AC cVEMP, the range of normal amplitudes extends down to an absent response in older age groups (41, 45, 46). There is only a small effective window for AC stimulus intensity: between the vestibular threshold for AC sound and the safe upper limit of cochlear sound exposure. Factors such as conductive hearing loss, aging, and weak stimulus intensity can all shift an ear out of this effective range (and may affect the ears reasonably symmetrically, producing bilateral test abnormalities). In addition, for the cVEMP, muscle contraction strength and its measurement are also important considerations (47–50). Very weak contractions may erroneously lead to absent or abnormal responses (50). For the oVEMP, angle of vertical gaze and stimulus type are important factors (51). BC stimulation produces robust oVEMPs that are only mildly affected by age, while AC stimulation produces very small responses that are significantly affected by age and often absent, leading to high rates of abnormality in normal subjects (41). For both reflexes, it is important to ensure results are reliable and valid before a decision is made about normality/abnormality. Apart from using correct stimulation and recording techniques, a major factor is a good signal-to-noise ratio, which can be optimized by comparing fewer, longer recordings for each ear, rather than multiple short recordings, and obtaining a relatively flat prestimulus baseline. It is also important for laboratories to have their own normal data, particularly in the upper age ranges. However, even with good normal data, it can be theoretically problematic to define a lower limit of normal, as bilaterally small or absent responses are a normal finding in older patients. Agrawal et al. (26) defined abnormal amplitudes as those below the fifth percentile of normal control data, which is reasonable as it assumes the same level of error as commonly applied in statistical analysis. Similar problems with false positives and negatives can also be ascribed to the caloric test and there are different conventions across laboratories regarding the lower limits of normal SPV (6).

CONCLUSION

Vestibular-evoked myogenic potential studies have shown a range of otolith function in patients with BVP. This variability can be partly attributed to the heterogeneous nature of BVP but is also due to the nature of the VEMP tests and the large range of responses present in normal subjects. It is appropriate that VEMPs remain a complementary test in BVP: while not helpful to the diagnosis of BVP, VEMP-vHIT-caloric dissociations may prove useful in determining its etiology and provide information about the extent of disease within the labyrinth. They may also be helpful in monitoring disease progression and guiding rehabilitation. As vHIT and VEMPs become more widespread, we hope to see more large studies of BVP patients with different etiologies to better understand the effects of BVP on canal and otolith function.

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ORIGINAL RESEARCH
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Clinical Characteristics and Etiology of Bilateral Vestibular Loss in a Cohort from Central Illinois

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Background: Previous series of bilateral vestibular loss (BVL) identified numerous etiologies, but surprisingly, a cause in a significant number of cases remains unknown. In an effort to understand possible etiology and management strategies, a global effort is currently in progress. Here, I contribute my 10-year experience with both acute and chronic BVL during the 2007–2017 decade.

Methods: This is a retrospective review of the charts and EMR of patients diagnosed with BVL in the last 10 years. Following Institutional IRB approval, we identified 57 patients with a diagnosis of BVL and utilized the current diagnostic criteria listed by the Barany society (1). The inclusion criteria included patients with BVL of any cause, within an age span older than 18 and a neuro-otologic examination supporting the clinical impression of BVL.

Results: During the current decade 2007–2017, I identified two broad categories of BVL (acute and chronic) in 57 patients; only 41 of them had records available. The etiology includes: idiopathic: $n = 9$, Wernicke's encephalopathy $n = 11$, superficial siderosis $n = 3$, paraneoplastic syndrome: $n = 3$, bilateral vestibular neuritis (recurrent AVS lasting days without cochlear symptoms) $n = 3$, simultaneous ototoxicity of aminoglycoside and chemotherapy toxicity $n = 2$, MELAS $n = 2$, Meniere's disease treated with intra-tympanic streptomycin in one ear $n = 1$, acute phenytoin intoxication: $n = 1$, combined chronic unilateral tumor-related vestibulopathy and new contralateral vestibular neuritis (this patient presented with Betcherew's phenomenon) $n = 1$, bilateral AICA stroke $n = 1$, mixed spinocerebellar ataxia type 3, $n = 2$ and CANVAS $n = 2$.

Conclusion: This cohort included a 28% overall incidence of acute and subacute BVL; among them, 65% improved with intervention. In the thiamine deficiency group, specifically, the vestibular function improved in 80% of the patients. Even though acute, subacute, or chronic showed slightly asymmetric horizontal-VOR gain loss, it never did cause spontaneous, primary straight gaze horizontal nystagmus. $n = 39/41$ patients had abnormal manual HIT, $n = 26/41$ BVL patients tested with video head impulse immediately after manual testing showed decreased VOR gain, including two with covert saccades. Two thiamine patients with positive bedside pretreatment manual HIT, tested after treatment with high-dose thiamine showed improved VOR. In acute thiamine deficiency, the horizontal VOR was abnormal and the vertical was either normal or mildly decreased. This series favored a neurologic cause of BVL. Finally, 20% of the chronic cases were idiopathic.

Keywords: bilateral vestibulopathy, acute bilateral vestibular loss, chronic bilateral, vestibular loss, neurologic disorders associated with bilateral vestibular loss

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INTRODUCTION

Bilateral vestibular loss is uncommon with an estimated incidence of 28/100,000 (1); however, despite advances in early diagnosis, and significant progress in vestibular testing, and imaging, parallel to molecular screening for genetic and immune BVL phenotypes, a significant number of patients remain idiopathic (2–4). One important and potentially preventable cause of BVL is exposure to ototoxic drugs with typical subacute onset of symptoms. Awareness of potential ototoxicity from antibiotics and close monitoring of patients with infections without other viable treatment led to preventive clinical measures and the use of serum levels to identify an early threshold of ototoxicity (5). In addition, I identified in these cohort patients with acute BVL due to thiamine deficiency and other less common causes. This group displayed overlapping symptoms and signs with the BVL but had acute onset, affected a specific group individuals at risk of nutritional deficiency and had additional clinical findings; timely recognition of this syndrome may lead to recovery. Although awareness of these higher risk patients is greater than 40 years (6–8). In this retrospective study, we analyze their clinical characteristics as a group (9–11). Here, I report my experience with 41 acute and subacute/chronic BVL patients studied during the past decade.

MATERIALS AND METHODS

The University of Illinois College of Medicine IRB approved this study. We report the result of a retrospective chart review of patients with BVL diagnosed between years 2007 and 2017, 57 patients had a final diagnosis of BVL at our Center. Here, I classified this cohort according to the duration of the symptoms, the first group comprised either acute (less than 24-h), or subacute (less than 1 month) duration; and a second group with long-standing symptoms (greater than 1 month), I utilized the recently published diagnostic criteria from the Barany Society (12); only 41 of them had records available. Inclusion criteria included comparatively better static than dynamic visual acuity (VA) (more than 3-line deterioration), truncal imbalance, positive manual head impulse test in horizontal canal planes, and in some cases, positive vertical canal compromise, in these cases, we confirmed decreased VOR gain (below: 0.7). Bilaterally reduced caloric response with maximum slow phase velocity of <5°/s and torsional chair with decreased gain (<0.6), phase lead greater than 68° and bilaterally low time constants of the step rotational induced nystagmus (<5 s). All patients underwent a neurologic and vestibular clinical evaluation that included a mental status assessment to assess orientation and determine level of awareness and ability to follow the examination protocol.

Patients with a history of alcohol dependence or nutritional deficiency underwent a specific protocol. The acute cases had a vestibular and ocular motor examination at bedside including manual and video head impulse (vHIT) followed by a neurologic examination. I repeated these tests after the intravenous administration of 500 mg of thiamine intravenously (9, 11). I ordered MRI of the brain in all cases. In patients with a subacute history, we measured serum thiamine levels and began oral thiamine replacement.

When the history suggested BVL, I implemented the following protocol: static followed by dynamic VA, direct ophthalmoscopy, visual field testing, oculomotor and cranial nerve testing, nystagmus analysis if present (both with fixation and with fixation block), manual head impulse in all six-canal planes. Truncal posture including Romberg test with eyes open and closed and balance while standing on a foam cushion. I tested gait and tandem gait whenever possible. Acute patients unable to stand had their ability to sit at the side of the bed with the arms crossed and eyes closed. At this point, I tested fine motor limb coordination, muscle tone, strength, and pathologic reflexes. We concluded the examination with nystagmus provocative maneuvers (routinely hyperventilation, mastoid vibration, Valsalva maneuver, horizontal head shaking, and positional testing). Simultaneous visual vestibulo-ocular reflex (VVOR) testing was performed only in our most recent cases.

If the clinical assessment suggested BVL, the work-up ordered included pure tone audiometry and vestibular testing including: Nystagmus recordings, bithermal caloric stimulation, torsion swing chair testing, and the vHIT; I did not order additional otolith function tests. At least one test of vestibular function in each case. Ideally, bithermal caloric testing; the vHIT measure different vestibular receptor frequencies and thus preferably in all patients, particularly if Meniere's disease is suspected (4, 13, 14). VOR testing with the torsion/swing chair was performed in a few patients as well; however, several patients in this cohort underwent only one test of vestibular function, due to cost or availability issues. After 2012, all patients with BVL had manual and video HIT. With two exceptions, I tested acute cases at the bedside. MRI of the cerebellopontine angle included pre- and post-contrast images. Temporal bone CT scan with if necessary and routine blood tests to screen for metabolic abnormalities, vasculitis, autoimmune disorders, syphilis and Lyme's serology, thiamine, folate and vitamin B12 serum levels and cerebrospinal fluid studies in selective patients with BVL and additional neurologic abnormalities. In addition, patients with BVL and additional neurologic abnormalities underwent testing in search of an autoimmune and paraneoplastic ataxia.

Follow-up longer than 1 year or greater was accomplished in $n = 31/41$ patients, some have been followed for ~10 years; this follow-up allowed us to assess the clinical course and the effect of medical treatment if any and assessment of the contribution of a defined Physical Therapy rehabilitation protocol.

RESULTS

I made a diagnosis of BVL in 57 patients at our Center; only 41 of them had records available (**Tables 1** and **2**). The average age was 58, with a range of 19–86; the gender distribution was 21 females and 20 males. The clinical course was characterized by a slowly progressive bilateral isolated vestibular or cochleovestibular loss in 29 patients and an acute vestibular syndrome in eight and acute sequential in four patients. BVL was associated with simultaneous CNS compromise in 28 and was isolated vestibular or cochleovestibular loss in 13 patients. Bilateral mixed cochleovestibular loss was present in three patients with superficial siderosis and two with MELAS, unilateral postsurgical deafness (unilateral

jugular paraganglioma resection), and unilateral Meniere's (post-unilateral transtympanic streptomycin injection).

The etiology distribution (**Tables 1** and **2**) includes: idiopathic: 9, Wernicke's encephalopathy: 11, superficial siderosis: 3, paraneoplastic syndrome: 3, bilateral vestibular neuritis (recurrent AVS lasting days without cochlear symptoms): 3, simultaneous ototoxicity of aminoglycoside and chemotherapy toxicity: 2, MELAS: 2, Meniere's disease treated with intratympanic streptomycin in one ear: 1, acute phenytoin intoxication: 1, combined chronic unilateral tumor-related vestibulopathy and new contralateral

TABLE 1 | Acute and subacute bilateral vestibulopathy.

Patient	Age	Vestibular test	Classification	Etiology and CNS clinical imaging findings	Video head impulse (vHIT)	Previous vertigo attacks	Outcome over time
1	53	Manual HIT+ Absent Calorics	Subacute	Alcoholism Vitamin B1 deficiency Gaze evoked nystagmus (GEN) DBN Ataxia Vermis Atrophy	RH 0.72[a] LH 0. 75 RA 0. 76 LA: 0.41 RP: 0.51 LP: 0.76	No	Partial Improvement Truncal Ataxia DBN
2	50	Horizontal Manual HIT+ Vertical Normal Manual HIT Absent Calorics	Acute Vestibular Syndrome	Alcoholism Vitamin B1 deficiency GEN	Not performed	No	Improved
3	55	Manual HIT+Absent Calorics	Subacute	Alcoholism Vitamin B1 deficiency GEN	Not Performed	No	Improved
4	37	Manual HIT+	Subacute	s/p Gastric Bypass Vitamin B1 deficiency GEN/UBN	Not performed	No	Improved
5	39	Manual HIT+ Absent Calorics No ice response	Acute	s/p Gastric Bypass Vitamin B1 deficiency Abducens Paresis GEN	Not performed	No	Improved
6	60	Manual HIT+ Absent Calorics No ice response	Subacute	s/p gastric Bypass Vitamin B1 deficiency Abducens Paresis GEN	RH: 0.50 LH 0.40	No	Improved
7	28	Manual HIT+ vHIT+	Subacute	s/p gastric Bypass Vitamin B1 deficiency	RH: 0.58 LH: 0.64	No	Improved
8	45	Manual HIT+ vHIT+	Acute	Alcoholism Vitamin B1 Deficiency Signal Changes in the medial Vestibular Nuclei and CC Marchiafava Bignami encephalopathy UBN	RH 0.51 LH 0.60 RA 0.93 RP 0.78 LA 0.51 LP 095	No	Improved
9	45	Manual HIT+ vHIT+ (normal months later)	Acute	Alcoholism Vitamin B1 Deficiency Encephalopathy UBN Transition DBN	RH: 0.75[a] LH: 0.83 LA: 0.65 RP: 0.82 RA: 0.73 LA: 0.75	No	Partial Improvement Truncal Ataxia DBN

(*Continued*)

TABLE 1 | Continued

Patient	Age	Vestibular test	Classification	Etiology and CNS clinical imaging findings	Video head impulse (vHIT)	Previous vertigo attacks	Outcome over time
10	60	Manual HIT+ vHIT+	Acute	Alcoholism Vitamin B1 Deficiency Encephalopathy UBN Transition DBN MRI Signal changes in midbrain, pons and medulla	RH 0.34 LH 0.39 LA 0.80 RP 0.17 RA 0.15 LP 0.20	No	No Improvement Permanent Low VOR gain Truncal Ataxia DBN Encephalopathy Improved
11	22	Manual HIT+ vHIT+	Acute Encephalopathy With UBN Transition To DBN	s/p gastric Bypass Vitamin B1 Deficiency	RH 0.62 LH 0.57 LA 0.82 RA 0.62 LP 0.69 RP 0.60	No	No Improvement Permanent Low VOR gain Truncal Ataxia DBN Encephalopathy Improved
12	63	Manual HIT+ vHIT+	Acute phenytoin (level: 26.6)	Phenytoin Overdose Ataxia GEN	RH 0.38 LH 0. 43 RA 0.67 LA Not done RP Not done LA 0.27	No	Improved
13	67	Manual HIT+ vHIT+	Acute Rapidly progressive	Anti-Yo PNS Cerebellar Cancer Esophagus DBN Ataxia	RH 0.57 LH: 0.89	No	Progressive course Despite PLEX Chemotherapy steroids
14	62	Manual HIT+ vHIT+	Acute	Anti-Hu PNS Prostate Neuro-endocrine Syndrome Eventually INO = UBN	RH: 0.42 LH: 0.31 RA: 0.15 LP: 0.22 RP: 0.15 LA: 0.17	No	Progressive course Despite PLEX Chemotherapy steroids
15	64	Manual HIT+ vHIT+	Slowly Progressive Sudden worsening	PNS? Ataxia Neuropathy + P/Q Channel antibodies Old ovarian ca	RH 0.53 LH 0.44 RA 0.74 La 0.03 RP 0.46 LP 0.85	No	Did not want immuno-suppression or PLEX
16[a]	63	Manual HIT + vHIT done ~ after new VN	Chronic unilateral Acute Contralateral	Chronic left Vestibular loss Acute right vestibular neuritis	RH 0.86[b] LH: 0.58 RA 0.45 LA 0 75 RP 0 66 L 0 22	No	Improved Spontaneously. Had Betcherew's Phenomenon

[a]*vHIT performed 2 weeks after treatment initiation.*
[b]*vHIT performed after discharge when she improved.*
VN, vestibular neuritis.

vestibular neuritis (this patient presented with Betcherew' s phenomenon): 1, bilateral AICA stroke: 1 (**Figure 1**), spinocerebellar ataxia type 3: second CANVAS: 2.

All patients underwent clinical testing as described in the protocol with the following result. Dynamic VA was abnormal in all patients. In five patients with primary gaze up (UBN) or downbeat (DBN), the nystagmus was a cofactor associated with impaired VA. We performed the manual HIT in all patients and recorded the vHIT in 30 patients examined when the vHIT device was first available to us. 39 patients had an abnormal manual HIT and two had covert saccades and low VOR gain (**Figure 2**). Prior to 2012, the patients underwent conventional bithermal caloric testing and 15 of them had absent caloric responses with conventional temperature stimulation, even when we utilized ice water stimulation. In few cases, standard caloric stimulation generated a weak horizontal nystagmus with slow phase velocities

TABLE 2 | Chronic bilateral vestibulopathy.

Patient	Age	Vestibular test	Classification	Etiology and CNS clinical imaging findings	Video head impulse (vHIT) gain	Previous vertigo events	Audiometry
1	64	Manual and vHIT+ Torsion swing Abnormal Calorics: depressed	Recurrent Vertigo Bilateral vestibular loss (BVL)	Idiopathic Sjogren's	RH 0.53 LH 0.39 RA 0.27 LA 0.40 RP 0 12 LP 0 01		Normal
2	78	Manual and vHIT+ All canals	Slowly Progressive BVL	Ataxia MRI Superficial siderosis	Not done	No	Bilateral deafness
3	19	Manual and vHIT+ Torsion swing Calorics: No ice response	Slowly Progressive BVL	Idiopathic History Of migraine	RH 0.62 LH 0.77 RA 0.32 LA 0.58 RP 0 54 LP 0.62		Normal
4	62	Manual and vHIT+	Recurrent Vertigo BVL	Idiopathic	RH 0.14 LH 0.47 RA 0.39 LA 0.51 RP 0.28 LP 0.40	Yes	Normal
5	73	vHIT Calorics Depressed Max slow phase velocities (SPV)* 4°/s	Slowly Progressive BVL	CANVAS DBN Ataxia neuropathy	RH 035 LH 0 28 RA 069 LA 0.36 RP 0 36 LP 0 35	No	Normal
6	57	Manual and vHIT+	Slowly Progressive BVL	Presumed Siderosis Old SA Hemorrhage DBN Ataxia	RH 0 55 LH 0 27 RA 030 LA 0 56 RP 0 47 LP 0 91	No	60 dB loss R > L
7	54	Manual and vHIT+	Slowly Progressive BVL	Gentamicin and Carbo-Platinum For Uterine Cervix cancer	RH 0 01 LH 0 02 RA 0 23 LA 0 10 RP 0 14 LP 0 19	No	
8	39	Manual and vHIT+	Slowly Progressive BVL	Gentamicin Ototoxicity	RH 0 59 LH 0.64 RA 0 37 LA 0.61 RP 0 50 LP 0 18	No	Mixed hearing Loss R ear High frequency Hearing Loss L ear
9	86	Manual and vHIT+	Biphasic Sequential	Bilateral Vestibular Neuritis Sequential	RH 0 30 LH 0 21	Two Acute events	50 dB loss High frequency
10	84	Manual HIT+ Chronic Skew	Biphasic Sequential	L AICA MCP stroke R vestibular Root entry stroke	Not Done	Two Acute events	High freq Hearing Loss R > L

(*Continued*)

TABLE 2 | Continued

Patient	Age	Vestibular test	Classification	Etiology and CNS clinical imaging findings	Video head impulse (vHIT) gain	Previous vertigo events	Audiometry
11	58	Manual and vHIT+ Torsion swing Abnormal	Slowly Progressive BVL	Ataxia Saccade Hypermetria Abnormal pursuit Neuropathy SCA type 3 Cerebellar Atrophy	RH 0 22 LH 0 19 RA not done LA 0 09 RP 0 32 LP not done	No	Normal
12	49	Manual HIT Torsion swing Abnormal Calorics No ice response	Slowly progressive BVL	Idiopathic	Not done	No	
13	35	Manual and vHIT + Torsion swing Abnormal calorics: No ice response	Slowly Progressive BVL	Idiopathic	RH 0 14 LH 0 23 RA 0 38 RP 0 38 LA 0 35 LP 0 27	No	Normal
14	55	Manual and vHIT+ Torsion Swing Abnormal Calorics <5°/s SPV	Slowly Progressive BVL	Idiopathic	RH 0 72 LH 0 41 RA 0 71 RP 0 41 LA 0 42 LP 0 26	No	Normal
15	58	Manual and vHIT+	Slowly Progressive BVL	CANVAS Ataxia Neuropathy MRI Vermis atrophy	RH 0 29 LH 0 23 RA 0 22 LA 0 32 RP 047 LP 028	No	High frequency bilateral Hearing loss
16	43	Manual and vHIT+ Torsion swing Abnormal Caloric <5°/s SPV	Slowly Progressive BVL	Idiopathic	Not done	One episode	High frequency bilateral Hearing loss
17	79	T Manual and vHIT+ Torsion swing Abnormal Depressed SPV <5°/s	Slowly Progressive BVL	Idiopathic Hepatitis C	Not done	No	High frequency Hearing loss
18	82	Manual and vHIT+ Torsion Swing Abnormal Calorics depressed	Slowly Progressive BVL	Idiopathic	Nor done	Episodes for 5 years	High frequency Hearing loss
19		Manual and vHIT+ Audiogram	Slowly Progressive Cochleo-BVL	MELAS 3243 tRNA mutation Diabetes Retina Deg MRI Atrophy Calcifications	RH: 0.31 LH: 0.32 RP: 0.58 LP: 0.58 RA: 0.83 LA: 0.80	No	Deaf Unilateral Cochlear Implant
20		Manual and vHIT+ Audiogram Audiogram	Slowly Progressive Cochleo-BVL	MELAS 3243 tRNA Mutation Neuropathy	RH 0.31 LH 0.37 RP 0.58 LP 0.58 RA 0.83 LA 0,80	No	Severe Sensorineural loss Hearing loss. All frequencies

(*Continued*)

TABLE 2 | Continued

Patient	Age	Vestibular test	Classification	Etiology and CNS clinical imaging findings	Video head impulse (vHIT) gain	Previous vertigo events	Audiometry
21	59	vHIT Calorics: No ice response	Slowly Progressive Cochleo-BVL	Superficial Siderosis	RH 0.08 LH 0.02 LA 0.17 RP 0.19 RA 0.25 LA 0.19	No	Severe 60 dB Sensorineural Hearing loss L > R
22	74	vHIT	Acute Lethargy	Right Meniere's Intra-tympanic Streptomycin Left Idiopathic?	RH 0.29 LH 0.28 LA 0.26 RP 0.35 RA 0.26 LP 0.06	Yes	Deaf right ear Decreased Hearing left ear high frequency
23	68	Manual and vHIT+ Calorics Depressed	Episodic	R > L Vestibulopathy Sequential Neuritis	RH: 0.34 LH: 0.10	Yes	R > L sensorineural Hearing loss
24	59	Manual and vHIT+	Acute	SCA 3? Polycystic kidneys	RH: 0.58 LH: 0.60 LA 0.74 RP 0.64 RA 0.69 LP 1.03	No	Normal
25	66	Manual and vHIT+	Slowly Progressive	Anti-GAD Antibody +	RH 0.18 LH 0.32 LA 0.45 RA 0.45 LP 0.33 RP 0.33	No	Normal

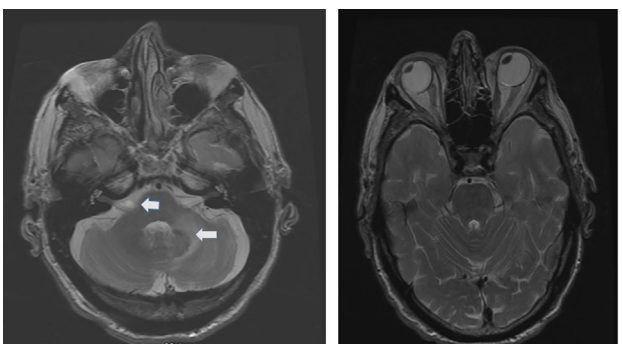

FIGURE 1 | Axial T2 MRI: left panel shows a small area of increased signal intensity due to a small stroke involving the lateral pons, near the root entry of the right vestibular nerve (smaller arrow) and a larger stroke involving the left lateral pons and middle cerebellar peduncle (left panel larger arrow). Notice the conjugate ocular deviation of the eye to the right, coinciding with the slow phase of the nystagmus related to the second lacunar stroke in the right pons.

(SPV) of <5°/s. In some instances, the patients had caloric testing prior to our evaluation and we did not repeat it. Eight patients underwent torsion/swing chair testing decreased VOR gain and demonstrated phase lead when measured; the per-rotational and post-rotational nystagmus time constant was decreased (<5 s). Even though we did not routinely compare test of vestibular function in this series, we found them to be generally concordant in this small series (**Figure 2**).

In the patients with BVL due to Wernicke's encephalopathy, the pretreatment seem thiamine levels were low in $n = 8/11$ cases, the remaining three had an infusion of high-dose intravenous thiamine without preceding serum level. Four of them had abnormal MRI findings typical for Wernicke's encephalopathy.

DISCUSSION

In this cohort, BVL in $n = 9/41$ (~20%) was idiopathic as noted in previous reports (2–4). In addition, this series is biased toward BVL associated with a neurologic disease and thus differs from previous BVL series; therefore, the etiology frequency in our population must be interpreted with this fact in mind; however, we identified several BVL patients in the context of acute and subacute neurologic syndromes in $n = 16/41$ (>25%).

Recently developed diagnostic criteria provided precise clinical and laboratory signs of BVL (12). I utilized the proposed protocol in this retrospective series. Search for the BVL diagnostic gold standard test is a still matter of debate; because caloric testing, rotational testing, and manual or vHIT test lack 100% specificity/sensitivity, clinicians may use one or more of these modalities to confirm the clinically suspected diagnosis (3, 4, 15). However, the combination of head impulse test, dynamic VA, and Romberg testing while standing on a rubber foam cushion is a practical initial step in subacute and chronic to effectively select patients requiring additional investigation (16). I implemented further quantitative testing thereafter (4). In acute patients, the testing

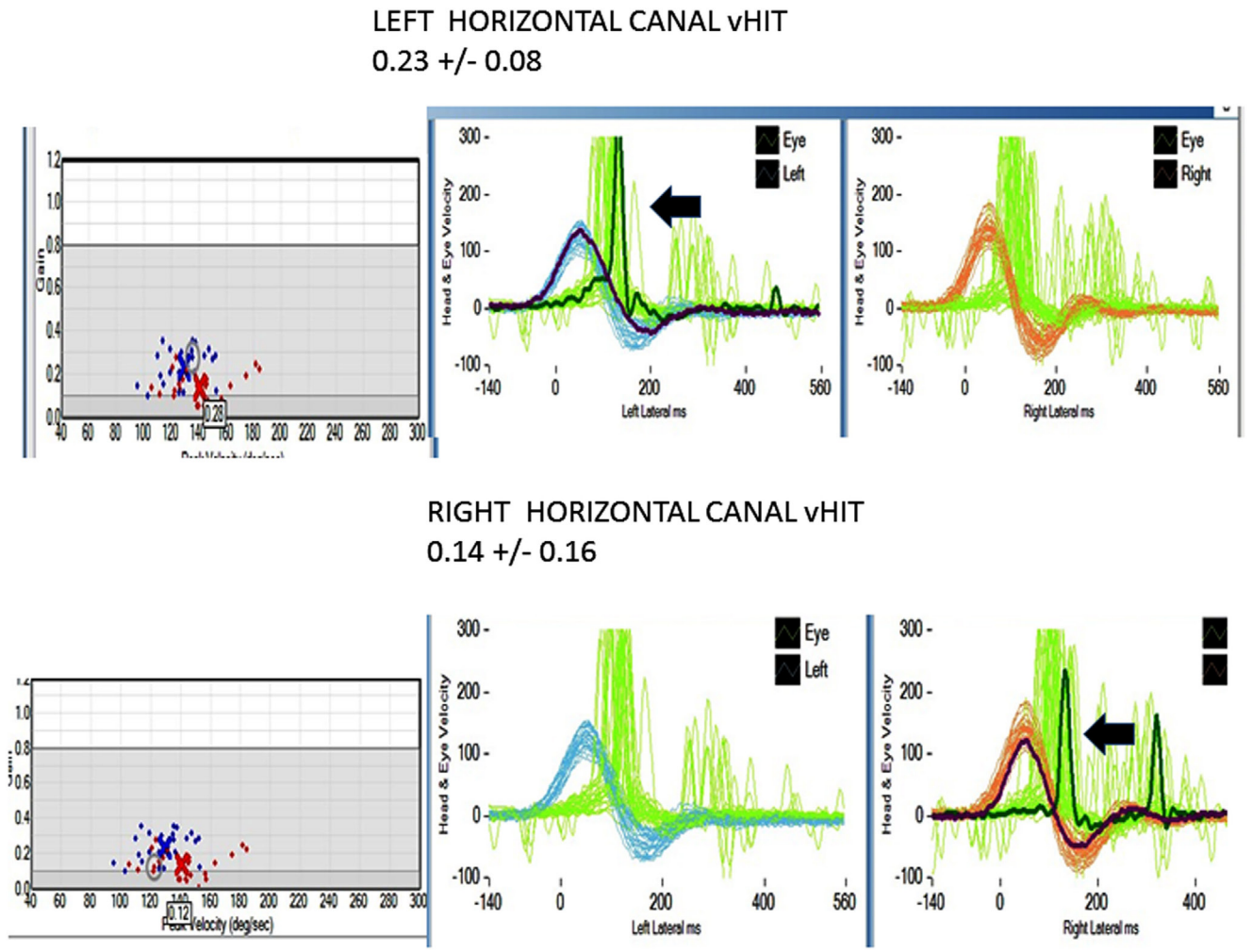

FIGURE 2 | Horizontal video head impulse (h vHIT). Upper panel left h a-VOR gain is low 0.23 ± 0.08 (normal >0.7–1.0). The arrow points to a covert, corrective saccade, which was not apparent during the manual HIT. Lower panel right h a-VOR gain is low (0.14 ± 0.16). The arrow points to a covert, corrective saccade, which was not apparent during the manual HIT. The vertical canal gain was also low (not shown).

protocol varied and included dynamic VA and both manual and vHIT in all six semicircular canal (SCC) planes. I paid special attention to comparing the horizontal versus vertical canal VOR gain; in central, BVL lesions preferentially affecting the MVN and suggests thiamine deficiency as a potential cause (8, 10, 17), which may be confirmed with pretreatment serum thiamine levels and a favorable response to vitamin supplementation and normal diet (8–10, 17). Similarly, selective peripheral vestibulopathies may spare the anterior canal VOR (18). The value of testing the VOR gain in plane of all six-SCC cannot be overemphasized. I did not identify in this series, a single case of acute simultaneous, bilateral peripheral vestibulopathy.

Analysis of our findings suggest that an acute etiology is more frequent than anticipated. Neurologic patients now undergo routinely manual HIT and vHIT testing in acute in-patient units. The referral population served at our Center represents a mixed small urban and rural population; however, the referral base is large, probably in the order of three million patients. To facilitate the discussion will divide our cohort in acute and subacute bilateral vestibular loss (BVL) (symptom evolution <1 month duration) (**Table 1**) and chronic vestibular loss (**Table 2**) evolving over a period greater than 1 month, but usually of longer duration. In the chronic BVL group, several patients had either isolated bilateral peripheral loss, cochleovestibular loss, or mixed peripheral/central vestibular loss in the context of a neurodegenerative process.

Acute BVL

Among the 41 cases, 16 patients had an acute/subacute presentation (11 Wernicke's encephalopathy (WE), three paraneoplastic syndromes, and two additional cases included one with acute phenytoin intoxication and one acute right vestibular neuritis and with chronic posttumor resection-related contralateral vestibulopathy, who displayed Betcherew's phenomena) (**Table 1**) (19). In WE, the presumed location of the lesion in WE is the medial vestibular nucleus (8, 17, 20); however, at present, temporal

bone studies in WE have not been performed to my knowledge; therefore, it is unknown if a co-existent peripheral vestibulopathy is also present. None of our acute BVL patients had spontaneous primary gaze horizontal nystagmus, except for the one sequential patient with Betcherew's phenomenon. $n = 15/16$ patients with acute/subacute bilateral vestibulopathy had direction changing, symmetric horizontal gaze evoked nystagmus (GEN). UBN in straight-ahead fixation was noted in five patients with acute thiamine deficiency (four with encephalopathy and one without) and in one PNS patient. UBN switched to chronic DBN in three cases and resolved in two. UBN was present in one PNS and DBN in a second PNS patient.

In the acute cases, and in concert with the subacute and chronic BVL cases, primary gaze horizontal nystagmus was absent. Development of bilateral symmetric or minimally asymmetric horizontal vestibular loss, regardless of acuity does not cause fixation horizontal nystagmus (21). To explain the horizontal GEN, failure of the horizontal neural integrator is likely responsible; this is the most common type of nystagmus present in Wernicke's Encephalopathy (20) and other brainstem lesions (22, 23). Several acute patients had vertical nystagmus in primary gaze; however, the precise location of the lesion responsible is unknown. Candidate locations could be the medulla (nucleus intercalatus and nucleus of Roller) (17, 24, 25), the pons (superior vestibular nucleus) (26), or the interstitial nucleus of Cajal (27).

The overall outcome of the acute BVL patient was favorable. Among 11 thiamine, six deficient patients responded to thiamine replacement and a normal diet with complete recovery and three of them had normal h-VOR gain but developed chronic DBN and gait ataxia.

In addition, the acute phenytoin intoxication patient slowly normalized the VOR gain once the medication was properly titrated; the patient with Betcherew's' phenomenon improved spontaneously over a few days. Two of three paraneoplastic syndrome patients treated with immunosuppression, cancer specific management had continuous neurologic and medical deterioration, and died, and one of them declined treatment.

Chronic BVL

The patients in this group comprised 25 patients (**Table 2**). Nine patients had isolated, idiopathic BVL, a number roughly comparable with previous BVL series (2–4, 28) Those patients with BVL due to ototoxic medications, together with those due to presumed sequential vestibular neuritis remain either clinically stationary, or are slowly improving through vestibular adaptation. One patient with bilateral sequential AICA strokes eventually had partial improvement after the second stroke (**Figure 1**); he was the only patient with chronic diplopia due to persistent, low-amplitude skew deviation.

In peripheral vestibulopathy, the manual HIT was abnormal in the plane of all canals tested, the vertical HIT in the plane of the posterior canal was, in our experience, easier to detect than the anterior canal, thus, often requiring vHIT for confirmation; however, the anterior canal VOR gain, as mentioned before, may be selectively spared in peripheral vestibulopathy (18). In previous series, exposure to ototoxic drugs is a frequent cause of BVL. Two patients in this series had BVL caused by exposure to gentamicin; curiously, both patients had gynecologic malignancies and had treatment with carboplatin and Taxol, they had discontinued all these medications when I first saw them. The lowest vHIT gain recorded in the series affected the ototoxic and idiopathic groups (near vestibular areflexia).

Patients with acute and those with chronic peripheral and central vestibular abnormalities had GEN, which was not present in isolated peripheral lesions. Eye movement abnormalities were frequent with central lesions (often diplopia due to extraocular muscle weakness, internuclear ophthalmoplegia, or skew deviation). We found additional eye movements abnormalities due to brainstem or cerebellar dysfunction. We did not test the VVOR routinely, thus, we cannot comment in its diagnostic value in this series; however, this would be another possible differentiating characteristic pointing to central localization and frequently present in CANVAS (29). In this series, the CANVAS patients had an abnormal VVOR (9). Sensorineural loss was more frequent with peripheral vestibulopathies.

A summary of the prognosis in this 41-patiet cohort includes Recovery in $n = 14/41$ cases, partial recovery, and progressive deterioration in $n = 12/41$. Two of the paraneoplastic syndromes died within 6 months after the diagnosis, because of cancer management complications and six patients are wheelchair bound (BVL with neurodegenerative disorders and two with superficial siderosis), the remaining 15 cases remain stable as noted in previous series (28).

TABLE 3 | Comparative findings in bilateral vestibular loss.

Subacute/chronic bilateral peripheral vestibulopathy	Acute or subacute presumed central bilateral vestibulopathy
Impaired dynamic visual acuity	Impaired dynamic visual acuity
Abnormal manual and video head impulse (vHIT) horizontal head impulse test	Abnormal manual and vHIT horizontal head impulse test
Abnormal Manual vertical head impulse test The anterior canal gain may be selectively spared	Vertical manual and vHIT maybe normal or less affected than horizontal
Absent or depressed caloric responses	Absent or depressed caloric responses
No spontaneous horizontal fixation nystagmus Horizontal gaze evoked nystagmus (GEN) is generally not present (May have GEN or vertical nystagmus more commonly in CANVAS and SCA 3). In such cases, a combined peripheral and central vestibulopathy is present.	No spontaneous horizontal fixation nystagmus Horizontal GEN is present May have vertical nystagmus UBN in Wernicke's, focal lesions of the brainstem, paraneoplastic syndrome DBN may be present in the chronic phase
Neurologic examination is usually normal, unless there is an associated neurodegenerative disorder	Neurologic examination is usually abnormal. Encephalopathy may be present
Sensorineural hearing loss may be frequently present, particularly in bilateral Meniere's	Sensorineural hearing loss is usually not present
Imaging is usually normal, except when loss is associated with neurodegenerative disorder, superficial siderosis, and MELAS	Imaging is usually abnormal (acute signal changes in the gray matter surrounding the ventricles), cerebellar atrophy

In conclusion, the incidence and distribution of BVL varies with the population that attends the different centers and the specialty of the clinicians evaluating BVL interests in acute BVL is increasing because of portable technology and the possibility of BVL improvement. **Table 3** is a summary of the main vestibular findings identified in the two groups of BVL patients.

ETHICS STATEMENT

This study was approved by the University Of Illinois College Of Medicine IRB and follows the tenants of the declaration of Helsinski.

AUTHOR CONTRIBUTIONS

This is a single author paper. I examined each patient and conducted a retrospective review.

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Conflict of Interest Statement: Otometrics corporation loaned research equipment (beta site in 2012). This unit is no longer being used.

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SYSTEMATIC REVIEW
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Full Spectrum of Reported Symptoms of Bilateral Vestibulopathy Needs Further Investigation—A Systematic Review

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Objective: To systematically review the symptoms reported by patients with bilateral vestibulopathy (BV) in clinical studies and case reports. This would serve as the first step in establishing a validated patient-reported outcome measures (PROM) for BV.

Methods: A search on symptoms reported by patients with BV was performed in PubMed, and all publications covering these symptoms were included. Exclusion criteria comprised reviews and insufficient details about the frequency of occurrence of symptoms.

Results: 1,442 articles were retrieved. 88 studies were included (41 clinical studies, 47 case reports). In consensus, 68 descriptions of symptoms were classified into 6 common and generic symptoms. Frequency of symptoms in clinical studies and case reports were reviewed, respectively; imbalance (91 and 86%), chronic dizziness (58 and 62%), oscillopsia (50 and 70%), and recurrent vertigo (33 and 67%). BV could be accompanied by hearing loss (33 and 43%) and tinnitus (15 and 36%). 15 clinical studies and 10 case reports reported symptoms beyond vestibular and hearing deficits such as limited social activities, depression, concentration, and memory impairment and reduced quality of life in general.

Conclusion: The literature on BV symptomatology mainly focuses on classic symptoms such as imbalance and oscillopsia, while only few report additional symptoms such as cognitive memory impairment and performing dual tasks. In fact, none of the reviewed clinical studies and case reports provided a comprehensive overview of BV symptoms. To develop a validated PROM, qualitative research using semi-structured and unstructured interviews is needed to explore the full spectrum of BV symptoms.

Keywords: bilateral vestibulopathy, symptoms, dizziness, vertigo, imbalance, oscillopsia, bilateral vestibular hypofunction, patient-reported outcome measures

INTRODUCTION

Bilateral vestibulopathy (BV) is a heterogeneous chronic condition in which the vestibular function is bilaterally absent or reduced (1). BV can be due to a dysfunction of the vestibular organs, nerves, and/or the brain (1, 2). In 2017, consensus was reached by the Classification Committee of the Bárány Society about the diagnostic criteria of BV (3). Symptoms for diagnosis include unsteadiness when walking or standing, movement-induced blurred vision/oscillopsia during walking or quick head movements, or worsening of unsteadiness on uneven ground and/or darkness (1, 3, 4). However, clinical experience and current literature point to a wider variety of symptoms (5). For example, many patients report a negative impact on physical and social functioning, and compromised cognitive abilities (6–8).

At this moment, questionnaires like the dizziness handicap inventory (DHI) exist to quantify the dizziness symptoms. However, these questionnaires are not specific for vestibular loss (9). Therefore, the objective of this study was to systematically evaluate the nature and frequency of BV symptoms reported in clinical studies and case reports. This would serve as the first step in establishing validated patient-reported outcome measures (PROM) specifically for patients with BV (10). This is a tool to measure patient perceptions of their own functional status and well-being (11).

METHODS

Information Source and Search Strategy

A systematic literature search was performed according to the PRISMA statement in the bibliographical database PubMed based on the following keywords: Bilateral[All Fields] AND ((Vestibular[All Fields] AND (Hypofunction[All Fields] OR Failure[All Fields] OR Loss[All Fields])) OR Vestibulopathy [All Fields]) (12). At the beginning, a full search was performed followed by entering some additional restrictions. The outcomes of this selection were first screened by title and then also by abstract. The last selection included a complete reading of the articles found. The selections and full article analysis was performed by the first two authors (Florence Lucieer and Stijn Duijn).

Selection Criteria and Study Selection

A requirement in the basic search was that all articles were written in English. All publications reporting on symptoms of patients with BV were considered, including all types of BV (central, peripheral, or mixed etiology).

Title Screening

Articles were excluded in case of animal studies, if they did not report on BV, if they did not report on symptoms of patients with BV, if no or insufficient details on the frequency of symptoms were available, and in case of systematic reviews, comments, errata, or books.

Abstract Screening

Exclusion criteria were the same as for title screening. In case an abstract was not available, the full article was screened to search for any of the exclusion criteria.

Full-Text Review

In case the full article was not available, the article was excluded. Whenever the inclusion or exclusion criterion of an article included only "unsteadiness" or "oscillopsia," or "unsteadiness and oscillopsia," the article was excluded, so few reported symptoms could lead to a bias of interpretation of the frequency of the symptoms.

Data Collection Process and Risk of Bias Assessment

Title selection, abstract selection, full read through selection, and the analysis of the included articles were performed by the first and second author (Florence Lucieer and Stijn Duijn). The list of articles found in the PubMed search was exported to EndNote X8 for Windows and Mac (Clarivate Analytics, Philadelphia). This Endnote library was then used to perform the title, abstract, and full article selection by the two researchers separately. After the title and abstract screening the articles of both researchers were combined and duplicates were removed. After full article selection, articles were combined. Discrepancies between the two authors were discussed and a consensus was reached about selecting the articles for data analysis. A Cohen's kappa of the full article selection was calculated to evaluate the interrater reliability (13).

The nature and frequency of symptoms and the total number of patients were extracted by the first two authors and compiled using Microsoft Excel. If only percentages were reported, the authors were contacted to get the exact number of patients. The method of symptom collection in the articles was collected to assess risk of bias of the studies. Clinical studies and case reports were analyzed separately.

Qualitative Data Synthesis

The primary outcome measure of this systematic review was a detailed overview regarding nature and frequency of symptoms of BV as reported in clinical studies and case reports. Three authors (Florence Lucieer, Stijn Duijn, and Raymond van de Berg) reviewed the list of descriptions. In consensus, these descriptions were categorized into common symptoms. The frequency of these common symptoms was calculated.

RESULTS

Search Process

The search was conducted in the bibliographical database PubMed on October 25, 2017. The initial search resulted in 1,442 publications. For a schematic overview of the search strategy, see **Figure 1**. A high level of interrater reliability was reached on the full article selection with a Cohen's kappa of 0.98. Finally, 1,385 unique patients from 41 clinical studies and 86 patients from 47 case reports were included (2, 5, 14–99). The characteristics of these articles can be found in Tables A1 and A2 in Supplementary Material.

Demographic Data of the Articles

Twenty-two of the clinical studies were European, 12 North-American, 4 Asian, 3 Australian, and 1 South-American, dated

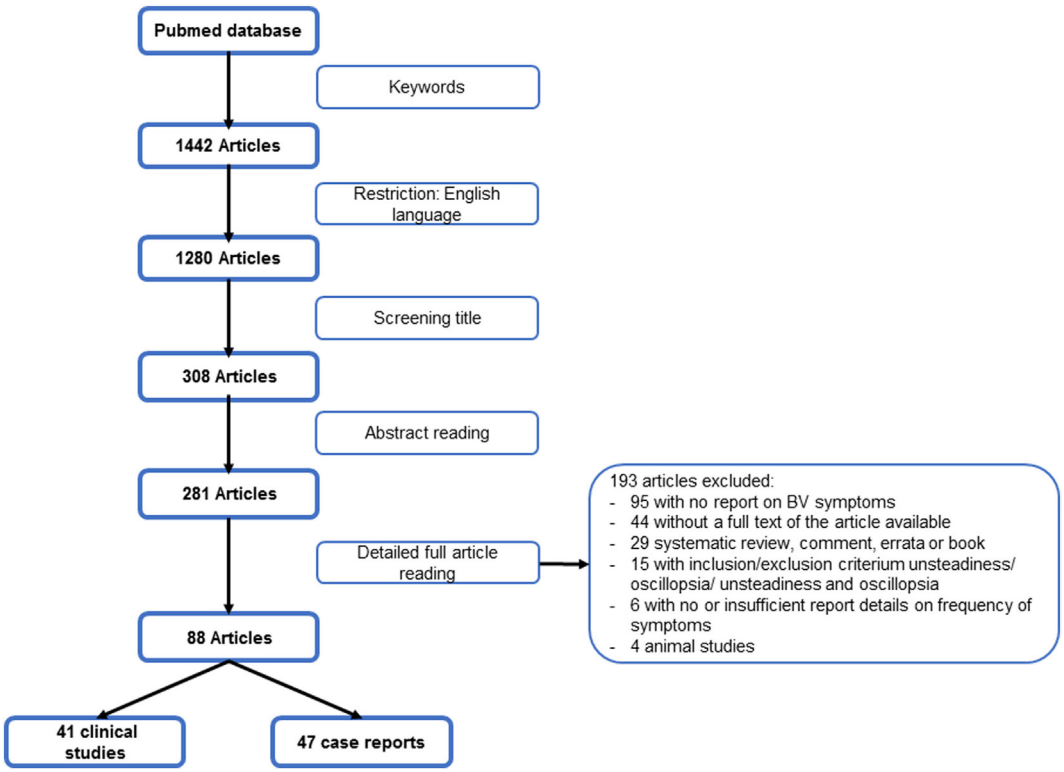

FIGURE 1 | Flowchart search strategy.

between 1984 and 2017. Twenty-one case reports were European, 13 North-American, 11 Asian, 1 Australian, and 1 South-American, originated from 1985 until 2017.

Classification of Symptoms

Sixty-eight descriptions of BV symptoms were retrieved. In consensus, these descriptions were classified into six universal symptoms: imbalance (including worsening in darkness or on uneven grounds), chronic dizziness, oscillopsia, recurrent vertigo, hearing loss, and tinnitus. Data from these six universal symptom classes can be found in Table A3 in Supplementary Material.

Clinical Studies

Symptoms found in clinical studies are presented in **Table 1**. Two times, two publications were merged in the results because of reporting duplicate data (24, 74, 97, 98). Imbalance was the most frequent symptom (91.4%). Fifteen clinical studies reported additional symptoms, for example, socio-economic impacts, depression, cognitive impairment, and increased risk of falling (5, 16, 27, 32, 43, 45, 54, 60, 63, 75, 76, 81–83, 90).

Case Reports

Symptoms found in case studies are presented in **Table 2**. Imbalance was the major symptom (86.1%). Ten case reports reported additional symptoms like sleep disturbances, unable to perform daily chores, and appearing to be depressed (18, 28, 30, 62, 67, 68, 70, 89, 91, 94). For a complete overview

TABLE 1 | Nature and frequency of most common symptoms reported by patients with bilateral vestibulopathy in clinical studies.

Symptom	n/t	Reported (%)
Imbalance	1,025/1,121	91.4%
Worse in darkness	110/115	95.7%
On uneven ground	12/12	100%
Chronic dizziness	86/149	57.7%
Oscillopsia	559/1,116	50.1%
Recurrent vertigo	267/808	33.0%
Hearing loss	256/787	32.5%
Tinnitus	59/398	14.8%

n, number of patients reporting the symptom; t, total number of patients in subset.

TABLE 2 | Nature and frequency of most common symptoms reported by patients with bilateral vestibulopathy in case reports.

Symptom	n/t	Reported (%)
Imbalance	62/72	86.1%
Worse in darkness	28/42	66.7%
On uneven ground	7/13	53.8%
Chronic dizziness	21/34	61.8%
Oscillopsia	40/57	70.2%
Recurrent vertigo	36/54	66.7%
Hearing loss	30/70	42.9%
Tinnitus	10/28	35.7%

n, number of patients reporting the symptom; t, total number of patients in subset.

of additional symptoms in clinical studies and case reports, see **Table 3**.

DISCUSSION

After a structural review until October 2017, 41 clinical studies and 47 case reports were reviewed to determine the nature and frequency of symptoms experienced by patients with BV. No study was identified that created an inventory of patient-reported outcomes. Almost all patients suffered from imbalance, chronic dizziness, and oscillopsia, next to other inner ear problems like hearing loss and tinnitus. The high rate of imbalance and oscillopsia comply with the recent diagnostic criteria for BV (3). However, additional symptoms were rarely mentioned.

Hearing loss and tinnitus most likely shared the same etiology as BV or resulted from aging, rather than from vestibular dysfunction. A typical example for this is aminoglycoside toxicity is a well-known cause of sensorineural hearing loss and vestibular dysfunction (2, 97, 100). In addition, the average patient with BV in the literature was 60–62 years old and the prevalence of hearing loss in the United States is 25.1 and 42.7% for the age groups 55–64 and 65–84, respectively (101). The same conclusion could be drawn for recurrent vertigo. Vertigo is most likely an expression of the shared etiology, but is not the result of BV since an absent or reduced vestibular function is most likely not the cause of attacks of vertigo (2, 4).

Only 15 clinical studies and 10 case reports reported additional symptoms. The existence of these symptoms is supported by other literature that suggested that patients with BV could also suffer from cognitive deficits (7, 8), autonomic (102–104) and psychological symptoms (6, 105, 106), tiredness (6), visually induced dizziness (7, 107, 108), and impaired quality of life (6, 90, 106). Unfortunately, these symptoms could not reliably be quantified since they were not often mentioned in clinical studies and case reports. At this moment, it is uncertain why these symptoms were reported so infrequently. It could be hypothesized that these symptoms did have a low occurrence, that they were not part of routine history taking, or that patients were not aware of the link between their vestibular deficit and these types of symptoms (4). Therefore, structured patient interviews with open-ended questions should be conducted in which patients with BV are specifically asked to describe all of their symptoms and thereby evaluate in which words they describe their own symptoms, to determine the nature and frequency of all symptoms related to BV. This is necessary to develop PROM for BV (10).

At this moment, vestibular specific PROM exist like the DHI (109) and the vestibular disorders activities of daily living scale (VADL) (110). The DHI evaluates different aspects of vestibular complaints (function, physical, and emotional) and the VADL assesses the independency in activities of daily living. However, both questionnaires only focus on balance and do not assess the classic BV symptoms like oscillopsia, recurrent vertigo, hearing loss, and tinnitus. Therefore, there is also a need for PROM for BV specifically.

Several limitations of this systematic review were identified. Almost all articles gathered data differently and many of them were of retrospective nature. It was uncertain whether all publications used an open interview and whether all symptoms were explicitly mentioned or not. In addition, it was not possible to determine whether symptoms were mentioned but denied, or not even mentioned at all. Moreover, patients can describe the same complaint (e.g., dizziness and vertigo) differently. As a result, the same complaints could be categorized into different universal symptoms (4, 111). In addition, different articles used various diagnostic criteria for BV, resulting in a heterogeneous patient population, which made direct comparison of the patient population between articles difficult. Furthermore, it is known that BV is often misdiagnosed and missed (4, 90). This implies that even the percentages mentioned in literature do not reflect the real prevalence of the symptoms. Finally, only three clinical studies and one case report measured quality of life (e.g., DHI and HADS), therefore, outcomes could not be pooled for analysis (27, 30, 41, 42).

In this review, clinical studies and case reports provided complimentary information. Clinical studies were better in quantifying the established symptoms and case reports were better in giving an overview of the array of symptoms.

TABLE 3 | Additional symptoms in bilateral vestibulopathy reported in articles.

	Additional symptoms
Clinical studies	– Prevented from doing things they could otherwise do (90) – Change or limited social activities (90) – Missed days from work or school (90) – Depression (90) – Tiredness (5) – Concentration difficulties (5) – Memory impairment (5) – Disorientation in space (5) – Muscular pain (5) – Ashamed (5) – Needing walking aid (16, 27) – Falling (5, 19, 27, 43, 54, 75, 76, 81–83) – Sleep efficiency was reduced (63) – Headache (32)
Case reports	– Unable to work (30) – Headaches (62, 68, 70) – Occasional sleep disturbances (62) – Difficulties with functional tasks in daily living (62) – Needing walking aid (68) – Anosmia (18) – Ageusia (18) – Dysarthria (18) – Tired (89, 91) – Unable to perform daily chores (28) – Appeared depressed (28, 67, 91) – Hitting walls (28) – Falling (28, 91) – Fear of falling (94) – Avoided crowded places and the use of public transport (94) – Hypersensitive to changes in environment (94) – Dizzy when exposed to lights other than natural white light (94) – Dizziness worsened in a crowded place such as a shopping mall or after working several hours on a computer (94) – Difficulty driving over rough surfaces (91) – More anxious (91) – Feelings of disorientation (91)

In the future, a qualitative research model would be of added value. This would allow getting a clear overview of all symptoms patients with BV experience, including additional symptoms.

CONCLUSION

Current literature on BV symptomatology mainly focuses on classic symptoms such as imbalance and oscillopsia, while only a few report additional symptoms such as cognitive memory impairment and dual tasking. In fact, none of the reviewed clinical studies and case reports provided a comprehensive overview of BV symptoms. To develop validated PROM, a qualitative research using semi-structured and unstructured interviews is needed to explore the full spectrum of BV symptoms.

AUTHOR CONTRIBUTIONS

All authors contributed extensively to the work presented in this paper. FL and SD conducted the analysis and wrote the manuscript. RB supervised the writing and edited the manuscript. HK supervised the writing and reviewed the manuscript. VR, AF, NG, and JP reviewed the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fneur.2018.00352/full#supplementary-material.

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REVIEW
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Bilateral Vestibular Weakness

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Bilateral vestibular weakness (BVW) is a rare cause of imbalance. Patients with BVW complain of oscillopsia. In approximately half of the patients with BVW, the cause remains undetermined; in the remainder, the most common etiology by far is gentamicin ototoxicity, followed by much rarer entities such as autoimmune inner ear disease, meningitis, bilateral Ménière's disease, bilateral vestibular neuritis, and bilateral vestibular schwannomas. While a number of bedside tests may raise the suspicion of BVW, the diagnosis should be confirmed by rotatory chair testing. Treatment of BVW is largely supportive. Medications with the unintended effect of vestibular suppression should be avoided.

Keywords: bilateral vestibular weakness, oscillopsia, ototoxicity, vestibulo-ocular reflex, rotatory chair testing, vestibular testing

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INTRODUCTION

Reduced or absent vestibular function on both sides, resulting from deficits in the labyrinths, or vestibular nerves, or their combination, is referred to in the recent consensus statement from the Bárány Society (1) as "bilateral vestibulopathy." Although much of the literature designates this phenomenon "bilateral vestibular *loss*," that phrase is inappropriate when the deficit is partial rather than complete. In this review, we prefer the more neutral designation *bilateral vestibular weakness* (BVW).

We discussed this topic in 2013 (2), but a considerable number of publications since that time warrant inspection in the context of a broader review. Here, we discuss additional etiologies of BVW, we reassess the category of "idiopathic" cases, and we review the relevance of emerging diagnostic technologies for this disease.

Bilateral vestibular weakness can involve different combinations of labyrinthine components. For example, gentamicin ototoxicity affects the entire labyrinth (with variable degrees of severity), whereas bilateral sequential vestibular neuritis tends to involve the superior divisions of the vestibular nerves (see discussion below).

In this review, we will use terms such as mild, moderate, and severe BVW, recognizing that there are currently no generally accepted quantitative criteria associated with these designations.

CLINICAL FEATURES AND SYMPTOMS OF BVW

Oscillopsia

Bilateral vestibular weakness almost invariably produces the symptom of oscillopsia—the illusion that the environment moves when the head does. Oscillopsia is due to malfunction of the vestibulo-ocular reflex (VOR), is nearly always due to a peripheral vestibular deficit, and is only rarely due to a central (e.g., brainstem) vestibular deficit. Oscillopsia can occur even with small, "natural" head movements, such as when walking. During ambulation there is rhythmic, modest flexion-extension of the neck in the sagittal plane with each step; in a healthy person the VOR ensures that such head movement is exactly offset by equal but opposite movement of the eyes, such that the seen world appears stationary to the individual. In BVW, the VOR fails to drive this compensatory eye movement

adequately, so the individual will perceive the seen world as swaying or bouncing with each step. Similar disturbances occur with abrupt passive movements, such as when riding in an automobile on a bumpy road (3). The heavily "visual" nature of the symptom of oscillopsia often misleads patients into thinking that their imbalance arises from a primary ophthalmological disorder.

Imbalance

Patients with BVW almost always complain of imbalance. This symptom is sensitive, though not specific for BVW. In order to determine one's position, orientation in and movement through space, the brain draws on three main sensory modalities (visual, proprioceptive, and vestibular input) and on internally generated estimates (derived from differences between those sensory inputs and motor efference copies). In a patient with BVW, the brain will try to compensate for the reduced vestibular input by relying more heavily on the unaffected sensory modalities (visual and proprioceptive) and on internal estimates. If the previously unaffected sensory inputs are impaired, then the symptom of imbalance will worsen. For example, if vision is impaired abruptly (such as by trying to walk in a poorly illuminated area) or gradually (such as from cataracts or macular degeneration), or if proprioception is challenged abruptly (such as when walking on a soft or uneven surface) or deteriorates gradually (such as with diabetic peripheral neuropathy), then the balance in a patient with BVW will suffer.

Auditory Symptoms

Auditory symptoms such as hearing loss and tinnitus are not common features of BVW. One plausible reason for this is that the common cause of BVW, gentamicin ototoxicity, is predominantly vestibulotoxic rather than cochleotoxic. Even in cases of BVW of undetermined etiology, auditory symptoms are uncommon. Of the uncommon causes of BVW, etiologies that damage the entire inner ear (such as meningitis or congenital labyrinthine hypoplasia) cause both vestibular and auditory symptoms.

Epidemiology

The prevalence of BVW is low. A rough estimate of prevalence was provided by Ward et al. (4), who surveyed more than 21,000 adults for symptoms of oscillopsia and ataxia, lasting at least 1 year, with symptoms being "a big problem." They estimated that the prevalence of BVW is 28/100,000. While a valuable step forward, this estimate obviously has a rather wide error margin, as there were no vestibular measurements made.

Another method of estimating prevalence is determining its relative frequency of diagnosis. Of cases accrued in our clinical practice over 20 years, 213 patients (out of a total of approximately 25,000) were diagnosed with BVW, amounting to approximately 0.7%. So, whether one considers prevalence in the population, or frequency of presentation in a "dizzy" clinic, BVW is rare.

Etiologies

The etiologies of BVW are usually listed as including ototoxicity, autoimmune inner ear disease (AIED), bilateral versions of what are more commonly unilateral diseases (e.g., vestibular neuritis, Ménière's disease, and tumors), with the remainder designated "undetermined" or "idiopathic" (5). One series of 53 cases (6) reported that 39% were associated with neurological disorders (13% cerebellar degeneration, 11% meningitis, and 9% had an association with cranial or peripheral neuropathies), 21% were "idiopathic," 17% were due to gentamicin ototoxicity, 10% were due to autoimmune disease, 8% were attributed to bilateral occurrence of what would usually be unilateral disease (e.g., temporal bone fracture, Ménière's disease), and 6% were associated with tumors.

Other case series of BVW patients (6–8) reported "idiopathic" or "unknown" to be the largest single subcategory, aminoglycoside ototoxicity the second most common, and infections (such as vestibular neuritis or meningitis) the third most common.

Familial BVW, with or without hearing loss, is rare and has been reviewed elsewhere (9). Another possibly genetic syndrome is cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS), in which the "vestibular areflexia" refers to bilateral vestibular weakness (10); this is exceedingly rare.

The causation of BVW is usually estimated from clinical data. The distribution of BVW cases accrued in our practice in Chicago, IL, is displayed in **Figure 1**. Of 213 patients with bilateral weakness diagnosed on rotatory chair testing (RCT) (which, as we shall discuss below, is regarded as the gold standard for assessing BVW), the most common etiologies, in order of descending frequency, were "idiopathic" (50.7%), followed by gentamicin ototoxicity (27.7%), bilateral vestibular neuritis (8.9%), tobramycin ototoxicity (4.7%), head injury (3.8%), autoimmune (3.3%), Ménière's disease (1.9%), streptomycin ototoxicity (1.4%), and congenital (0.9%).

Age

The median age in our series of patients with BVW was 56 years. While this may be due in part to the age distribution of the general population in Chicago, it more likely reflects that BVW tends to be a disease of older age. As one grows older, there is simply more opportunity to suffer ear damage, such as from vestibular neuritis or ototoxicity.

The prevalence of balance problems increases with age (11–13). Histopathological studies of the temporal bones of otherwise healthy individuals demonstrate a steady decline of vestibular

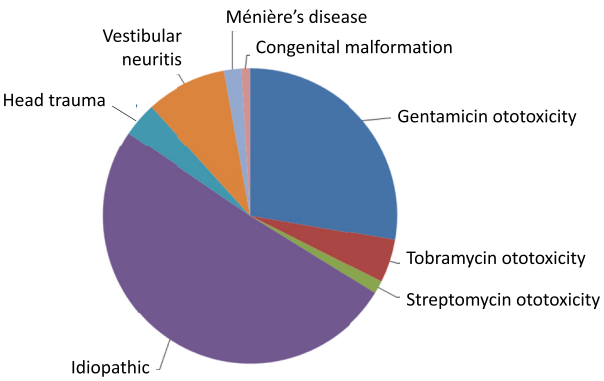

FIGURE 1 | Distribution of etiologies of bilateral vestibular weakness at Chicago Dizziness and Hearing, $n = 213$.

hair cells over time (14). Studies of the vestibular nerve show that by the age of 80, the number of fibers in the vestibular nerve declines by about 30–50% (15–17). Despite this loss, the evidence for age-related loss of semicircular canal function is not compelling; for instance, a 30–50% deficit in semicircular canal function in otherwise healthy individuals does not appear to increase the risk of falls significantly (18).

In contrast, there is far stronger evidence for age-related loss of otolith function than loss of semicircular canal function, as clinical tests of otolith function such as vestibular-evoked myogenic potentials (VEMPs) are generally greatly diminished with age (19). Thus, at this writing, it seems likely that while imbalance may be fairly strongly correlated with age and VEMP amplitude, it is only weakly attributable to loss of the canal mediated VOR. When attrition of labyrinthine function is combined with decline of other sensory inputs (such as visual or proprioceptive loss), vestibular symptoms are magnified.

OTOTOXIC CAUSES OF BVW

Aminoglycoside Antibiotics

After idiopathic sources are excluded, the aminoglycoside antibiotics, gentamicin, and tobramycin, are the single most common source of severe BVW.

All aminoglycoside antibiotics are potentially ototoxic, though some (such as gentamicin and streptomycin) are predominantly vestibulotoxic (20), while others (e.g., neomycin) are preferentially cochleotoxic.

Of the vestibulotoxic agents, gentamicin is the most frequently encountered in vestibular clinics. Tobramycin (which is both vestibulotoxic and cochleotoxic) is the second most common because of its use in the treatment of cystic fibrosis; its risk of ototoxicity is relatively higher when administered intravenously (21–27), and is very low when inhaled (28–31). Streptomycin is rarely used anymore in the United States, and consequently it is seldom the cause of BVW.

The high prevalence of gentamicin ototoxicity is due to several features of its pharmacology. First, gentamicin does not produce auditory "warning signs" (hearing loss or tinnitus) that would alert a patient or treating physician to impending toxicity. Second, even though most aminoglycosides (including gentamicin) are renally excreted within hours, gentamicin accumulates over months in the inner ear (32), and it is this accumulation that accounts for the drug's ototoxic effects even in patients whose serum concentration has remained within normal limits over the course of treatment. Third, gentamicin is both ototoxic and nephrotoxic; as renal function declines and gentamicin excretion decreases, the drug level (and its ototoxic and nephrotoxic effects) escalates, resulting in a positive feedback loop of toxicity. Fourth, gentamicin's ototoxicity is potentiated by vancomycin (33), which is commonly administered simultaneously.

In some individuals, particular susceptibility to gentamicin ototoxicity appears to be due to genetic factors (NOS3, GSTZ1, and GSTP1) (34). Finally, gentamicin is inexpensive and readily available, which may promote its use.

Aminoglycoside ototoxicity usually occurs in the context of intravenous or (less commonly) intraperitoneal administration. However, if aminoglycoside-containing agents are instilled directly into the middle ear (such as through a tympanic membrane perforation), they can diffuse through the round window membrane to the inner ear and cause damage. For this reason, when considering direct aural administration of aminoglycoside-containing agents such as Cortisporin Otic® (which contains neomycin), or gentamicin ophthalmic solution (used off-label), one should ensure that no tympanic membrane perforation is present (35–37).

Chemotherapeutic Agents

Several chemotherapeutic agents have cochleotoxic potential. Only cisplatin is clearly vestibulotoxic (38), yet this is rarely seen, probably because the drug's other toxicities limit its use before vestibulotoxicity becomes manifest.

Other Medications

There are scattered reports of various medications appearing to cause BVW, though isolated case reports comprise weak evidence. The evidence for some of these appears stronger, such as a series describing 15 out of 126 patients (12%) with what otherwise appeared to be "idiopathic" BVW who had been treated with amiodarone (39).

NON-OTOTOXIC CAUSES OF BVW

Autoimmune Inner Ear Disease

Autoimmune inner ear disease and its subtypes are rare causes of BVW. AIED tends to affect both auditory and vestibular function. This condition generally presents with bilateral sensorineural hearing loss that progresses over weeks to months, and the diagnosis is confirmed when this hearing loss improves significantly (or resolves) after a brief course of high-dose steroids (40, 41). Diagnosis of AIED by antibody-based assays (e.g., HSP-70) has proven unreliable (42). Although a steroid burst can improve the hearing loss in AIED, the high doses that are required generally preclude their long-term use. Long-term pharmacologic management can be attempted with TNF-alpha blockers [e.g., etanercept (43, 44), adalimumab (45), or possibly rituximab (45, 46)]. If that fails, then cochlear implantation can be considered—though obviously this does not address BVW, if present. Approximately half of cases of AIED also involve vestibular symptoms (47). There are case reports of AIED presenting exclusively with vestibular symptoms and no hearing loss (48), but it is unclear how one could be confident in the diagnosis if there is no opportunity to assess for steroid-responsive hearing loss.

There are a few other inner ear conditions that appear to be immunologically mediated. First, patients who have undergone inner ear surgery on one side may develop auditory and vestibular symptoms in the opposite (un-operated) ear; this condition is thought to be a "sympathetic autoimmune reaction," analogous to the ocular involvement of Vogt–Koyanagi–Harada syndrome of the eye (49). Second, Cogan syndrome (50) is similar to AIED but additionally has ocular symptoms; in some respects it resembles post-meningitic hearing loss (see below), as the labyrinth may be occluded with fibrous tissue.

Meningitis

Meningitis can damage the entire labyrinth (51), but tends to affect cochlear function more than vestibular function (52). The meningitic inflammation likely reaches the ear through the vestibular and cochlear aqueducts (53); these passages are more patent during childhood, which may be the reason that children are more likely than adults to develop hearing loss following meningitis (54). In many cases of meningitis, the hearing loss and vestibular deficits manifest immediately, while in other cases the vestibular weakness may develop more gradually; such delay is often attributed to the slow development of fibrosis or ossification of the inner ear, which can sometimes be visualized on high-resolution MRI. In **Figure 2** is displayed a brain MRI in a patient with meningitis, showing enhancement in both internal auditory canals.

Bilateral Vestibular Neuritis

Vestibular neuritis can affect any combination of afferent fibers (55), and thus can involve the superior or inferior divisions, or both. Perhaps due to anatomical factors (56, 57), vestibular neuritis more commonly involves only the superior division of the vesbitular nerve (55, 58), less commonly involves both the superior and inferior divisions (55), and uncommonly affects only the inferior division (59–61). Given this pattern, it is unsurprising that when vestibular neuritis is bilateral, it tends to involve the superior division on both sides (62, 63). It is possible, though uncommon, for bilateral sequential vestibular neuritis to involve the superior division on one side and the inferior division on the other (64). Rare cases of bilateral inferior division deficits [identified on cervical VEMPs (cVEMPs)] have been reported (65), but it is unclear whether these are due to bilateral vestibular neuritis. The tendency of vestibular neuritis to involve the superior division of the vestibular nerve can have diagnostic value in bilateral cases; for instance, if a patient has evidence of bilateral superior division weakness [on caloric testing, RCT, or video head impulse testing (vHIT)] but preserved inferior division function (with intact cVEMPs), then this pattern is more likely to be due to bilateral vestibular neuritis (rather than due to processes that involve the entire labyrinth or the entire vestibular nerve). Loss of caloric function, by itself, is insufficiently specific as caloric testing assesses the horizontal canal alone.

Bilateral Vestibular Schwannomas

Neurofibromatosis type 2 can manifest with bilateral vestibular schwannomas (66) resulting in BVW. This is exceedingly rare.

Bilateral Ménière's Disease

The most notable features in the typical clinical history of Ménière's disease are the dramatic episodes of vertigo and accompanying auditory symptoms, but the overall trajectory—typically over years to decades (67)—is one of gradually progressive sensorineural hearing loss. However, it is rare for the disease to progress to profound deafness. It is similarly rare

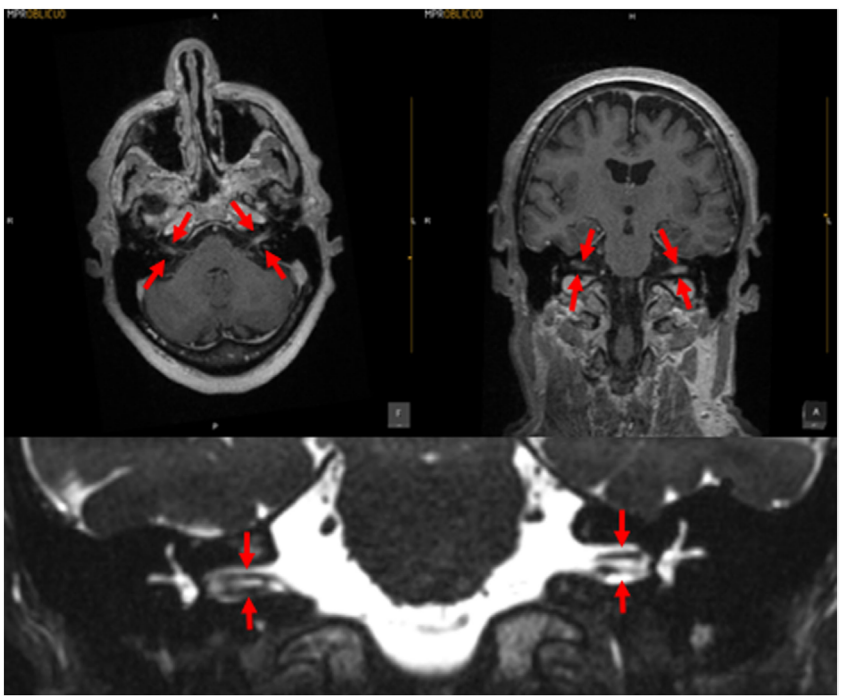

FIGURE 2 | MRI of a patient with meningitis. The upper left panel is a post-contrast T1 axial image; the upper right panel is a post-contrast coronal image; the arrows indicate enhancement of the vestibulo-cochlear nerves. The lower panel displays a coronal CISS sequence image; the structures indicated by the arrows demonstrate that the vestibulocochlear nerves are of relatively normal caliber, with no evidence of vestibular schwannoma. Images courtesy of Dr. Manuel Perez Akly.

to develop the vestibular analog—severe vestibular weakness. In cases of bilateral Ménière's disease (68), hearing usually remains in the aidable range, and patients generally do not develop severe BVW.

Neurosyphilis

When neurosyphilis involves the ear, the usual presentation is hearing loss. Vestibular manifestations are reported in 42% (69) to 52% (70) of cases. Some series report that 80% of patients with vestibular symptoms have electronystagmographic abnormalities (71), and some of these are BVW (70, 72). The widespread use of antibiotics has dramatically reduced the prevalence of neurosyphilis, so testing for this is low yield. Nevertheless, some clinicians advocate checking for this routinely, as it is one of the few potentially treatable causes of BVW.

Superficial Siderosis

There are scattered case reports of superficial siderosis resulting in BVW (73, 74). It is usually suggested that the pathological process involves deposition of hemosiderin along the glial segment of the vestibulocochlear nerve (75–77) rather than direct damage of the labyrinth. Superficial siderosis can damage auditory function, vestibular function, or both. In our clinical practice, we encountered a patient with total deafness due to superficial siderosis who had preserved vestibular function. We have also encountered a patient (MRI displayed in **Figure 3**) with both hearing loss and BVW.

Vascular Causes

Bilateral vestibular weakness seldom results from focal circulatory disturbances. Vascular supply to the inner ear is *via* the labyrinthine artery (generally a branch of the anterior inferior cerebellar artery). Unilateral labyrinthine infarction is very rare (78); in order for bilateral labyrinthine infarction to occur, both labyrinthine arteries or AICAs would need to be compromised, which is a statistically extremely unlikely event. If BVW arises from a circulatory disturbance, the etiology is more likely to be a more diffuse vasculopathic/vasculitis process; for instance, we have encountered BVW in one patient with granulomatosis with polyangiitis (Wegener's granulomatosis); there are also several published cases of what appears to be BVW (based on RCT) in patients with Behçet's disease (79).

Neurosarcoidosis

Sarcoidosis has no particular propensity for the vestibular nerve or labyrinth. It is a very rare cause of unilateral ear damage (80), and thus a very implausible etiology of BVW.

Congenital Malformations

Malformations of the vestibular end organs occur in a number of congenital disorders (81), though very few such disorders have been sufficiently studied to ascertain whether they truly involve BVW. Aplasia of the semicircular canals (82) occurs in a few rare conditions such as coloboma of the eye, congenital heart defects, choanal atresia, mental and/or growth retardation, genital hypoplasia, ear anomalies and/or deafness and Mondini malformations. Imaging in these cases may demonstrate partial or total absence of the labyrinth; these patients have congenital deafness (83). **Figure 4** shows labyrinthine hypoplasia in a patient with BVW.

Head Trauma

If head injuries damage the inner ear, they generally do so *via* a labyrinthine concussion or a traction injury of the vestibulocochlear nerves (84). Typically, an injury sufficient to cause such damage will result in both vestibular and auditory deficits. The temporal bone is the hardest bone in the body; any impact that damages the labyrinth or vestibulocochlear nerve *via* a temporal bone fracture (85) will almost invariably result in brain injury as well.

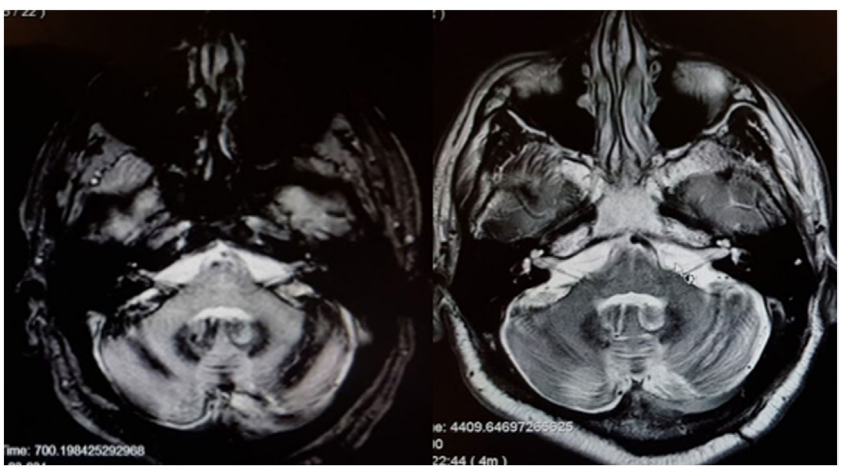

FIGURE 3 | MRI of a patient with siderosis showing hemosiderin deposition along the vestibulocochlear nerves. The image on the left is an axial gradient-echo (GRE) T2*-weighted sequence. The image on the right is an axial T2-weighted image. Both figures are through the internal auditory canals. The study was performed on a 1.5-Tesla strength MR.

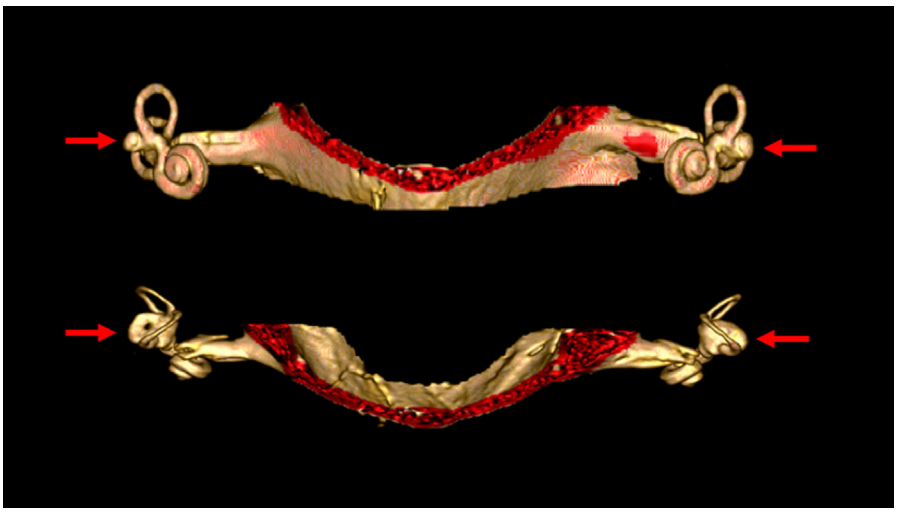

FIGURE 4 | High resolution three-dimensional reconstruction MRI of the internal auditory canals and inner ear structures of a patient with bilateral vestibular weakness from bilateral labyrinthine dysplasia. The top image is in the coronal aspect. The bottom image is in the axial aspect. In these images it is evident that the horizontal canals are dysplastic, with the horizontal canal and vestibule appearing as a single abnormal structure on each side (indicated by the arrows). The superior and inferior canals are present as true canals, but are somewhat hypoplastic.

ASSOCIATIONS OF OTHER CONDITIONS WITH BVW

Migraine

Several case series (86, 87) report an association between migraine and BVW. However, since migraine is so extraordinarily common, it is difficult to ascertain whether this combination truly represents a distinct subtype of migraine (88), or whether it is merely chance overlap of two independently occurring conditions.

Cerebellar Degeneration

The combination of cerebellar degeneration and BVW has been reported in several case series (6, 10, 89–91). Since both conditions can manifest with ataxia, a clinical examination can easily "catch" the cerebellar dysfunction but miss the BVW. The association of these two conditions with a third, peripheral neuropathy, has been designated CANVAS (10, 89, 90), as mentioned earlier. In our clinic, these patients comprise less than 2% of cases of BVW, and given their additional deficits (ataxia, peripheral neuropathy), their prognosis is poorer than those with BVW alone.

Idiopathic

Although we have discussed the literature as it pertains to known causation of BVW, as we previously mentioned, most clinical series find "idiopathic" to be the most common "diagnosis." In **Figure 1** showing 213 patients found in our clinic setting, half were idiopathic.

It seems possible that at least some of these patients are actually individuals with bilateral vestibular neuritis, as vestibular neuritis is a relatively common inner ear condition, and the bilateral variant of it is well established (62, 63). Nevertheless, this would imply that the prevalence of vestibular neuritis is much higher than generally accepted. One can deduce this by using Ward's prevalence figure of 28/100,000 (4) for BVW, and assuming all of the idiopathic cases are from bilateral vestibular neuritis, or 14/100,000, then the square root of this figure should be the prevalence of vestibular neuritis. This would imply a prevalence of about 1% for unilateral vestibular neuritis, which is much higher than the generally accepted figure.

DIAGNOSIS OF BVW: CLINICAL EXAMINATION

Dynamic visual acuity (DVA) testing, sometimes also called dynamic illegible E testing (92, 93), can be helpful bedside examinations when considering a diagnosis of BVW. This test is performed by comparing visual acuity while the patient's head is stationary, to that when the head is oscillated from side to side. Different methods have been described, but typically the passive sinusoidal rotation of the head is performed over an arc of 15–30° to each side, with a frequency of 1–2 Hz. Visual acuity in the stationary and oscillating conditions is assessed by having the patient read the smallest letters he or she can on an eye chart whose lines are arranged by descending LogMARs (logarithmic change in the minimum angle of resolution)—different from the organization of a Snellen chart. An example of a LogMAR-based eye chart is available on our website (94). Some authors suggest that a loss of more than two lines (0.2 LogMARs) should be interpreted as supporting a diagnosis of BVW, though in our experience some normal individuals can perform in this way. The requirement of a loss of four lines (0.4 LogMARs) is more specific. In patients with BVW from gentamicin ototoxicity, their performance on the DVA rarely improves to a difference less than 0.4 LogMARs.

The bedside HIT was originally recognized as a method for detecting unilateral vestibular weakness (95), but can also serve

for detecting bilateral weakness. The underlying concept is similar to DVA, but the technique differs. Whereas the DVA depends on the patient's report of what line on the LogMAR chart he or she is able to read, the bedside HIT instead depends on the examiner's ability to observe a catch-up saccade following a high acceleration, low-amplitude rotation of the patient's head while the patient is attempting to maintain his or her gaze fixed on a target; these compensatory saccades occurring after the head movement is completed are called "overt saccades." The sensitivity and specificity of the bedside HIT depends on patient cooperation, as well as on the examiner's skill (both in executing the maneuver and observing the compensatory saccades). Patients with cervical pain or limited cervical range of motion may not tolerate this test well. An additional problem is that as patients improve they may learn to produce the compensatory saccades during (rather than after) the head rotation; these are called "covert" saccades and are more difficult for the examiner to observe (96)—in other words, the sensitivity of this test may diminish over time. The problem of identifying covert saccades can be addressed by a computerized version of the HIT called vHIT (discussed below).

Ophthalmoscope Test

The principle underlying this test is similar to DVA, but the technique is different. Whereas the DVA depends on the patient's report of what line on the LogMAR chart he or she is able to read, the ophthalmoscope test instead depends on the examiner's ability to observe (with an ophthalmoscope) the patient's retina during passive oscillation of the patient's head. Keeping the retina in view during movement of the patient's head can be challenging, so the amplitude of oscillation should be 10–20°, and the frequency of oscillation should be approximately 1 Hz (97). During the passive oscillation of the head in a healthy person, the retina should appear (to the examiner) to remain still. In contrast, a BVW patient's retina will appear to oscillate in synchrony with the head oscillation, because the vestibular system is unable to generate compensatory eye movements to offset the head movements. The ophthalmoscope test should be performed while the patient is wearing any corrective lenses that they usually wear for distance viewing. Similar to the bedside HIT, a patient's performance on the ophthalmoscope test can improve over time (98). The ophthalmoscope test is highly specific, but it is not sensitive (99).

General Comments About Bedside Testing for BVW

Dynamic visual acuity testing, bedside HIT, and the ophthalmoscope test are performed when vision is available, and with high acceleration, and are therefore termed "light, high-frequency tests." However, BVW is more evident when visual fixation is unavailable, and when the head acceleration is smaller (i.e., in "dark, low-frequency" conditions), so the DVA, bedside HIT, and ophthalmoscope test are not nearly as sensitive as RCT (discussed below). If a there is a high index of suspicion for BVW but the DVA, bedside HIT and ophthalmoscope test are normal, then one should proceed to RCT.

BVW: VESTIBULAR LABORATORY TESTING

Rotatory Chair

Rotatory chair testing is still regarded as the gold standard test for BVW (100, 101). This is due to the fact that it measures responses ranging from high to low frequencies (i.e., high to low acceleration), unlike the situation with the caloric test (see below) that assesses only the very low frequencies, and the vHIT test (see below) that assesses only the high frequencies. The responses to the range of stimulus frequencies are plotted during part of the RCT termed slow harmonic acceleration. The deficits in BVW are most evident in the lower frequencies, where one observes low gain and phase lead (if phase can be measured at all), as shown in **Figure 5**. The equipment required for performing RCT properly is expensive, so its availability is mostly limited to major academic medical centers. Consequently, there have been attempts to develop less expensive devices, such as the VORTEQ® ("VOR test equipment") (102, 103), but these apparatuses actually only provide "light, high-frequency" assessments and are thus no more sensitive than the bedside tests (DVA, HIT, and ophthalmoscope

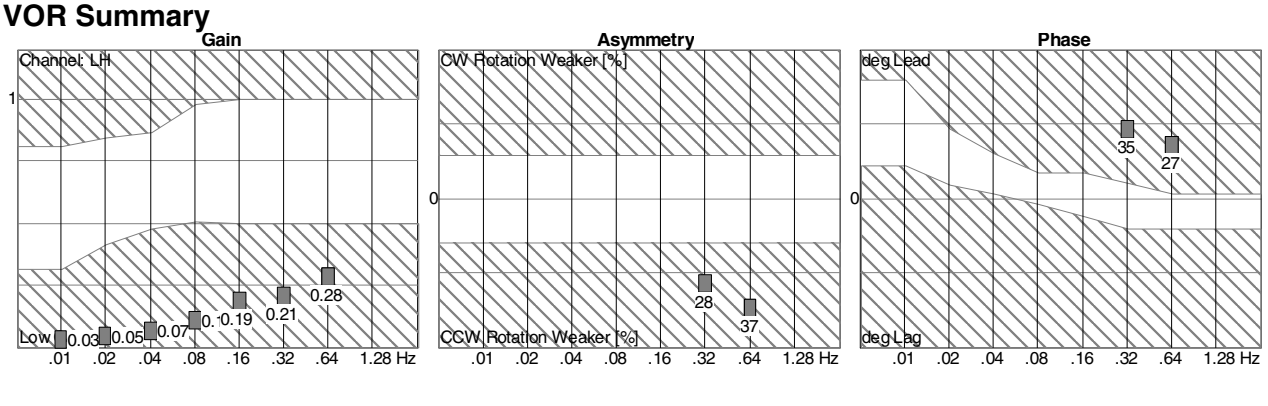

FIGURE 5 | Slow harmonic acceleration from rotatory chair testing. The panel on the left is a plot of the gain, which is low at all frequencies. The panel on the right is a plot of the phase, which could not be calculated at 0.01–0.16 Hz, and showed phase lead at 0.32–0.64 Hz.

test) described above, so they cannot truly substitute for RCT. It should also be noted that tests (such as the VORTEQ®) in which the patient actively rotates his or her head (rather than having it passively oscillated by the examiner) reduce the sensitivity of the test, because active performance of head-on-neck movements also enables "pre-programming" of ocular movements that has been shown to augment the VOR (104).

Videonystagmography

The caloric portion of videonystagmography (VNG) is sensitive to bilateral vestibular weakness. The thermal stimulus delivered by warm and cool water caloric testing is generally cited as equivalent to an oscillation frequency of 0.003 Hz (101, 105–107), thus it is a "low frequency test," hence its sensitivity for bilateral vestibular loss (108). The total caloric response is the sum of two cool calorics (one in each ear) and two warm calorics (one in each ear). The average total caloric response in healthy individuals is usually cited as 100°/s (109). The threshold beneath which BVW can be diagnosed is debated; Zapala et al. (109) state that, "Fewer than one in 100 otherwise normal subjects demonstrates a T(otal) E(ye) S(peed) of less than 27°/s"; the Bárány Society Consensus document on BVW (1) states that, "the lower limit of the normative data… varies among laboratories from 20 to 25°/s," yet lists the diagnostic criterion (for VNG) as "reduced caloric response [sum of bithermal max(imum) peak S(low) P(hase) V(elocity) on each side <6°/s]," implying that a total caloric response <12°/s is diagnostic. Even if one uses a very stringent criterion [such as ≤10°/s as the cutoff studied by Furman and Kamerer (100)], some individuals identified on caloric testing as having BVW nevertheless have normal responses on RCT (100, 110), showing that caloric testing can render falsely positive results. False positives may be a consequence of a number of factors, including the presence of cerumen, narrow ear canals, or the use of weak stimuli such as balloon irrigation or air caloric stimulation (111). Conversely, caloric testing can miss moderate BVW, and can thus also render falsely negative results. False negatives are probably due to the fairly wide range of normal responses in healthy controls. One difficulty in interpreting the results of caloric testing is that many laboratories do not report whether caloric testing was performed with air or water stimulation; air calorics comprise a weaker thermal stimulus and pose a greater risk of false positives. In the appropriate clinical context, if caloric testing reports BVW, this should be confirmed on RCT.

Video Head Impulse Testing

The first reports of the clinical utility of the bedside version of the HIT emerged in the 1980s (95), but it was recognized that the maneuver can be difficult to execute and the observation of the elicited saccades can be difficult. Technology has been developed to address this in the form of vHIT. The early versions of this technology were custom designed and restricted to research settings (112–115), but the technology has evolved and is now more readily available and affordable. Commercially available products both monitor the movement of the head during the impulse (to ensure that head acceleration is adequate) and process the video of the elicited eye movement (to characterize the resulting compensatory saccades), making it easier to recognize corrective saccades and quantifying the gain, as shown in **Figures 6** and **7**. It appears that vHIT is superior to bedside HIT (116). There is a modest literature (73, 75, 115, 117) suggesting that vHIT can play a valuable role in the identification of BVW, but its sensitivity and specificity (compared with the gold standard of RCT) has yet to be established. Comparison of vHIT with RCT is complicated by several factors that can introduce variability into calculation of VOR gain on vHIT; the first reason is physiologic, and has to do with the fact that target viewing distance (which may not be carefully controlled) can have a significant effect on gain both in healthy individuals (118–120) and in patients with peripheral vestibular disease (121); the second reason is technological, as it has been demonstrated that different devices and different algorithms can render different results in gain (122).

Advantages of the vHIT include that it can be performed rapidly, the equipment is far less expensive than the rotatory chair device, it can assess all six semicircular canals (as shown in **Figure 7**) and the vHIT is relatively difficult to affect with use of medication or lack of patient cooperation. Nevertheless, the vHIT test is not as capable as the rotatory chair as it is not designed to detect low-frequency vestibular responses. The predominant frequency of stimulation in the vHIT is 2.5 Hz (123). In our opinion, using the vHIT as one's sole vestibular test is similar to testing the hearing at 4 kHz, and suggesting that this is a proxy for hearing at all frequencies. In our clinical practice, we view the vHIT as a convenient screening test, but still rely on RCT for confirmation of BVW.

Cervical Vestibular-Evoked Myogenic Potentials

In clinical practice, the VEMP response is most commonly measured from the sternocleidomastoid muscle and is usually designated a cVEMP. The response is believed to be mediated by the saccule and its afferents through the inferior division of the vestibular nerve (124). The presence of conductive hearing loss makes sound-conducted VEMPs non-diagnostic, so in this circumstance the stimulus must be delivered by bone vibration. All VEMPs are also known to decline significantly with age (19), so their diagnostic utility diminishes in the elderly. In a young or middle age person with no conductive hearing loss, cVEMPs can help distinguish whether BVW is due to a condition affecting the entire inner ear (such as gentamicin ototoxicity or meningitis, in which the cVEMP should be reduced or absent) or due to a condition with an incomplete lesion (such as bilateral sequential vestibular neuritis, which more commonly involves the superior division of the vestibular nerve and thus will have preserved cVEMPs).

A related evoked potential test, ocular VEMPs (oVEMPs), has been developed more recently (125, 126) and is believed to evaluate the function of the utricle and its afferents through the superior division of the vestibular nerve (127, 128), but has not yet been studied well in the population of patients with BVW. As oVEMP amplitudes decline precipitously with age, and bilateral loss tends to affect an older population, one would expect that

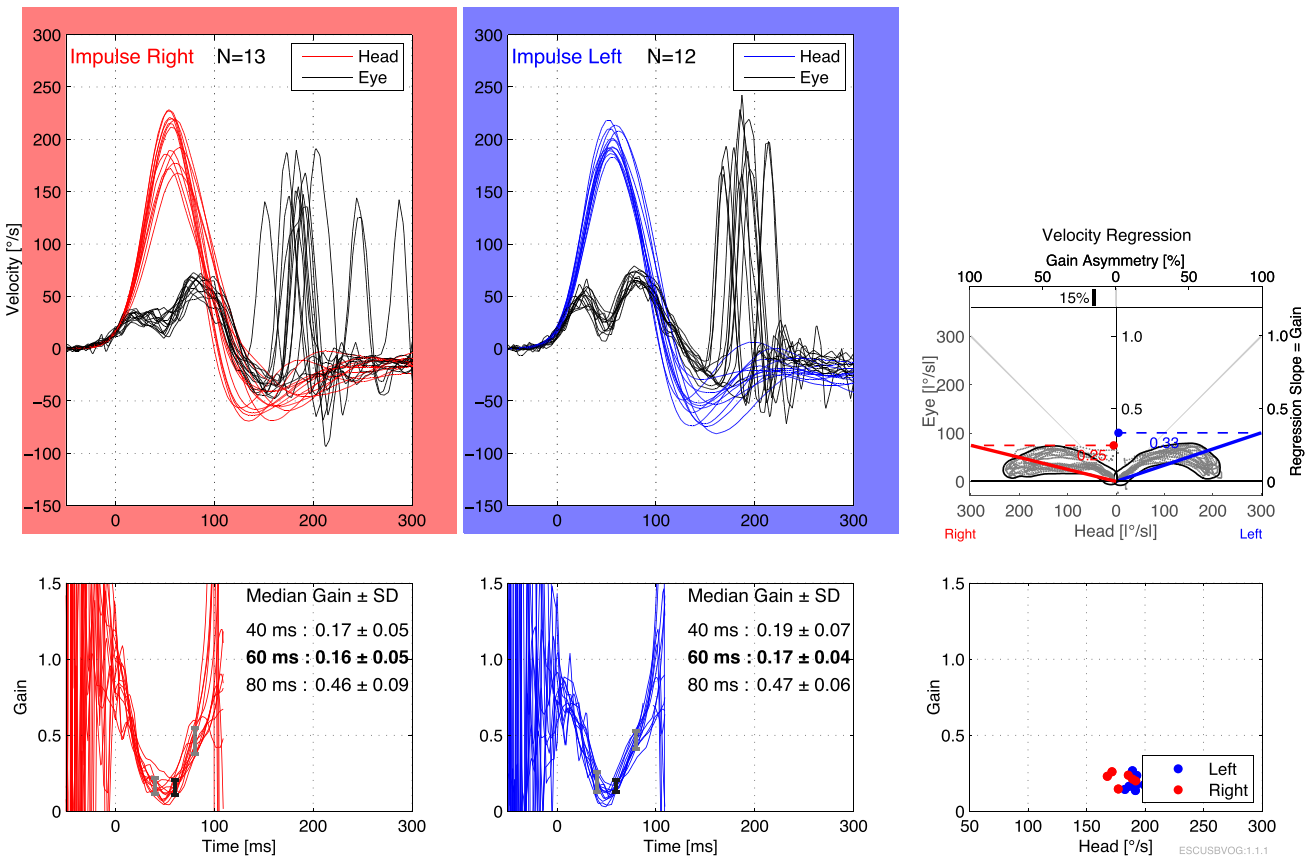

FIGURE 6 | Video head impulse testing of the horizontal canals in bilateral vestibular weakness, showing bilaterally low gain and overt saccades.

oVEMPs would be far less useful than tests that depend on semicircular canal function, as canal function is little affected by age (129).

Computerized Dynamic Posturography (CDP)

Computerized dynamic posturography, while sensitive for BVW, is not specific insofar as it fails to distinguish BVW from several important and more common neurological causes of imbalance [e.g., ataxia from cerebellar lesions (130)]. On CDP, BVW patients will generally exhibit a low-composite score, a "vestibular" pattern on sensory organization testing (SOT), and an ankle dominant sway pattern in conditions 5–6. CDP has some utility in distinguishing malingering of imbalance (131) from BVW; however, patients with severe BVW can be falsely categorized as "aphysiologic" on SOT algorithms (132), so the result should not be interpreted in isolation. These ambiguities pose difficulties in medico-legal situations, as can arise in cases of gentamicin ototoxicity.

TREATMENT FOR BVW

It is rare that the underlying cause of BVW can be directly treated, so it is important to recognize such cases (e.g., treatment of syphilis or AIED, stopping an aminoglycoside antibiotic). Vestibular hair cells do not seem to exhibit any regenerative capacity (133) in humans, so it is unlikely that any treatment will improve or reverse peripheral vestibular damage. Central compensation, likely mediated by plasticity of the commissural connections between the vestibular nuclei (134), appears to require that there be some minimum residual peripheral vestibular function (135) but even when this mechanism is available, improvement in the VOR is very limited (136–138), and cannot restore the VOR to its premorbid level. In clinical practice, the lack of substantial plasticity in the VOR is easily appreciated when one does vHIT testing in patients with longstanding gentamicin-induced bilateral loss. Even after many years, VOR gain remains extremely low.

Thus, recovery of the VOR in bilateral vestibular loss is based on substitution. Most BVW patients improve with physical therapy, though this must be appropriately targeted vestibular rehabilitation therapy (139). Such therapy attempts to teach patients compensatory strategies by relying more heavily on their intact sensoria (vision and proprioception) and improving their internal estimates of motion.

Some entrenched practice patterns in medicine can be problematic for BVW patients. Regrettably, many of these patients are "diagnosed" with "vertigo" and started on vestibular suppressants such as meclizine or a benzodiazepine, which will diminish the

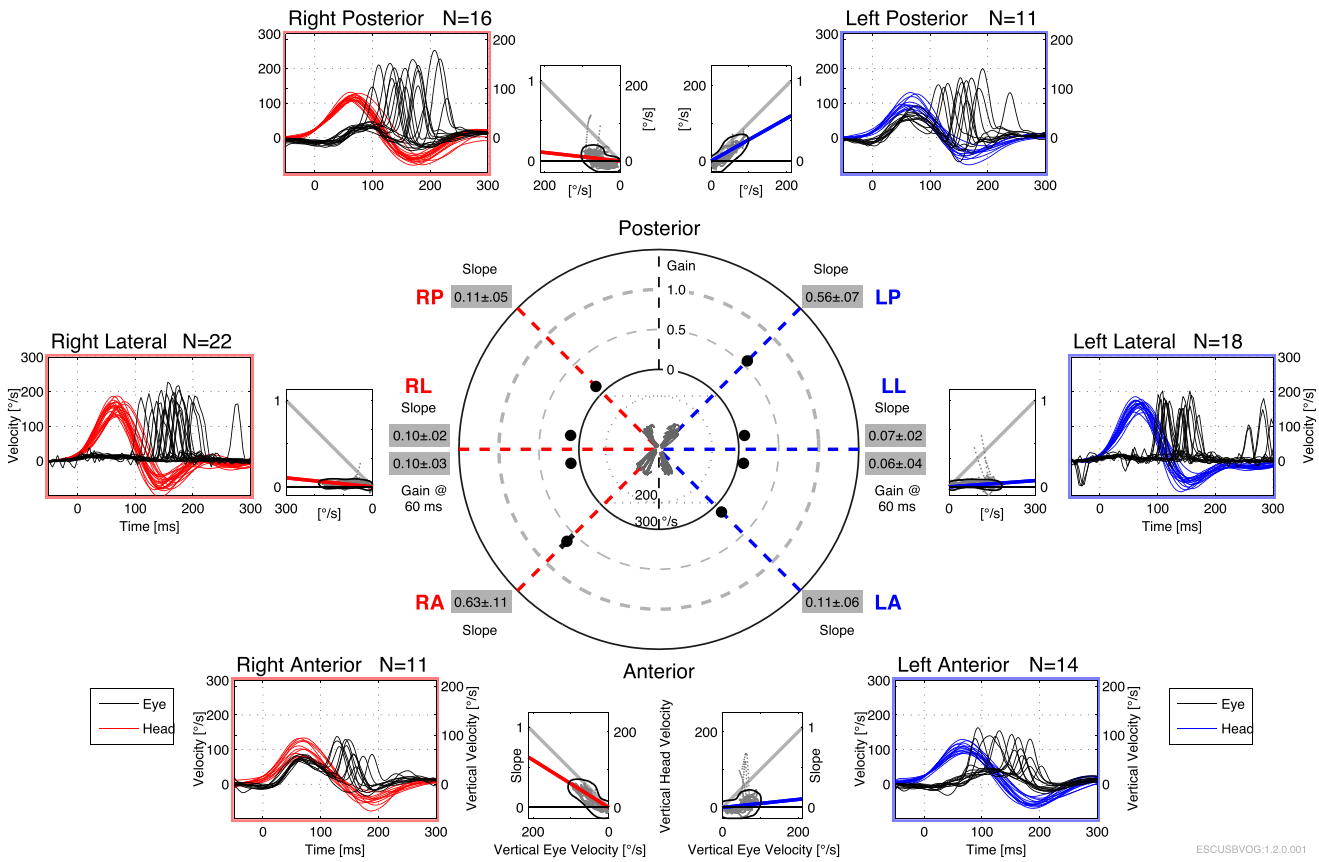

FIGURE 7 | Video head impulse testing of all six semicircular canals in bilateral vestibular weakness, showing diffusely low gain and overt saccades.

already deficient peripheral vestibular input and worsen imbalance. More insidious than this is the use of medications that have the unintended adverse effect of vestibular suppression, and care should be taken to avoid such medications. For example, when treating depression in BVW patients it would be preferable, where medically feasible, to avoid medications with anti-histaminic or anti-cholinergic effects (such as tricyclic compounds); when treating anxiety it would be preferable to avoid benzodiazepines.

Vestibular prosthetic devices (140) are being developed and tested, but remain investigational. Another approach involves technology intended to improve or restore inner ear function by coaxing human inner ear hair cells to regrow, similar to some species of birds (141, 142).

NATURAL HISTORY OF BVW

The more extensive the damage in BVW, the more pronounced the symptoms (143). After 1–2 years, patients with mild BVW may be indistinguishable from normal controls. Patients with moderate BVW will complain of persistent ataxia and oscillopsia. Patients with severe BVW complain not only of ataxia and oscillopsia, but also of limited function in their daily activities; for example, severe BVW patients generally refrain from driving. The presence of other relevant sensory deficits (e.g., visual impairment from macular degeneration, proprioceptive impairment from peripheral neuropathy) or motor deficits (e.g., paresis from stroke, mechanical limitations from orthopedic problems involving the spine or legs) interferes with the development of compensatory strategies, and such patients tend to have worse outcomes.

While most patients with BVW can improve to some extent, the degree of improvement depends on the underlying etiology (143, 144). In cases of gentamicin ototoxicity, the medication's active toxicity continues for some time even after the offending agent is stopped due to some of its pharmacologic properties (see discussion above). Nevertheless, measurable improvement in the VOR begins within about 3 months and can continue for up to approximately 2 years (145). In moderate to severe BVW cases, patients rarely return to their previous level of function; on physical examination they will continue to perform poorly on the DVA (see above). Patients with mild BVW, and even some with moderate BVW, may eventually resume driving, though may still avoid driving at night. If a patient's occupation is sedentary or at least does not rely on having good balance, they are often able to resume work.

MECHANISMS FOR IMPROVEMENT

Maximum medical improvement is usually reached after about 2 years. The main mechanisms of improvement are central compensation, peripheral recovery, and behavioral adaptation.

Central compensation refers to the idea that the brain re-prioritizes sensory input by relying more heavily (in engineering terms, "upweighting the gain") on non-vestibular input (e.g., vision, proprioception) (146). Data from animal studies suggest that the process of central compensation involves neural plasticity *via* new synapse formation in the vestibular nuclei of the brainstem (147). In humans, there is also evidence from fMRI studies that cortical reorganization occurs (148). Central compensation, defined as increasing the VOR gain, seems to limited to roughly a factor of 2 (149, 150). Considering that many bilateral patients have lost all or perhaps 90% of their VOR, a factor of 2 is woefully inadequate.

Evidence from animal studies suggests that vestibular hair cells that are merely damaged (but not dead) may have some capacity to recover function (151); it is plausible that this occurs in humans as well. Similarly, there is sometimes recovery of nerve function in vestibular nerve injuries due to vestibular neuritis; by 6 months after a vestibular nerve injury, any recovery that is going to occur is probably complete by approximately 6 months (144, 152).

Behavioral adaptations, whether instinctive or planned, play a role in adjusting to BVW. Patients tend to avoid activities and situations in which an unanticipated loss of equilibrium would endanger them. Most BVW patients with moderate to severe BVW avoid driving at night, riding bicycles, climbing, and standing on ladders. They are also aware of circumstances that would temporarily limit their vision (e.g., walking in a poorly illuminated area) or challenge their proprioception (e.g., walking on a rough or uneven surface). We have not personally encountered patients with BVW experiencing problems with swimming; however, swimming imposes proprioceptive and visual challenges, and there are additionally theoretical grounds (153) to suspect that swimming may be difficult for these patients.

CONCLUSION

Bilateral vestibular weakness refers to reduced or absent vestibular function on both sides, and nearly always arises from disease affecting the labyrinths or vestibular nerves. Presenting symptoms are oscillopsia and imbalance. BVW is rare; the typical causes include gentamicin ototoxicity; less common causes include AIED, meningitis, and bilateral vestibular neuritis; in about half of the cases no etiology can be determined. Bedside examination techniques (DVA testing, HIT, and ophthalmoscope test) can be helpful but are not sensitive. RCT remains the gold standard for diagnosing BVW; vHIT may be a reasonable screening test, but requires further study (specifically comparing it to RCT). VNG and VEMPs play a lesser role in diagnosis. Treatment is with vestibular rehabilitation therapy, focusing on sensory substitution. Central compensation is believed to be the mechanism underlying any measurable improvement in the VOR. Clinical improvement generally plateaus at approximately 2 years.

AUTHOR CONTRIBUTIONS

TH came up with the main concepts for the article and wrote sections of a preliminary draft. MC and DY edited and added to the draft. MC rewrote the manuscript into its final form.

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MINI REVIEW
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Central Lesions With Selective Semicircular Canal Involvement Mimicking Bilateral Vestibulopathy

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Bilateral vestibulopathy (BVP), which is due to peripheral lesions, may selectively involve certain semicircular canal (SCC). Recent eye movement recordings with search coil and video head impulse test (HIT) have provided insight in central lesions that can cause bilateral and selective SCC deficit mimicking BVP. Since neurological signs or ocular motor deficits maybe subtle or absent, it is critical to recognize central lesions correctly since there is prognostic and treatment implication. Acute floccular lesions cause bilateral horizontal SCC (HC) impairment while leaving vertical SCC function unaffected. Vestibular nuclear lesions affect bilateral HC and posterior SCC (PC) function, but anterior SCC (AC) function is spared. When both eyes are recorded, medial longitudinal fasciculus lesions cause horizontal dysconjugacy in HC function and catch-up saccades, as well as selective deficiency of PC over AC function. Combined peripheral and central lesions may be difficult to distinguish from BVP. Anterior inferior cerebellar artery stroke causes two types of deficits: 1. ipsilateral pan-SCC deficits and contralateral HC deficit and 2. bilateral HC deficit with vertical SCC sparing. Metabolic disorders such as Wernicke encephalopathy characteristically involve HC but not AC or PC function. Gaucher disease causes uniform loss of all SCC function but with minimal horizontal catch-up saccades. Genetic cerebellar ataxias and cerebellar-ataxia neuropathy vestibular areflexia syndrome typically do not spare AC function. While video HIT does not replace the gold-standard, search coil HIT, clinicians are now able to rapidly and accurately identify specific pattern of SCC deficits, which can aid differentiation of central lesions from BVP.

Keywords: bilateral vestibulopathy, central vestibular disorders, semicircular canal, head impulse test, eye movements

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INTRODUCTION

Bilateral vestibulopathy (BVP) is a chronic vestibular syndrome defined by bilaterally impaired vestibulo-ocular reflex, variably involving semicircular canal (SCC) and otolith function (1), as typically assessed by individual SCC head impulse test (HIT) (2, 3) and vestibular evoked myogenic potential (4), respectively. Peripheral lesions, such as gentamicin vestibulotoxicity, autoimmune inner ear diseases, bilateral Meniere's disease, and bilateral vestibular schwannomas are well recognized in BVP (5, 6). Central lesions, however, are increasingly recognized to affect SCC and otolith function bilaterally, thus potentially mimicking BVP (7–11). As neurological signs or other ocular motor finding may not be readily appreciable or rapidly evolving, it is important that central lesions are considered as a cause of BVP especially if a specific pattern of SCC involvement is apparent. Clinical or bedside HIT remains a useful screening test as no equipment is required and should be performed first before selecting patients for quantitative HIT

such as search coil HIT (scHIT) and video HIT (vHIT). While scHIT is the gold-standard for evaluating individual SCC function (3), it is time consuming and semi-invasive, and, with the advent of modern video-oculography, rapid and reliable assessment of each SCC function is now possible in the clinic with vHIT (12, 13). In this review, we discuss current understanding of pattern of SCC abnormality in central lesions that can mimic BVP, drawing data from both scHIT and vHIT studies.

PERIPHERAL LESIONS

Bilateral vestibulopathy is commonly defined by bilateral symmetrical horizontal SCC (HC) deficit (14), but also VEMP impairment (15), without clinical or radiological involvement of central vestibular structures such as brainstem and cerebellum. In severe BVP, the loss of function of all six SCC is usually total if not near total, and it is usually assumed that horizontal and vertical SCC function is equally affected. However, vHIT has shown that anterior SCC (AC) function may be selectively spared compared to posterior canal (PC) function in BVP due to gentamicin vestibulotoxicity and bilateral Meniere's disease, whereas such sparing does not occur with idiopathic cases, those associated with sudden hearing loss and infection (11, 16). The mechanism of AC function sparing is thought to be disease specific. Isolated bilateral PC loss of function is an uncommon manifestation of BVP (17), often without an identifiable cause, and additional SCC deficits are usually unilateral rather than bilateral. Such cases would invariably be missed if only HC function is tested. Expectedly compensatory or catch-up saccade cumulative amplitude increases with decrease in SCC function so that gaze position error is minimized (14).

VESTIBULAR NUCLEAR LESIONS

Isolated vestibular nuclear stroke may be clinically indistinguishable from acute peripheral vestibulopathy (18). In two cases of isolated acute vestibular nuclear stroke mapped to the medial vestibular nucleus on MRI, scHIT revealed bilateral HC and PC deficit while "skipping" AC (19). As AC afferents project to both superior and medial vestibular nuclei (20), selective lesions of medial vestibular nucleus would theoretically leave ipsilesional AC function intact. It should be noted that there is significant overlap of afferents to different parts of vestibular nuclei; in particular, HC afferents project to superior vestibular nuclei too (21). Contralesional HC deficit is possibly mediated by inhibitory interneuronal adaptive process, similar to the explanation for isolated floccular lesions (22). Thus, it may be impossible to differentiate isolated vestibular nuclear stroke from BVP with scHIT or vHIT, and correct identification should rest on the finding of additional eye movement abnormalities, such as direction-changing, gaze-evoked nystagmus, or skew deviation. Fortunately, isolated vestibular nuclear stroke is rare.

CEREBELLAR LESIONS

Acute cerebellar lesions, whether unilateral or bilateral, can lead to selective moderate bilateral HC impairment sparing vertical SCC function (7, 23) as recorded by scHIT. This pattern is of potential diagnostic value as AC but not both AC and PC function is spared in peripheral lesions. Isolated unilateral floccular stroke, in the territory of anterior inferior cerebellar artery (AICA), causes bilateral HC deficit, slightly worse contralesionally, but discordant caloric and sinusoidal rotational responses (22). The unusual finding of unilateral cerebellar lesions causing bilaterally impaired HC function is thought to be due involve ipsilateral inhibitory floccular projection on the vestibular nuclei, the inhibitory vestibular interneurons and contralateral floccular adaption. The reason for sparing of vertical SCC function is unknown, perhaps related to preferential response of floccular Purkinje cells to vertical rotation (24, 25). Cerebellar stroke, mainly unilateral (70%) and involving the nodulus and uvula in the posterior inferior cerebellar artery (PICA) territory, causes mild reduction (25%) in HC function (7), but AC and PC function is not affected (**Figure 1**), as measured by scHIT. This is possibly due to preference for horizontal over vertical rotation of the eye-movement sensitive neurons, which consist of 20% of the nodulus target neurons, in the vestibular nuclei (26). The mechanism for lack of vertical SCC involvement is unclear, but is theoretically related to directional property of nodular/uvular Purkinje cells, which preferentially align with vertical SCC plane (27, 28). In contrast to BVP in cerebellar lesions, catch-up saccade cumulative amplitude does not necessarily correlate with SCC function. Compared to unilateral peripheral lesions, e.g., acute peripheral vestibulopathy, it is small during ipsilesional head impulses and may be larger during contralesional impulses (7). Dorsal vermal lesions can cause ipsilesional saccade hypometria (29) and the larger cumulative amplitude in cerebellar lesions might represent refixating eye movements in the face of saccade hypometria during contralesional impulses.

MEDIAL LONGITUDINAL FASCICULUS (MLF) LESIONS

Lesions of the MLF disrupt binocular horizontal eye movement and causes the clinical syndrome of internuclear ophthalmoplegia: during horizontal volitional saccades, the abducting eye overshoots the target with or without nystagmus while the adducting slows and/or undershoots (30). Both horizontal and vertical SCC function is abnormal in MLF lesions, though there are some differences between bilateral and unilateral lesions (31, 32). In bilateral MLF lesions, horizontal SCC deficit is characterized by dysconjugacy in gain, as measured by the ratio of eye to head velocity, between the adducting and abducting eye, mirroring the dysconjugacy in horizontal volitional saccades: gain of the adducting and abducting eyes is both reduced, but is more severely affected in the adducting eye (31). Several explanations have been put forward to account for abducting eye impairment, including additional abducens nerve or nuclear involvement (33) and impaired inhibition of antagonist medial rectus (34, 35). Impaired inhibition of medial rectus is unlikely to account for abducting eye impairment, since only excitatory but not inhibitory responses have been recorded when electrically stimulating the MLF (36). We have proposed another mechanism that

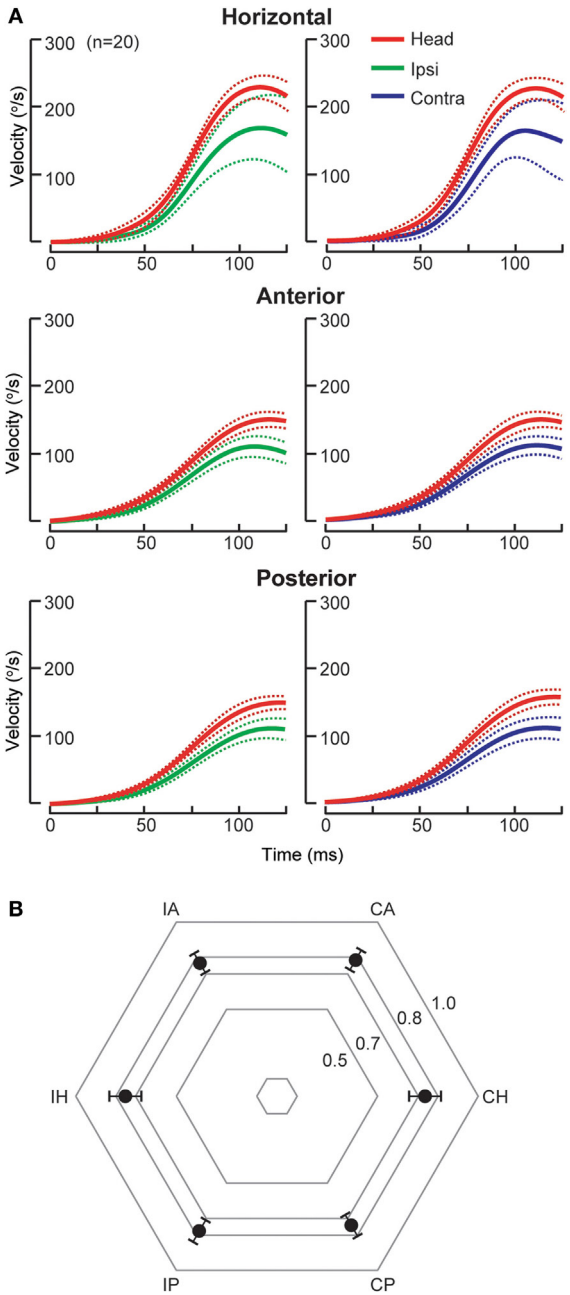

FIGURE 1 | Individual semicircular canal (SCC) function in posterior inferior cerebellar artery ($n = 17$) and superior cerebellar artery stroke (SCA, $n = 3$). **(A)** Group data (mean, solid lines; 95% confidence interval, dashed lines) displayed as time series of inverted eye and head velocities during the first 125 ms of head impulses, recorded using search coil HIT (scHIT). SCC function is indicated by the gain, the ratio of eye to head velocity. There is mild bilateral HC impairment (gain: ipsilateral 0.75 ± 0.09, contralateral 0.74 ± 0.08), while both AC (gain: ipsilateral 0.76 ± 0.06, contralateral 0.78 ± 0.06) and PC function (gain: 0.77 ± 0.06, contralateral, 0.74 ± 0.06) is intact. Note for SCC function evoked by scHIT, the lower limit normal for gain is ~0.8 for HC and ~0.7 for vertical SCC. **(B)** Radar plot depicting group data (mean, solid circles; 95% confidence interval, bars) displayed as gain for each SCC. IH, ipsilesional horizontal canal; IA, ipsilesional anterior canal; CA, contralesional anterior canal; CH, contralesional horizontal canal; CP, contralesional posterior canal; IP, ipsilesional posterior canal.

could account for abducting eye impairment in bilateral MLF lesions: during impulses toward one MLF lesion, disfacilitation of the medial rectus motoneurons of the abducting eye, which normally receives excitatory input *via* the abducens interneurons traveling in the opposite MLF and is inhibited by type I vestibular neurons, is defective (31). Horizontal catch-up saccades are expectedly dysconjugate, in keeping with volitional saccade dysconjugacy. However, there is discrepancy between gain and catch-up dysconjugacy: despite little or no adducting eye catch-up saccades, there is partial preservation of adducting eye gain. The ascending tract of Deiter's (37) is an extra-MLF pathway that mediates excitatory projection from vestibular nucleus to ipsilateral medial rectus motoneurons and could possibly account for the partial preservation of adducting eye gain. In unilateral MLF lesions, abducting eye gain deficit is absent, as disfacilitation of medial rectus motoneurons is intact *via* the unaffected contralateral MLF.

The pattern of vertical SCC deficits is similar for both bilateral and unilateral MLF lesions although the severity differs. PC contralateral to the MLF lesion is universally affected, consistent with all PC signals being transmitted *via* the MLF (38, 39). AC function is relatively less affected, due to the some AC signals being relayed through extra-MLF pathways such as the brachium conjunctivum and ventral tegmental tract (3). There is less AC function sparing in bilateral MLF lesions, possibly explained by three different mechanisms: relative strength of extra-MLF pathway for AC signal (40), on–off direction asymmetry in the vertical SCC plane (41, 42), and property of the vertical secondary vestibular neurons such as lower resting rate (43) and higher sensitivity to rotation (44).

The clinical implication is that there is potential for misdiagnosis of MLF lesions as BVP. All vHIT devices record monocular eye movements so that it will be not possible to determine horizontal gain dysconjugacy. Some vHIT devices measure only the right eye, whereas others can be adjusted to record either eye. For right eye systems, if there is a right MLF lesion, HC function will be deficient on rightward impulses, and there will be left PC deficit with some AC sparing. This should not be confused with a patchy BVP, as left HC function would be intact. If there is a left MLF lesion then both HC function would be intact, and the isolated AC–PC dissociation would be diagnostic. In bilateral MLF lesions without binocular eye movement recording, it would be easy to make the mistake of diagnosing BVP, as there would be HC deficit (due to adducting eye deficit from one MLF lesion and abducting eye deficit from impaired disfacilitation from the other MLF lesion), and variable bilateral AC-PC dissociation. Until binocular vHIT system becomes established, it is important to examine the horizontal saccades carefully.

COMBINED CENTRAL AND PERIPHERAL VESTIBULAR LESIONS

It may be difficult to diagnose a combined central and peripheral vestibular lesion if only peripheral signs, e.g., SCC deficits consistent with BVP, or central signs, e.g., gaze-evoked nystagmus and impaired smooth pursuit are considered (45). However,

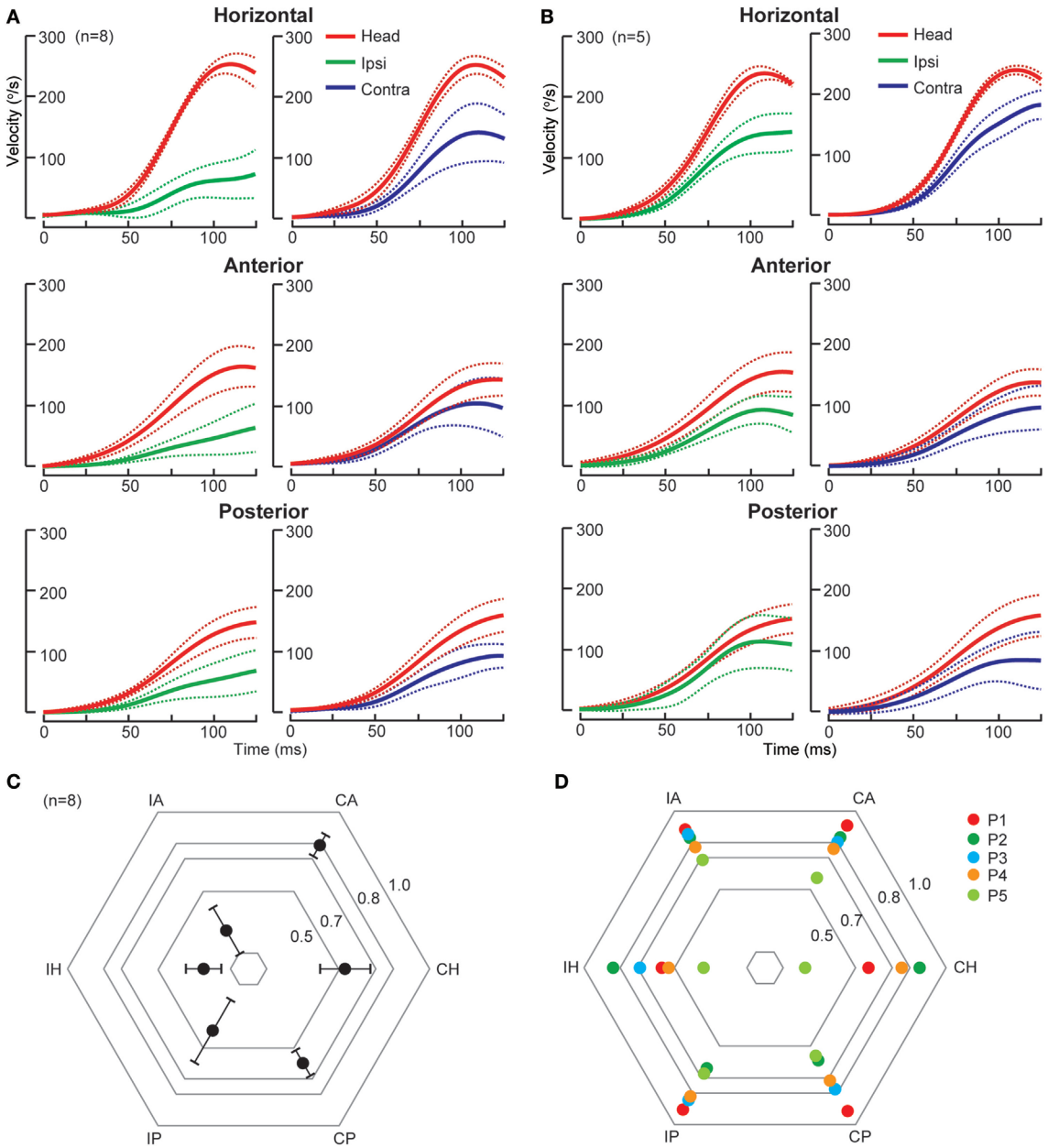

FIGURE 2 | Individual semicircular canal function in anterior inferior cerebellar artery (AICA) stroke. **(A)** In the first type of AICA stroke ($n = 8$), group data displayed as time series of inverted eye and head velocities during the first 125 ms of head impulses, recorded using search coil HIT. Ipsilesional HC (gain 0.25 ± 0.10), AC (gain 0.24 ± 0.15), and PC (gain 0.39 ± 0.20) function was deficient, while only contralesional HC (gain 0.53 ± 0.14) but not AC (gain 0.79 ± 0.07) function was impaired. Contralesional PC function (gain 0.60 ± 0.08) function was slightly reduced, probably consistent with the severe ipsilesional AC deficit and reflects the on–off direction asymmetry. **(B)** In the second type of AICA stroke ($n = 5$), there is mild bilateral symmetrical HC deficit while AC and PC function is preserved. Radar plots depicting mean gain ± 95% confidence interval for the first type of AICA stroke ($n = 8$) and individual values for the second type of AICA stroke ($n = 5$) are presented in **(C,D)**, respectively. IH, ipsilesional horizontal canal; IA, ipsilesional anterior canal; CA, contralesional anterior canal; CH, contralesional horizontal canal; CP, contralesional posterior canal; IP, ipsilesional posterior canal; P, patient.

certain patterns of SCC deficits and catch-up saccade characteristic should still prove helpful. Recent studies have highlighted a number of disorders that can present with combined central and peripheral lesions: AICA strokes and cerebellopontine angle (CPA) tumor (7, 23), metabolic disorders such as Gaucher disease(GD) (8, 46) and Wernicke encephalopathy (10, 47), and cerebellar degeneration (9, 48, 49). By far, over 70% are accounted for by AICA stroke and CPA tumor (45).

AICA Stroke

The AICA supplies the vestibulocochlear nerve, root entry zone, dorsolateral pons including the vestibular nuclei and flocculus (50).

Thus, in AICA stroke, a spectrum of audiovestibular loss is expected (51). There are two patterns of SCC deficits as identified by scHIT (**Figure 2**), likely reflecting variable combination of peripheral and central involvement. In the first type, there are ipsilesional pan-SCC deficits, i.e., involving HC, AC, and PC, and contralesional SCC deficit involving HC, but not AC or PC. In the second, while there is variable bilateral HC involvement, vertical SCC is not affected. While both types are characterized by unilateral lesions causing bilateral HC impairment, which is probably explained by inhibitory floccular target neurons and interneurons between vestibular nuclei (7, 22), in the first type, ipsilesional vertical SCC is affected, suggestive of additional involvement of vestibular end organs/primary afferents/root entry zone, whereas in the second, lack of vertical SCC involvement suggests sparing of vestibular end organs and afferents. Horizontal catch-up saccade size is smaller when compared to acute peripheral vestibulopathy, despite similar HC impairment (7); the flocculus is possibly implicated since it modulates saccades (52) and an experimental lesion causes backward postsaccadic drift (53). CPA tumors expand progressively and cause compression of the brainstem and cerebellum, resulting in variable lesion of anatomical substrates that are similarly affected by AICA stroke.

Gaucher Disease

Gaucher disease is a hereditary storage disorder due to glucocerebrosidase deficiency. Type 3 GD causes slowed saccades, more selective for horizontal than vertical (54), and vestibular impairments (8, 46). All SCC function is impaired, and due to saccade slowing, there is a paucity of catch-up saccades, most marked for HC. After a horizontal head impulse, the eyes may be "locked up" transiently until a resetting impulse in the opposite direction occurs. These findings may be accounted for by neuronal loss in the abducens and vestibular nuclei (55). If a patient with BVP does not consistently fixate on the center target, i.e., there would appear to be no catch-up saccade then this can potentially mimic GD. Repeated instruction to the patient and careful examination of saccade should minimize diagnostic confusion.

Wernicke's Encephalopathy

Acute Wernicke's encephalopathy (WE), due to thiamine deficiency, may not present with the classic triad of encephalopathy, ataxia, and ophthalmoplegia (56). SCC deficit is characterized by selective, symmetrical HC impairment, with sparing of the vertical SCC, as demonstrated by both scHIT (47) and vHIT (10). Presumably, the medial vestibular nucleus, which receives afferents from HC, is particularly vulnerable to the effect of thiamine deficiency (57). Prompt recognition and treatment not only restores SCC deficit (58) but also potentially prevent permanent neurological impairment. The major differential consideration of acute WE is AICA stroke presenting isolated bilateral HC deficit, and MRI is likely to provide additional diagnostic clarification.

Cerebellar Degeneration

A characteristic abnormality of simultaneous cerebellar and vestibular involvement is the impaired visually enhanced vestibulo-ocular reflex (48), which may be present in certain types of cerebellar degeneration. This sign, along with gaze-evoked nystagmus, is of particular diagnostic importance as AC function sparing may not occur in cerebellar degeneration. In Friedreich's ataxia (FA), SCC function is globally reduced (9), whereas in spinocerebellar ataxia type 6 (SCA6), SCC function may be increased or decreased depending on disease severity (49). The reason for this difference is not known, but is potentially related to anatomical substrate and pathogenesis: in FA, vestibular end organs and afferents are involved, whereas in SCA6, increased function is thought to be related to initial disinhibition of deep cerebellar nuclei due to cerebellar long term depression in suppressing Purkinje cell activity and decreased in function due to later neuronal loss in the flocculus. Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) is a sensory ganglionopathy (59), which causes bilateral HC and vertical SCC deficits (16). Both CANVAS and FA are associated with impaired visually enhanced vestibulo-ocular reflex and bilateral SCC deficits not sparing AC function.

CONCLUSION

A number of central lesions can mimic BVP and poses diagnostic dilemma. Correct identification of central lesions is important, as both prognosis and treatment differ from BVP. In central lesions, specific patterns of SCC deficit may provide diagnostic clue and horizontal catch-up saccade size does not always correlate with SCC function. While scHIT remains the gold-standard for assessment of individual SCC function, the availability of vHIT has allowed clinicians to rapidly evaluate individual SCC function at point of care. In general, neurology practice vHIT availability is likely limited and clinical or bedside HIT remains a good screening test. Combined central and peripheral lesions are perhaps the most challenging to diagnose, and other eye movement abnormalities and MRI findings may be required to establish the diagnosis.

AUTHOR CONTRIBUTIONS

LC designed the study, analyzed eye movement data, and prepared and interpreted all the research data and figures. He was principally in charge of drafting, revising for intellectual content, and submitting the manuscript. GMH assisted in designing the study, interpreted research data figure, and in revising the manuscript for intellectual content.

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Amiodarone: A Newly Discovered Association with Bilateral Vestibulopathy

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Background: Bilateral vestibulopathy (BVP) is a debilitating disorder characterized by the hypofunction of both vestibular end organs or nerves. The most frequent identifiable causes of BVP are ototoxic drug effects, infectious and autoimmune disorders. However, the majority of cases remain idiopathic. Very recently, the first discovery of a clinical case of Amiodarone-associated BVP has been reported.

Methods: An overview of the literature concerning the relation between amiodarone toxicity and BVP is presented and discussed.

Results: Older reports on amiodarone-induced symptoms of vertigo and gait instability lack a description of vestibular function test results. Recent evidence from retrospective studies including vestibular function testing in patients taking amiodarone have identified the drug as the hitherto unsuspected potential cause of a relatively large proportion of cases with "idiopathic" BVP.

Conclusion: Patients who receive amiodarone should be monitored with vestibular function testing in order to recognize potential adverse effects on the vestibular system and allow for an informed decision on possible drug reduction or withdrawal.

Keywords: head impulse test, inner ear, vertigo, ototoxicity, adverse drug reactions

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Bilateral vestibulopathy is a debilitating disorder characterized by the hypofunction of both vestibular end organs or nerves. It accounts for about 3% of the diagnosis in a tertiary neurotology clinic (1), and its prevalence has been reported as high as 81 per 100,000 (2). The most frequent identifiable causes of BVP are ototoxic drug effects, infectious and autoimmune disorders (3). The majority of cases, however, remain idiopathic. Very recently, the first discovery of a clinical case of amiodarone-associated BVP was reported (4). Here, the existing evidence for the concept of amiodarone-induced BVP is summarized and discussed.

Amiodarone is an iodinated benzofuran derivative (**Figure 1**) with Class I, II, III, and IV anti-arrhythmic properties. It is the most commonly used antiarrhythmic drug for the indication of supraventricular and ventricular arrhythmias. It has a long elimination half-life of about 50–140 days, and therefore, it may take several months before an adverse effect is reversed when the drug is stopped (5, 6).

Thorough follow-up is essential to the care of patients taking amiodarone. Adverse effects are common, with prevalence rates reaching 15% during the first year of use and 50% during long-term use (**Table 1**). Especially when amiodarone is used for non-life-threatening arrhythmias, such as atrial fibrillation, the risk may outweigh the benefit if serious adverse effects occur. In a recent study

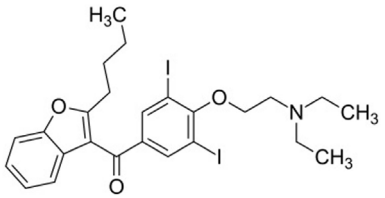

FIGURE 1 | Structural formula of amiodarone.

TABLE 1 | Overview of amiodarone-induced adverse effects [modified after Ref. (8)].

System	Adverse effect	Incidence (%)
Neurologic	Ataxia, paresthesia, neuropathy, sleep disturbance, memory disturbance, tremor	3–30
Ocular	Halo vision	<5
	Optic neuropathy	<1
	Photophobia, visual blurring, microdeposits	>90
Thyroid	Hypothyroidism	4–22
	Hyperthyroidism	2–12
Pulmonary	Cough, dyspnea	2
Cardiac	Bradycardia, AV block	5
	Ventricular proarrhythmia	<1
Gastrointestinal	Nausea, anorexia, constipation	30
	AST/ALT level increase	15–30
	Hepatitis, cirrhosis	<3
Genitourinary	Epididymitis, erectile dysfunction	<1
Cutaneous	Blue discoloration	<10
	Photosensitivity	25–75

AST, aspartate aminotransferase; ALT, alanine aminotransferase; AV, atrial-ventricular.

in patients below 65 years of age with atrial fibrillation, the drug was discontinued in the first year by 52% (7).

ADVERSE EFFECTS OF AMIODARONE

The reported frequencies of neurologic adverse effects are quite variable, ranging from 2.8 (9) to 28% (10). Also, the correlation between therapy duration and adverse effect severity is not uniformly reported, but was found to be positive in one study (9). Neurological complications are not always reversible with amiodarone discontinuation (11). High doses have even been reported to cause quadriplegia. Muscle weakness and tremor are more frequent findings. The neuropathy seems to be rather of the demyelinating type than the axonal loss type. The management strategy for neurological toxicity is to discontinue or decrease the amiodarone dose and wait for its elimination or decreased effects. Concerning the dose–adverse effect relationship, **Table 2** shows the impressive correlation between the daily amiodarone maintenance dose and the frequency of neurotoxic adverse effects in previously published reports.

Toxic effects on the thyroid may cause both hypo- and hyperthyroidism. Typically, amiodarone-induced hypothyroidism occurs within the first 1–24 months of treatment (20). Amiodarone-induced thyrotoxicosis is less prevalent. It can occur

TABLE 2 | Prevalence of amiodarone neurotoxicity according to the daily maintenance dose.

Source	Mean or usual daily dose (mg)	Prevalence of neurotoxic effects (%)
Greene et al. (12)	600	74
Morady et al. (13)	600	35
Charness et al. (14)	580	54
Palakurthy et al. (15)	468	44
Coulter et al. (10)	277	27.5
Vorperian et al. (16)	152–330	4.6
Cairns et al. (17)	208–308	3.1
Orr and Ahlskog (9)	223.8	2.8
Ahmed et al. (18)	200	1.6
Julian et al. (19)	200	0.5

In previously published series, there is an impressive correlation between the daily amiodarone maintenance dose and the frequency of neurotoxic adverse effects [modified after Ref. (9)].

suddenly at any time during or even months after treatment. Since amiodarone also exerts beta-blocking effects, the typical signs of thyrotoxicosis are often missing. Common findings include loss of weight or a significant change in warfarin dosing (8).

Pulmonary amiodarone-induced toxicity most commonly presents as diffuse interstitial lung disease or hypersensitivity syndrome that may mimic an infection. It generally presents in the first year of therapy with acute or subacute cough; later symptoms include progressive dyspnea and, occasionally, fever. Other manifestations include respiratory distress syndrome, pulmonary nodules or solitary masses, or pleural effusions (8).

In the gastrointestinal system, nausea, anorexia, and constipation are relatively common side effects of amiodarone. They are dose-related and usually do not require specific interventions. In less than 1% of the patients treated annually, clinically significant liver toxicity occurs.[1] Liver dysfunction is more frequent when high doses are used and with a long treatment duration. Given the potential accumulation and persistence of amiodarone in hepatic tissue, even a long time after the cessation of therapy, the total cumulative dosage may play a prominent role. Typical symptoms include nausea, loss of weight, fatigue without jaundice, and the examination reveals an enlarged liver and elevated serum aminotransferase and alkaline phosphatase levels.

INDIRECT EVIDENCE FOR AMIODARONE-INDUCED BVP

A 76-year-old man was reported to suffer from increasing imbalance over the past 2.5 months (21). His examination revealed finger-nose-dysmetria, an unsteady gait with a leftward tendency, a positive Romberg test (unable to stand with feet together and arms outstretched while eyes are closed), and increased instability on difficult gait tasks (heel-to-toe-walk). His past medical history included myocardial infarction, paroxysmal atrial fibrillation, peripheral vascular disease, chronic obstructive lung disease, arterial hypertension, and chronic kidney disease. On re-evaluation of his medications, the patient was found to have

[1] NIH, National Library of Medicine. Available from: https://livertox.nlm.nih.gov/Amiodarone.htm

been inadvertently taking the loading dose of 3 × 400 mg of amiodarone ever since the drug was started 2.5 months ago during a hospitalization. His amiodarone was consequently stopped, and his ataxia slowly improved over a few weeks, with complete resolution after 5 months. The patient had reported that he could walk without difficulty but "felt drunk" without using a cane. Although no vestibular function tests were performed in this patient, the description of his symptoms is consistent with BVP rather than, e.g., cerebellar ataxia, since the latter typically leads to a more severe disturbance of gait and stance and since finger-nose-dysmetria in elderly patients is a rather unspecific finding.

A previously active 95-year-old lady was reported to notice progressive gait instability 8 months after initiating an amiodarone treatment for her paroxysmal atrial fibrillation (22). She was not suitable for treatment with a beta blocker even at small doses because of a symptomatic reduction of blood pressure. She was initiated on amiodarone 200 mg three times a day for 1 week, followed by 200 mg twice a day for 1 week, and then 200 mg once a day. Fourteen days after the loading dose, she reverted to sinus rhythm. Her amiodarone-induced hypothyroidism was treated with 75 μg thyroxine. On examination, she had a wide-based gait, bilateral dysdiadochokinesia, signs of peripheral neuropathy, and "bilateral nystagmus." The dose of amiodarone was reduced to 100 mg once a day, and 1 month later she felt steadier. One month after the amiodarone was stopped, the gait imbalance had resolved. No explicit tests of vestibular function were performed in this case. The term "bilateral nystagmus" may possibly refer to a bilaterally pathologic head impulse test or may possibly indicate a spontaneous nystagmus oscillating horizontally. The corresponding author of this case report was contacted for further clarification of this "bilateral nystagmus," but did not respond. Overall, the description of this case is reminiscent of BVP.

A prospective study on neurological toxicity of amiodarone was conducted in New Zealand and included data from 408 patients at the time of its market introduction (10). The authors provided the prescribing doctors with a questionnaire to be filled out at the next patient visit, which included questions about paresthesia, neuropathy, tremor, vertigo, ataxia, impaired intellect, muscle weakness, cerebrovascular accident, transient ischemic attack, diplopia, speech disorder, migraine, and other neurological problems. Within this cohort, 28% of the patients had at least one neurological adverse effect. Of note, the most frequent adverse effects were vertigo (9%) and gait imbalance (9%). Furthermore, these two symptoms were highly significantly correlated. Vertigo and gait imbalance were also the most frequent causes of withdrawal or reduction of amiodarone in this patient cohort. The gait imbalance was described as an unsteadiness, and five patients were reported having falls. Three patients were reported as "cerebellar ataxia." However, since vestibular function tests or other differentiating tests such as the Romberg test were not reported, there is little evidence to locate the lesion to the cerebellum in these cases.

Among a patient cohort with relatively high daily maintenance dose (15), ataxia/gait instability was reported in about 7% of the patients. In one patient, the authors noted the presence of nystagmus, but did not further describe the nature of this nystagmus nor did they perform any vestibular tests. Therefore, similar to other studies, in hindsight it may well be suspected that the reported symptoms of ataxia/gait instability were actually (at least partially) caused by BVP.

Another study (9) that analyzed medical records with a retrospective design described 11 patients who were referred to the neurology clinic after the start of an amiodarone treatment and had a plausible amiodarone-related averse effect. These patients were identified among a total of 707 patients receiving amiodarone within one county. Of those, two patients had gait ataxia/instability. However, among nine further patients with possible amiodarone-induced toxicity but who were not referred to the neurology clinic, five suffered from gait instability. Including those cases, the authors calculated an overall prevalence of amiodarone neurotoxicity of 2.8%. Comparing the two groups with and without amiodarone neurotoxicity, there was no difference in age, sex, type of arrhythmia, and daily dose. However, the length of time receiving therapy was a significant risk factor for amiodarone toxicity, in accordance with a previous meta-analysis that found that exposure to amiodarone therapy for at least 12 months doubled the odds of neurologic adverse effects with placebo (despite low doses of 150–330 mg/day) (16).

Further support for the adverse effect of amiodarone on gait stability comes from a recent study which examined the risk of falls in patients diagnosed with atrial fibrillation (23). The authors examined patients aged above 60 years with a history of atrial fibrillation and subdivided them into two groups: those with no history of falls in the previous year and those with a history of one or more falls in the previous year. Among the clinical and epidemiological parameters assessed with multivariate logistic regression, the use of amiodarone could be identified as an independent risk factor for falls.

DIRECT EVIDENCE FOR AMIODARONE-INDUCED BVP

In 2017, the first case of amiodarone-induced BVP was published (4). A 73-year-old man presented to the neurotology clinic with progressive gait imbalance, beginning 6 months after starting amiodarone therapy. Previous clinical investigations including repeated MR imaging excluded alternative pathologies such as cerebellar/brainstem infarction or atrophy and only yielded peripheral neuropathy as diagnosis. Vestibular function testing revealed a bilaterally pathologic head impulse test, profoundly reduced responses on caloric videonystagmography and severely reduced vestibular ocular reflex gain as well as pathological compensatory saccades bilaterally on video head impulse testing. After amiodarone discontinuation, in contrast to a previous case of suspected amiodarone-induced BVP described above, his symptoms only partially resolved. A possible explanation for this may be the fact that he had been taken amiodarone for more than 3 years. A single-center retrospective evaluation of 14 patients treated with amiodarone who were referred to a vertigo center found that 6 of these patients (43%) had BVP (4), which is a surprisingly high prevalence. A very recent retrospective multicenter study in five dizziness clinics (24) approached the subject of amiodarone-induced BVP from a different perspective: The authors analyzed 126 patients with "idiopathic" BVP (i.e., of

previously unknown etiology) and found that 15 of these patients were actually taking amiodarone. In all of these patients, the gait instability was progressive over time and two of them reported repeated falls. This prevalence of amiodarone intake of 12% within a cohort of patients with so-called "idiopathic" BVP lies far above an expected random coincidence, and further supports the data of a previous report from a single center.

POSSIBLE MECHANISMS OF AMIODARONE NEURO-/OTOTOXICITY

There are no histopathologic reports of the effects of amiodarone on the vestibular nerve or the labyrinth. It is therefore not yet possible to pinpoint the exact location of the lesion in amiodarone-induced BVP along the vestibular system pathways.

Histologic studies of sural nerve biopsies reported both axonal degeneration and demyelination (25). A histopathological report on two patients with amiodarone-induced neuropathy (25) reported loss of myelinated fibers, the presence of lysosomal inclusion bodies in Schwann cells, and widening of Ranvier nodal gaps. Schwann cell abnormalities seemed to precede the breakdown of myelin, suggesting that amiodarone-induced neuropathy could be described as a schwannopathy. These changes are likely a result of the effects of amiodarone upon the lysosomal system. They correspond to the observation in animal studies that amiodarone has strong inhibitory effects on lysosomal phospholipases A1 and A2 responsible for catabolizing phospholipids (26), causing formation of the characteristic lysosomal bodies. Further manifestations of this interference of amiodarone with the lysosomal system are microdepositions of lipofuscin in the cornea and the skin frequently encountered in amiodarone-treated patients (**Table 1**) as well as hepatic and pulmonary toxicity (26).

Experimental animal studies with amiodarone (27) indicate that, in common with other amphiphilic drugs, its distribution among tissues is restricted by vascular barriers, such as the blood–brain barrier, whereas its pathologic cellular effects can be found with a dose-related intensity in regions located outside these barriers, such as dorsal root, area postrema, myenteric plexus, and gasserian and autonomic ganglia. This would be in accordance to the predilection of the amiodarone neurotoxicity for the peripheral nervous system *vs.* the central nervous system, since the blood–nerve barrier is less tightly controlled than the blood–brain barrier (25). Clinical or subclinical disease causing blood–nerve permeability changes may also underly this observation, since a clinical study of amiodarone-associated neuropathy reported two cases with a history of diabetes mellitus (28).

In summary, older reports on amiodarone-induced symptoms of vertigo and gait instability lack a description of vestibular function test results. Recent evidence from retrospective studies including vestibular function testing in patients taking amiodarone could identify the drug as the hitherto unsuspected potential cause of a relatively large proportion of cases with "idiopathic" BVP. Therefore, patients who receive amiodarone should be monitored with vestibular function testing in order to recognize potential adverse effects on the vestibular system and allow an informed decision on a possible drug reduction or withdrawal. Furthermore, in order to precisely determine the dynamics and the prevalence of amiodarone-induced BVP, a prospective study of vestibular function in patients taking amiodarone is recommended.

AUTHOR CONTRIBUTIONS

RG conceived, drafted, and revised the manuscript.

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Postural Control in Bilateral Vestibular Failure: Its Relation to Visual, Proprioceptive, Vestibular, and Cognitive Input

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Patients with bilateral vestibular failure (BVF) suffer from postural and gait unsteadiness with an increased risk of falls. The aim of this study was to elucidate the differential role of otolith, semicircular canal (SSC), visual, proprioceptive, and cognitive influences on the postural stability of BVF patients. Center-of-pressure displacements were recorded by posturography under six conditions: target visibility; tonic head positions in the pitch plane; horizontal head shaking; sensory deprivation; dual task; and tandem stance. Between-group analysis revealed larger postural sway in BVF patients on eye closure; but with the eyes open, BVF did not differ from healthy controls (HCs). Head tilts and horizontal head shaking increased sway but did not differ between groups. In the dual task condition, BVF patients maintained posture indistinguishable from controls. On foam and tandem stance, postural sway was larger in BVF, even with the eyes open. The best predictor for the severity of bilateral vestibulopathy was standing on foam with eyes closed. Postural control of our BVF was indistinguishable from HCs once visual and proprioceptive feedback is provided. This distinguishes them from patients with vestibulo-cerebellar disorders or functional dizziness. It confirms previous reports and explains that postural unsteadiness of BVF patients can be missed easily if not examined by conditions of visual and/or proprioceptive deprivation. In fact, the best predictor for vestibular hypofunction (VOR gain) was examining patients standing on foam with the eyes closed. Postural sway in that condition increased with the severity of vestibular impairment but not with disease duration. In the absence of visual control, impaired otolith input destabilizes BVF with head retroflexion. Stimulating deficient SSC does not distinguish patients from controls possibly reflecting a shift of intersensory weighing toward proprioceptive-guided postural control. Accordingly, proprioceptive deprivation heavily destabilizes BVF, even when visual control is provided.

Keywords: bilateral vestibular failure, postural control, posturography, proprioception, multisensory integration

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INTRODUCTION

Bilateral vestibular failure (BVF) is characterized by unsteadiness of stance and gait and disabling oscillopsia during head movements (1). BVF has a wide spectrum of etiologies (2, 3), ranging from vestibulo-toxic agents such as antibiotics (4, 5), opioids (6), salicyl acid (7), amiodarone (8) and chemotherapy (9, 10); and polyneuropathies (11–13) to sequential vestibulopathies, e.g., due to

Menière's disease or vestibular neuritis. Most often BVF remains idiopathic. Rarer causes include systemic autoimmune diseases, e.g., Cogan's syndrome (14), in particular connective tissue disease, e.g., systemic lupus erythematosus, Behcet's disease, neurosarcoidosis but also infectious diseases (e.g., borreliosis), vitamine B1 deficiency (15), schwannoma, meningeosis, superficial siderosis (16) and it may present as part of neurodegenerative diseases, e.g., idiopathic cerebellar ataxia with BVF (17, 18) and additional polyneuropathy CANVAS syndrome (19). In line with the variety of etiologies, vestibular hypofunction may encompass semicircular canal (SSC) and otolith signal processing in the labyrinth or vestibular nerve separately or combined. Moderate vestibular hypofunction may also come from cerebellar disease (20) which also causes postural unsteadiness.

Postural ataxia in peripheral BVF may be related to abnormal otolith processing and/or SSC malfunction in the inferior and superior branch of the vestibular nerve or within the labyrinth (21). Since the SSC senses rotatory head acceleration patients might complain about dizziness and unsteadiness particularly on head and body rotations, whereas patients with abnormal otolith function might rather complain about dizziness on linear acceleration or tilted head positions. Using foam posturography postural ataxia increased with the severity of combined otolith and SSC hypofunction (22, 23). Vestibular hypofunction may be compensated by substitution by other sensory systems and/or central compensation (24). A few lines of behavioral and brain imaging (25) evidence indicate a change in intersensory weighing to compensate for postural ataxia (26). One example for a shift of sensory weighing is the increased visual dependence during transient vestibular loss in weightlessness [e.g., microgravity, spacelab (27, 28)]. Therefore, we hypothesized that BVF patients show increased sensitivity to proprioceptive and visual input. However, it is unknown how patients with partial, i.e., incomplete lesions of the vestibular afferents stabilize stance when vestibular otolith or SSC stimuli are applied during postural control. Our primary aim was to compare postural control in BVF and healthy control (HC) subjects by systematically modulating visual, SSC, otolith, and proprioceptive input. As postural control might be influenced by focused attention and/or cognitive distraction [dual task (29)] and more challenging balance tasks (tandem stance), we added these conditions to elaborate how these factors might unmask latent postural instability in BVF.

MATERIALS AND METHODS

Participants

Patients were diagnosed to have BVF based on clinical examinations, bithermal caloric irrigation [bilateral hyporesponsiveness with mean peak slow phase velocity (SPV) of <5°/s on both sides], and quantitative head impulse recordings of the vestibulo-ocular reflex (VOR, reduced gain <0.7), absence of clinical signs for cerebellar disease, and normal cranial MRI. On clinical examination, all patients showed gait ataxia without significant consistency in lateropulsion/gait deviation. Gait ataxia severely increased with horizontal head movements while attempting to fixate targets at gaze straight ahead. Romberg's test was pathological in all of them while the Unterberger test was not pathological (no consistent deviation) in any of the patients. A total number of 31 patients with chronic (>3 months, range: 3 months to 20 years) BVF were examined (mean VOR gain: 0.26). Nine patients had to be excluded due to comorbidity (polyneuropathy). This resulted in 22 eligible BVF patients [12 male; age: 64.0 ± 2.2 years (SE); disease duration: range 3 months to 20 years; mean 3.1 years]. The most common etiology of BVF was antibiotic ototoxicity ($n = 13$), unknown cause ($n = 8$), and sequential vestibular neuritis ($n = 1$). The patient and the HC group ($n = 28$, 17 male; age: 65.2 ± 1.7 years; mean gain 0.97 ± 0.02) did not differ significantly in age (two-sample t-test $p = 0.68$), gender (chi-square test $p = 0.77$), or Montreal Cognitive Assessment test score (two-sample t-test $p = 0.52$) [MoCA (30)].

Electrophysiological and Psychophysical Recordings

Semicircular canal function was investigated by electronystagmography with caloric irrigation and quantitative head impulse testing; otolith function by static (background stationary) and dynamic (moving visual background) subjective visual vertical (SVV) (31) and cervical and ocular vestibular-evoked myogenic potentials [VEMP (32)]. Cervical VEMP were elicited by asking the lying participants to slightly lift their heads and maintain a tonic rotational position of their heads to the contralateral side while EMG activity was recorded from the mid portion of the sternocleidomastoid muscles. Unilateral AC tone bursts of 500 Hz were used and p13-n23 components were analyzed [for details see Ref. (32, 33)].

All participants were examined by quantitative head impulse test using video-oculography. Eye and head movements were recorded by the EyeSeeCam® HIT System (Autronics, Hamburg, Germany) at a sampling rate of 220 Hz (34). VOR gain was determined by robust linear regression of eye and head velocity starting at head velocity >10°/s to 95% of peak head velocity using Matlab®(The Mathworks Inc., Natick, MA, USA, version R2016a). For further details, see Ref. (35–37).

Experimental Conditions

Posturography was recorded in the upright standing position with the hands hanging next to the trunk for 20 s. At baseline, subjects were asked to stand on the platform with feet (shoes) parallel to each other. We tested various experimental conditions (**Figure 1**) which differed in terms of (i) visual (eyes open/closed; EO/EC), (ii) graviceptive otolith (head tilted up, down vs. head erect, with the eyes open and closed) (38), (iii) SSC (horizontal head shaking) (iv) and proprioceptive (foam) input, (v) cognitive influence (dual task with backward counting), and (vi) complex motor challenging demands on postural control (tandem stance) (39). During horizontal head shaking (0.5 Hz) participants were asked to fixate a target 60 cm in front of the participants' forehead. Head movements were recorded and monitored with the ZEBRIS system (CMS70P, Zebris Medizintechnik GmbH, Isny, Germany) at a sampling rate of 50 Hz (40). The system determines the position [specified by

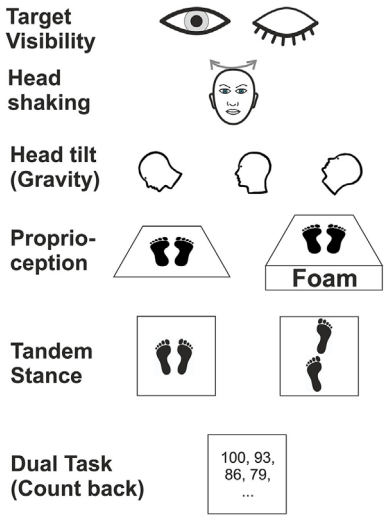

FIGURE 1 | Schematic illustration of six experimental conditions in which subjects were examined during posturography.

three values $v = (x, y, z)$] of an ultrasound-emitting marker relative to an array of three receivers. This condition was meant to compare the effects of vestibular semicircular canal stimulation on vestibulo-spinal postural control in patients with incomplete lesions of the vestibulo-ocular reflex, with and without visual feedback (eyes open vs. closed). Although this technique is not a selective stimulation of the horizontal canals, the effects on the horizontal SSC are expected to be much stronger than on the vertical SSC and on the utricles.

Head position was adjusted by an inclinometer (38). This recording assured that the different head positions (anteflection by 45°, upright head positions, 30° dorsoflection of the neck; with gaze straight ahead relative to head position) were maintained for the recording time. We used a slab of foam rubber (50 cm width, 60 cm length, height 10 cm, compression hardness: 3.3 kPa, volumetric weight: 40 kg/m^3) for testing balance control under attenuated proprioceptive feedback under two conditions: (a) with the head erect, gaze fixation of LED at the gaze straight ahead position and (b) with the eyes closed.

Posturography

We used a Kistler force platform (Model 9260AA6, Kistler Instrumente AG, Winterthur, Switzerland; 50 cm width, 60 cm length, height 10 cm) equipped with piezo-electric 3-component force sensors for recording postural changes during the above mentioned experimental conditions in a similar way as described elsewhere (41, 42). Postural sway signals were bidirectionally filtered (50 Hz Gaussian filter) to eliminate low amplitude recording noise (43). The platform recorded torques and sheer forces with six degrees of freedom using force transducers with an accuracy better than 0.5 N. The displacement of the center of pressure in the medio-lateral (ML) and the anterior–posterior (AP) directions were recorded and the sum vector calculated using Matlab®. Results are given as the mean postural sway speed (PSS, in centimeter per second), calculated from the AP and ML movements:

$$\mathrm{PSS} = \mathrm{mean}(\sqrt{(\mathrm{AP}_i - \mathrm{AP}_{i-1})^2 + (\mathrm{ML}_i - \mathrm{ML}_{i-1})^2} * \mathrm{SamplingRate})$$

Postural sway was recorded in intervals of 20 s duration for off-line analysis (sampling frequency 250 Hz) (39).

Statistical Analysis

Statistical analyses were performed with SPSS (22.0.0.2; IBM Corp., Somer, NY, USA). Analyzing the postural sway speed, the factors TARGET VISIBILITIY (eyes open/closed), HEAD POSITION, HEAD SHAKING, DUAL TASK (counting), PROPRIOCEPTION (foam), and TANDEM STANCE were taken as within-subject factors and group as between-subjects factor. Analyzing Romberg's ratio the factor TARGET VISIBILITY was eliminated, therefore all other factors were included in the ANOVA. In some comparisons sphericity requirement was violated. Therefore, we report *F*-values with Greenhouse-Geisser correction but report degrees of freedom (df) uncorrected in order to show the factorial analysis design. Statistical comparisons were performed parametric unless stated otherwise.

Multi-factorial ANOVA with the above mentioned factors were performed. Significance levels of these tests were Bonferroni corrected for multiple testing. Statistical differences were regarded as significant for values $p < 0.05$. Error bars indicate SEM. Correlation analyses were performed using Spearman-Rho coefficient unless otherwise stated. The effects of visual deprivation on postural stability were determined by Romberg's ratio computing PSS with the eyes closed/eyes open (22).

RESULTS

Electrophysiological Data

The mean VOR gain was reduced to 0.26 ± 0.04 indicating severe bilateral vestibulopathy. Mean peak SPV of caloric nystagmus was 4.5 ± 0.8°/s. oVEMP were recorded in 22 patients and 23 HC subjects; they were absent in 12 patients and revealed reduced amplitudes in the other 10 patients: peak amplitude differed significantly between groups (Mann–Withney *U* test, $p = 0.003$, median patients: 3.8 μV, median HC subjects: 6.95 μV). cVEMP were recorded in 22 patients and 23 HC subjects (median: 24.4 μV); they were absent in 17 patients and showed significantly reduced amplitudes in the other five patients (median 8.0 μV; $p = 0.028$). SVV did not show pathological tilts (>2.5°) and did not differ between patients and controls, neither during dynamic nor static SVV.

Postural Data

Generally, postural sway speed differed between paradigms ($F(13,36) = 71.716$, $p = 0.001$) and revealed an interaction of CONDITION × GROUP ($F(13,36) = 2.559$, $p = 0.038$). ANOVA showed a significant group difference ($F(1,48) = 7.596$, $p = 0.008$), i.e., BVF patients ($n = 22$) showed on average larger PSS than HC participants ($n = 28$).

Target Visibility

There was a main effect for GROUP ($F(1,48) = 6.08$; $p = 0.015$) and TARGET VISIBILITY (Eyes open/eyes closed; EO/EC) ($F(1,48) = 73.85$; $p < 0.001$), i.e., PSS in patients and controls (solid platform, parallel feet, head upright) was significantly larger during eye closure than during eyes open. With the eyes open, the between-group analysis of PSS, however, did not reveal differences between both groups ($p = 0.295$). There was a significant interaction for TARGET VISIBILITY × GROUP ($F(1,48) = 6.35$; $p = 0.015$), i.e., PSS increased on eye closure more in patients than in controls. The difference for Romberg's ratio (PSS ratio of EC/EO) between both groups (patients: 3.40 ± 0.0.44; controls: 2.49 ± 0.16) failed to reach significance level ($T(48) = 1.96$; $p = 0.061$). In short, Romberg's ratio at baseline standing condition was larger in BVF.

Head Position

An ANOVA on the PSS with the within-subject factors HEAD POSITION and TARGET VISIBILITY and the between-subject factor GROUP revealed main effects for GROUP ($F(1,48) = 6.070$, $p = 0.017$), TARGET VISIBILITY ($F(1,48) = 67.340$, $p < 0.001$), HEAD POSITION ($F(2,47) = 6.086$, $p = 0.004$), and an interaction of TARGET VISIBILITY × GROUP ($F(1,48) = 6.635$, $p = 0.013$) but no interaction of HEAD POSITION × GROUP ($F(1,48) = 2.161$, $p = 0.124$) or HEAD POSITION × TARGET VISIBILITY ($F(2,47) = 2.974$, $p = 0.061$) and no triple interaction ($p > 0.9$).

A separate ANOVA on PSS with the eyes open revealed no main effect of GROUP but a main effect of HEAD POSITION ($F(2,47) = 9.845$, $p = 0.001$): PSS increased in the head down (nose down) ($p < 0.001$) and head up (nose up) position ($p = 0.001$) with no difference between the gravity-dependent (up vs. down) head positions (**Figure 2A**). With the eyes closed, there was a main effect for GROUP ($F(1,48) = 6.453$, $p = 0.014$), HEAD POSITION ($F(2,47) = 3.821$, $p = 0.027$) but no interaction HEAD POSITION × GROUP ($p > 0.4$). Analyzing Romberg's ratio (**Figure 2B**) there were main effects of GROUP ($F(1,48) = 6.748$, $p = 0.012$) and HEAD POSITION ($F(2,47) = 7.758$; $p = 0.001$) but no interaction of HEAD POSITION × GROUP ($F(2,48) = 0.793$; $p > 0.45$). In BVF patients, Romberg's ratio was lower in the head up position ($p = 0.033$) and the head down position ($p = 0.017$). In HC, Romberg's ratio was lower in the head down ($p = 0.039$) but not the head up position. Thus, gravity-dependent tonic head positions in the pitch plane increased postural sway in both groups (no interaction of HEAD POSITION × GROUP) but the increase in postural sway was larger in BVF on eye closure.

Head Shaking

Analyzing PSS during HEAD SHAKING there was a trend for a main effect of GROUP ($F(1, 48) = 3.887$, $p = 0.054$), a main effect for TARGET VISIBILITY ($F(1, 48) = 50.138$, $p < 0.001$) but no interaction, i.e., higher PSS in the eyes closed condition (**Figure 3A**). Romberg's ratio during HEAD SHAKING did not differ between groups ($p > 0.8$).

Comparing HEAD SHAKING to baseline (head erect, parallel stance) there was a main effect for GROUP ($F(1,48) = 5.242$, $p = 0.026$), TARGET VISIBILITY ($F(1,48) = 72.111$, $p = 0.001$) as well as for the interactions TARGET VISIBILITY × GROUP ($F(1,48) = 4.335$, $p = 0.043$) and HEAD SHAKING × TARGET

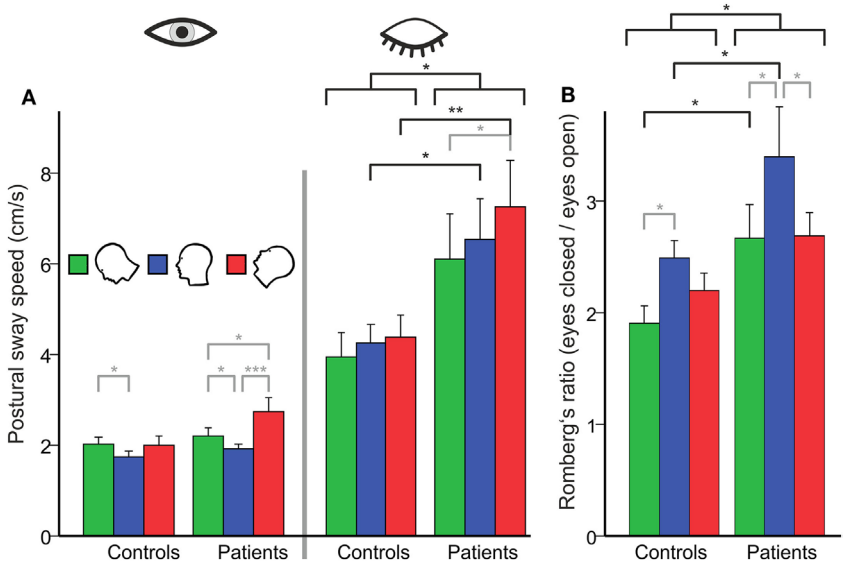

FIGURE 2 | **(A)** Head tilt (gravity)-related effects on postural control in subjects with (left side) and without (right) visual feedback and their relation [Romberg's ratio **(B)**]. **(A)** Using visual control there is no group difference in postural sway on the firm platform (PSS in centimeter per second). However, BVF patients show significant increases in PSS (left side) in the absence of visual control and during additional gravity effects (head tilt). **(B)** There is a significant higher Romberg's ratio (right) compared to controls, in contrast to other experimental conditions (dual task, head shaking). Error bars indicate SD; gray lines indicate within-subject differences, black lines indicate between-subject differences; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

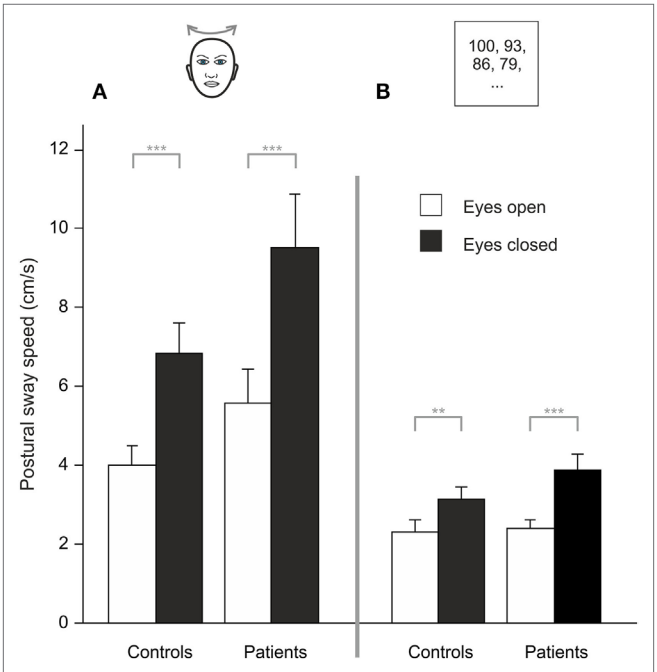

FIGURE 3 | During head shaking **(A)** and dual task **(B)**, patients did not differ from healthy participants but visual information (eyes open/eyes closed) improves postural stability; gray lines indicate within-subject differences; $^{**}p < 0.01$, $^{***}p < 0.001$.

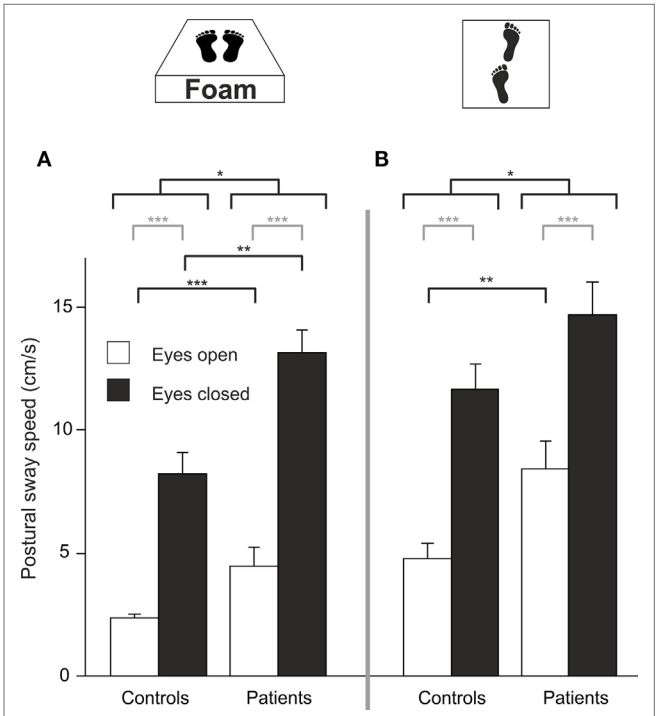

FIGURE 4 | Despite visual control patients show larger PSS on proprioceptive attenuation [foam **(A)**] and tandem stance **(B)**; gray lines indicate within-subject differences, black lines indicate between-subject differences; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

VISIBILITY ($F(1,48) = 4.303$, $p = 0.043$) but no triple interaction HEAD SHAKING × TARGET VISIBILITY × GROUP ($F(1,48) = 0.023$, $p > 0.8$). Romberg's ratio during HEAD SHAKING did not change to baseline condition ($F(1,48) = 3.164$, $p = 0.082$) and revealed no group-related differences ($F(1,48) = 1.920$, $p = 0.172$). In summary, postural unsteadiness during head shaking did not differ between groups.

Dual Task

Analyzing PSS during DUAL TASK, there was a main effect of TARGET VISIBILITY ($F(1,48) = 32.827$, $p < 0.001$) but no main effect of GROUP ($p > 0.15$) and no interaction of GROUP × TARGET VISIBILITY ($p > 0.08$), showing higher PSS for eyes closed condition (**Figure 3B**). Romberg's ratio did not differ between groups ($p > 0.13$).

Compared to baseline there was no main effect for the DUAL TASK condition ($F(1,48) = 0.105$, $p = 0.747$) and no GROUP difference ($F(1,48) = 4.002$, $p > 0.051$) but larger PSS during eye closure [TARGET VISIBILITY ($F(1,48) = 59.567$, $p = 0.001$)]. There were interactions of TARGET VISIBILITY × DUAL TASK ($F(1,48) = 12.765$, $p = 0.001$) and TARGET VISIBILITY × GROUP ($F(1,48) = 5.30$, $p = 0.026$) but no DUAL TASK × GROUP interaction ($F(1,48) = 1.843$, $p = 0.181$). There was a main effect for Romberg's ratio in GROUPs during DUAL TASK ($F(1,48) = 4.783$, $p = 0.034$) with larger ratios for BVF. Furthermore, Romberg's ratio was lower for DUAL TASK condition ($F(1,48) = 16.759$, $p < 0.001$) while there was no interaction DUAL TASK × GROUP ($p > 0.32$). All in all, cognitive distraction in the dual task paradigm did not dissociate postural performance of patients and controls.

Proprioceptive Deprivation (Foam)

Four patients required postural assistance and were excluded from this analysis. Analyzing PSS during sensory deprivation by foam, there were main effects of GROUP ($F(1,42) = 19.023$, $p < 0.001$) and of TARGET VISIBILITY ($F(1,42) = 133.218$, $p < 0.001$) but no interaction—showing higher PSS for patients and for eyes closed condition (**Figure 4A**). Romberg's ratio during FOAM did not differ between groups ($p > 0.6$). Comparing PSS to baseline, there was a main effect of the FOAM paradigm ($F(1,42) = 138.025$, $p < 0.001$) and of TARGET VISIBILITY ($F(1,42) = 169.573$, $p < 0.001$), with GROUP differences ($F(1, 42) = 14.278$, $p < 0.001$), significant interactions for TARGET VISIBILITY × FOAM ($F(1,42) = 34.104$, $p < 0.001$), for FOAM × GROUP ($F(1,42) = 14.654$, $p < 0.001$) and for TARGET VISIBILITY × GROUP ($F(1,42) = 4.661$, $p < 0.037$). Romberg's ratio on FOAM showed no significant interaction FOAM × GROUP ($p = 0.135$) and no main effects of FOAM ($p > 0.076$) or group differences ($p > 0.39$). With the eyes open, patients showed larger PSS compared to HC ($T(42) = -3.454$, $p = 0.003$). Alltogether, postural sway of patients increased during proprioceptive deprivation by foam compared to controls, with additional significant enlargements in the patients in the absence of visual control (target visibility) on postural stability.

Tandem Stance

Eight patients required postural assistance and were excluded from this analysis. Analyzing PSS during tandem stance, there were main effects of GROUP ($F(1, 37) = 6.164$, $p = 0.016$) and of TARGET VISIBILITY ($F(1,37) = 128.554$, $p < 0.001$) but no interaction—showing higher PSS for patients and for the eyes closed condition (**Figure 4B**). Romberg's ratio during tandem stance was higher for HC than for patients ($T(36) = 2.141$, $p = 0.039$). Compared to baseline, there was a main effect of TANDEM STANCE ($F(1,37) = 164.119$, $p < 0.001$), GROUP ($F(1,37) = 5.149$, $p = 0.029$) and TARGET VISIBILITY ($F(1,37) = 169.792$, $p < 0.001$), an interaction for GROUP × TANDEM STANCE ($F(1,37) = 7.022$, $p = 0.012$), an interaction for TARGET VISIBILITY × TANDEM STANCE ($F(1,37) = 32.609$, $p < 0.001$) but no triple interaction for GROUP × TANDEM STANCE × TARGET VISIBILITY ($p > 0.2$). For Romberg's ratio, there was no interaction of TANDEM STANCE × GROUP ($p > 0.12$) and no main effects of GROUP ($p > 0.42$) and TANDEM STANCE ($p > 0.27$). Thus, patients showed larger postural instability on tandem stance than controls, irrespective of visual control (target visibility).

Postural Sway As a Predictor for Vestibular Hypofunction

In a multiple regression using all conditions postural sway (PSS) explained 70% of the variance of the VOR gain ($R^2 = 0.704$, $F(14,38) = 4.085$, $p = 0.001$). The best—and the only significant—predictor for vestibular hypofunction (VOR gain) was the standing on foam condition with the eyes closed ($R^2 = 0.358$, $F(1,38) = 20.642$; $p < 0.001$). Accordingly, PSS of BVF patients increased in the foam paradigm on eye closure with the severity of vestibular impairment (VOR gain reduction, $n = 18$, $r = -0.486$, $p = 0.041$) (**Figure 5**) but not with disease duration ($p > 0.055$). In none of the experimental conditions, PSS ($p = 0.557$) or Romberg's ratio ($p = 0.558$) correlated with disease duration.

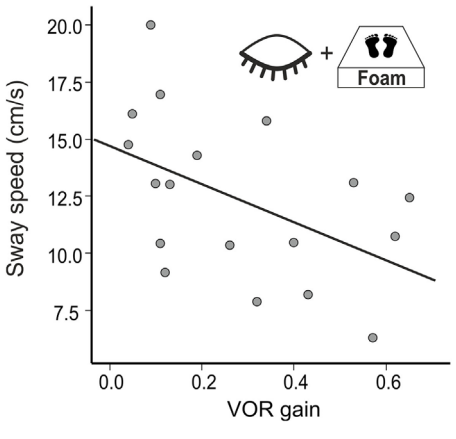

FIGURE 5 | Postural sway speed increases with the severity of vestibular impairment (VOR gain).

DISCUSSION

Sensory control of stable body posture is maintained by error signals deriving from the vestibular, visual, and proprioceptive system (44). They need to be processed, integrated, and weighted as a function of individual demand which may change in disease. Our main findings in our BVF patients were as follows: (1) postural control in BVF using visual and proprioceptive feedback was indistinguishable from HCs. (2) Without visual control BVF, patients consistently showed increased postural sway. (3) Romberg's ratio at baseline standing condition was larger in BVF. (4) Gravity-dependent tonic head positions in the pitch plane increased postural sway in both groups but the increase in postural sway was larger in BVF on eye closure. (5) Postural unsteadiness during head shaking tended to be larger in patients. (6) Weakening proprioceptive feedback (foam) on postural control heavily increased postural sway in BVF, independent of visual control. Combined proprioceptive and visual deprivation increased postural unsteadiness. (7) Postural control during attentional distraction by the dual task condition did not differ between the groups. (8) Tandem stance heavily destabilized BVF patients.

In comparison to previous studies on the postural control in BVF with proprioceptive and/or visual suppression (22, 45) this study sheds new light on the question how BVF patients stabilize stance when vestibular otolith (head tilt) or SSC stimuli (head shaking) or cognitive distraction tasks are applied during postural control. This constitutes the experimental ground for suggestions for vestibular rehabilitation recommending a decrease of the over-dependence on surface somatosensory inputs by increasing the use of remaining vestibular input (46).

Visual Control on Posture

From a clinical point of view, it is important to realize that postural control in BVF was indistinguishable from HCs as long as patients can use proprioceptive and visual feedback. Postural control of our BVF patients heavily depended on visual feedback as they showed a strong increase of postural sway on eye closure in all (even in the baseline) conditions compared to the age-matched HCs. This is in line with previous studies (22, 46–50). This increase is reflected by Romberg's ratio which is used as an indicator of visual and proprioceptive contribution to postural stability (42). In the baseline condition, it was larger in BVF. This dissociates postural control in BVF from patients with vestibulo-cerebellar disorders, e.g., downbeat nystagmus whose increase in postural sway on eye closure (Romberg's ratio) does not differ from HCs (39). Thus, postural behavior in postural ataxia in degenerative vestibulo-cerebellar disorders and BVF can be distinguished based on (i) baseline standing and (ii) Romberg's ratio.

Vestibulo-Spinal Control of Posture

Head Tilts

Head tilts in gravity-dependent positions in the pitch plane significantly increased postural sway in both groups. Head tilts activate both otolith ("head-in-space") signals and proprioceptive neck ("head-on-trunk") afferents. Both signals are used to calculate

the position of the trunk relative to earth-based coordinates such as the line of gravity ["trunk-in-space" (51)]. Vestibulopathic subjects are thought to estimate an erroneous trunk position (trunk-in-space) leading to postural imbalance (52).

The gravity-dependent increase in sway was found in both groups with visual feedback indicating that (i) impaired otolith signal processing in chronic BVF patients has little impact on postural control once the eyes are open and (ii) other factors might counterbalance otolith input to balance control. For example, increased gain in processing of afferent neck proprioceptive signals could substitute reduced/missing otolith contribution in stabilizing posture during head tilt. This intersensory shift could reflect one mechanism of vestibular compensation (24, 53). Another example could be visually mediated perception of body's posture [e.g., shifted subjective postural or body vertical (54)]. Vision can recalibrate the vestibular reafference signal used to reestablish postural equilibrium (55). Without visual feedback, however, head off-vertical axis weakened postural control in BVF suggesting that deficient otolith signals (reduced ocular vestibular-evoked myogenic potentials) cannot be used sufficiently to stabilize posture. In both groups, Romberg's ratio was largest in the standard head erect position, which is probably related to the larger sway of BVF in the gravity-dependent head positions at baseline with the eyes open, resulting in a smaller increase on eye closure.

Head Shaking

Head shaking modulates horizontal SSC input to vestibulo-spinal control of posture. It also activates proprioceptive neck afferents. Based on the assumption that postural control relies on visual information during head shaking we suspected that head shaking may lead to larger postural sway in BVF due to impaired gaze stabilization. In both groups postural sway increased with head shaking. With the eyes open, postural control in BVF patients did not differ from HCs, despite reduced VOR gain. This is in line with monkeys suffering from mild vestibular ablation which also showed no increase (in fact even a decrease) in postural sway during quiet stance (56) and horizontal head shaking (57). This has been explained by increased muscle-co-contraction ("stiffness"), using a head-fixed-to-foretrunk strategy (57, 58). However, our patients had incomplete but severely reduced VOR gain. Vestibular hypofunction disturbs head-movement related visual acuity in the light. This dynamic visual acuity gets smaller with decreasing VOR gain, at least with passive head movements (59). As our patients were severely impaired on both sides dynamic visual acuity should have been impaired. On a first glimpse, this could imply that visual contribution to postural control during head shaking in our patients is small, despite increased dependence of postural control on visual feedback in BVF (22, 60). However, our BVF patients performed active head movements during head shaking which may result in much smaller impairment and is possibly related to central compensation (61). In fact, 46% of BVF patients had normal dynamic visual acuity during active VOR which may be related to central pre-programming of eye movements or the use of efference copy signals during predictive head movements (62). This may explain why head shaking in our BVF patients had only little impact on postural control. It may have been different if we used passive head movements unpredictable in direction and velocity. This is in contrast to recent animal studies in monkeys suffering from severe bilateral vestibulopathy which showed an increased postural sway during active horizontal head shaking which could be reversed by prosthetic electrical stimulation that partially restored head velocity information (57). Alternatively, active head shaking might have also elicited anticipatory postural adjustments that prevented increased postural sway in BVF (63, 64).

Proprioceptive Control of Posture

Weakening proprioceptive feedback on postural control by standing on foam showed much stronger postural imbalance (PSS) in BVF compared to controls, even with visual feedback support. This is in line with the enhanced proprioceptive dependence of postural control in chronic BVF (22, 65) and the destabilizing effect of additional diseases affecting proprioceptive feedback control on posture, e.g., in polyneuropathy (66). In combined deprivation of visual and proprioceptive feedback signals (foam condition with the eyes closed), some BVF patients required short postural assistance and needed to be excluded. This explains the high sensitivity (80%) of the "Romberg's test on foam rubber" in BVF (67) as it provokes a stronger dependence of postural control on vestibular input. In healthy subjects, normal VOR is sufficient to maintain balance under these multisensory deprivations but BVF patients fall off the mattress if VOR is heavily impaired. Accordingly, there was an increase of postural sway the stronger VOR gain was reduced (**Figure 5**). Therefore, patients with severe BVF should be informed about increasing postural unsteadiness and risk of falls when they lack firm support beneath their feet or suffer from additional polyneuropathy.

Dual Task Effects on Posture

Dual postural-cognitive task conditions have been used to study the relationship between attention and postural control. This relation is highly age-dependent (68): older subjects have higher attentional demands for postural control and show slower reaction times during combined postural-cognitive task (69). This leads to a higher risk of falling during standing and walking while talking (70). Our BVF patients could maintain postural control during attentional distraction in the dual task condition indistinguishable from age-matched HCs as long as visual and proprioceptive feedback was assured. This distinguishes BVF patients from the elderly (71), cerebellar patients (72) or patients with phobic postural vertigo (PPV) (73). The increased and inadequate use of sensory feedback in PPV patients suspected to cause their postural imbalance normalizes by distracting cognitive tasks (74, 75). This is not the case in BVF patients who largely rely on closed-loop mechanisms of postural control. This dependence on proprioceptive feedback may probably be even stronger as they showed a higher Romberg's ratio in the dual task condition compared to controls. Unfortunately, severity of postural imbalance of our BVF patients did not allow us to investigate whether they maintain stance under more challenging dual task conditions (e.g., on foam).

Increased Motor Demand on Postural Balance (Tandem Stance)

Increased multisensory and motor postural demands (tandem stance) heavily destabilized BVF patients. Postural control of BVF patients was highly impaired compared to HCs, even when visual and proprioceptive input is used. Additional visual deprivation elicited a stronger postural imbalance compared to the HC group. Tandem stance requires multisensory integration, including vestibular input as visual and proprioceptive feedback is not sufficient to stabilize stance in BVF. This is in line with the concept of vestibular compensation in which postural control in vestibular failure is compensated by improving the sensory weight of unaffected sensory systems (24), i.e., they rely stronger on visual and proprioceptive feedback sources to maintain postural control (60). Accordingly, patients with uni-sensory deficit have a smaller risk of falling that patients with impairment of multiple sensory inputs required for postural control (66). It remains to be investigated whether the increased risk of falls in BVF (66) is related to increased co-contractions of antagonistic muscle groups as found in patients with cerebellar disease (72) and PPV (75).

Limitations of the Study

Individual BVF patients may vary in the extent they exercise vestibular rehabilitation and accordingly they may vary in the magnitude of vestibular compensation. At the time of recording, vestibular compensatory mechanisms should have been established with respect to the average disease duration of our patients (3.1 years), if they developed at all. Therefore, we cannot specify how individual exercise influenced the variability of postural sway but can only refer to the group effects.

CONCLUSIONS

In conclusion, diagnosis of BVF patients is often missed possibly because postural control in BVF at baseline is indistinguishable from HCs once visual and proprioceptive input is provided. In comparison with cerebellar DBN patients, BVF patients show a stronger visual dependency (increase in Romberg's ratio). The best postural predictor for BVF is the condition with standing on foam with the eyes closed. Accordingly, our data suggest that BVF should be tested with the eyes closed while standing on foam (mattress test). The strong dependency of postural control in BVF on proprioceptive and visual cues should be taken into consideration in vestibular rehabilitation.

ETHICS STATEMENT

The study protocol was approved by the institutional Ethics Committee of the University of Lübeck (project ID: 11-119; February 10, 2012). It was in accord with the ethical guidelines listed in the declaration of Helsinki and its subsequent amendments. This study was carried out in accordance with the recommendations of the Ethics Committee of the University of Luebeck (https://www.uni-luebeck.de/forschung/kommissionen/ethikkommission/sonstige-studien.html) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University of Luebeck.

AUTHOR CONTRIBUTIONS

AS contributed to study design, methodology, statistical analysis, critical reviewing, and editing of the manuscript. JFW and NMJ contributed to methodology, data acquisition, statistical analysis, and reviewing of manuscript. CH contributed to conceptualization and study design, project administration, data acquisition, supervision, drafting, editing, and approving the final writing of the manuscript.

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Bilateral Vestibulopathy in Superficial Siderosis

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Background: Superficial siderosis (SS) is a rare condition in which hemosiderin, an iron storage complex, is deposited in neural tissues because of recurrent subarachnoid bleeding. Hemosiderin deposition in the vestibulocochlear nerve (CN VIII), brain, spinal cord and peripheral nerve can cause sensorineural hearing loss (SNHL) and postural imbalance, but much remains unknown about the vestibular manifestations of SS.

Objectives: To report the clinical course, cochleovestibular status, and patterns of vestibulopathy during follow-up of a relatively large case series, and to discuss the possible pathophysiological mechanism of vestibular deterioration.

Methods: Six patients diagnosed with SS by magnetic resonance imaging (MRI) were enrolled. Their medical records and radiological findings were retrospectively reviewed, particularly in terms of progression of the vestibulocochlear manifestations and the radiological characteristics.

Results: All six patients had SNHL. Five of them exhibited progressive hearing loss over years, which was asymmetric in four. On their most recent evaluations, patients showed cerebellar ataxia with combined central and peripheral vestibulopathy on both sides ($n = 4$), a bilateral peripheral vestibulopathy ($n = 1$) or isolated central vestibulopathy ($n = 1$). Notably, the former four patients showed an evolution of isolated central vestibulopathy into combined central and peripheral vestibulopathy. Hypo-intense lesions on T2 weighted MRIs were evident around the cerebellum in all patients, but such lesions were observed around the brainstem in five and the CN VIII in four. The cochlea-vestibular dysfunction generally progressed asymmetrically, but no left-right asymmetry was evident on MRI.

Conclusions: SS typically presents as bilaterally asymmetric, progressive cochleovestibular dysfunction with cerebellar ataxia. The pattern of vestibular dysfunction is usually combined central and peripheral vestibulopathy on both sides. Thus, precise identification of audiovestibular dysfunction and central signs is essential in SS, and patients with SS should undergo regular, comprehensive neurotological evaluation to optimize their treatments and prognosis.

Keywords: superficial siderosis, vertigo, hearing loss, cerebellar ataxia, vestibulopathy

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INTRODUCTION

Superficial siderosis (SS) is a rare condition in which hemosiderin, an iron-storage complex, is deposited in neural tissues because of recurrent subarachnoid bleeding (1). SS may be considered as a central nervous system (CNS) disease that clinically manifests as cerebellar ataxia, pyramidal signs, and dementia (2). However, the symptoms can vary depending on the distribution of hemosiderin deposition; deposition in the cerebellum and vestibulocochlear nerve (CN VIII) can cause sensorineural hearing loss (SNHL) in addition to cerebellar ataxia and postural imbalance (3, 4). Furthermore, patients with SS mostly experience deterioration of vestibular function on both sides (5, 6). A recent case series showed that chronic bilateral central vestibulopathy coexisted with peripheral vestibulopathy, especially when hearing impairment was evident (7). However, another study reported that only bilateral peripheral vestibulopathy is evident in SS patients (8). Such inconsistent results suggest that misidentification of vestibular status in SS patients may pose diagnostic and therapeutic challenges, especially during rehabilitation therapy employing the vestibulo-ocular reflex (VOR) in which identification of the precise vestibular status is of critical importance (5, 9).

Although hemosiderin deposition in the CNS and around CN VIII is associated with vestibular manifestations, most publications have focused on audiological features including hearing deterioration (10). To date, vestibular deficits have been reported in less than 30 patients with SS, mostly without follow-ups for vestibular function (3, 5–9, 11–22). To the best our knowledge, not much attention has been paid to the evolution of vestibular function and its pathophysiological mechanisms in patients with SS.

Herein, we explore the progression of balance and hearing function, and patterns of vestibulopathy during follow-up of six patients. We also suggest a possible pathophysiological mechanism for the evolution of vestibular features.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed the charts of eight patients diagnosed with SS in Seoul National University Bundang Hospital between 2005 and 2016. Of these, long-term systematic neurotological evaluations were scheduled for six patients (the subjects of the present study). One included patient (subject 2) was previously described in a case report that we authored (23). This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (no. IRB-B-1710-427-106) and was conducted in accordance with all relevant tenets of the Declaration of Helsinki.

Neurotologic Evaluation

Pure tone audiometry (PTA) and speech audiometry (SA) were performed. Hearing thresholds were calculated by averaging the PTA thresholds at 0.5, 1, 2, and 3 kHz based on the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines. Progression of hearing loss was defined as declines in the audiometric thresholds >10 dB HL at three frequencies, ≥15 dB HL at two frequencies, and/or ≥20 dB HL at one frequency, over the follow-up period. The hearing thresholds for seven different frequencies (0.25, 0.5, 1, 2, 3, 4, and 8 kHz) were evaluated in a soundproof booth, and the audiometric configuration of each subject categorized as flat (the thresholds across the tested frequencies did not vary by >20 dB HL); high tone hearing loss (equal or successively increasing thresholds from 0.25 to 8 kHz and the difference between the thresholds at 250 and 8,000 Hz was >20 dB HL); and low tone hearing loss (equal or successively decreasing thresholds from 0.25 to 8 kHz and the differences between the thresholds at 250 and 8,000 Hz were >20 dB HL) (24).

Eye movements were assessed using a video-oculography (VOG) system or a videonystagmography (VNG) system (SMI, Teltow, Germany; or ICS Medical, Schaumburg, IL, USA) with patients in the sitting position during both spontaneous and induced nystagmus. Spontaneous nystagmus (SN) was analyzed both with and without fixation; all subjects attempted to look straight ahead. Gaze-evoked nystagmus (GEN) was also evaluated. Induced nystagmus was evaluated during positioning, head-shaking, and when vibration was applied to each side of the mastoid tip for 10 s with the aid of a VVIB 100 device (Synapsis, Marseille, France). Head-shaking nystagmus (HSN) was assessed 15 s after passive head-shaking with the neck flexed by 30° at a frequency of ≥2 Hz.

The bithermal caloric test was performed with water caloric stimulator NCI480 (ICS medical, Schaumburg, IL, USA) in the supine position with head elevation at 30°C. Caloric irrigation was delivered in the order of right cool (30°C), left cool (30°C), right warm (44°C), and then left warm (44°C) for 30 s with a flow rate of 300 ml/min. The maximum slow-phase velocity (SPV) of nystagmus was calculated after irrigation at each temperature, and canal paresis (CP) was determined using Jongkees' formula (25). If nystagmus was not induced during caloric stimulation, ice water test was conducted by using 40 ml of ice water (4°C) irrigation for 30 s in the supine position and then in the prone position to see if the direction of induced nystagmus changes (26).

The rotator chair test was performed in the earth vertical axis rotation unit (CHARTR RVT system, ICS Medical). The subject's head was positioned and restrained on the head rest with neck flexion by 30°C. Horizontal VOR was recorded with an electronystagmography system. Rotational stimulus was sinusoidal harmonic acceleration (SHA), and impulse acceleration and deceleration (step velocity). On SHA test, peak velocity was 60°C per second and rotation frequencies were 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz. Parameters of SHA test included gain, phase, and symmetry (27). Test protocol of the step velocity stimulation was angular acceleration of 100°C per second for 1 s, rotation at a constant velocity (100°C per second) for 60 s, and then deceleration to 0 degree per second within 1 s. Parameter for rotational test was time constant of nystagmus diminution after impulse acceleration and deceleration. The time constant after impulse acceleration toward the lesion side and that after impulse deceleration toward the healthy side were averaged (ipsilesional time constant, Tci), and the time constant

after impulse acceleration toward the healthy side and that after impulse deceleration toward the lesion side were averaged (contralesional time constant, Tcc). Normal value of Tc (mean T ± 2SD) obtained from this unit ranged from 11 to 21 s (28).

Head impulse test (HIT) was performed using a video HIT system for acquisition and analysis of the eyeball and head movements (SLMED, Seoul, Korea). The examinees were instructed to stare at a stationary target at a distance of 1 m in front of them while short lasting head rotations around an earth-vertical axis were randomly applied from behind the examinees. The test was repeated at least 10 times on each side in an unpredictable direction with 5–10º and peak accelerations of 750–6000º/sec (29). Only head rotations with a defined waveform within a predefined velocity and acceleration window were accepted. The movements of the right eyeball and the head were recorded. The area under the velocity curves of these two movements was obtained from head-impulse onset to the back crossing of zero. VOR gain on video HIT was defined as the ratio of the area under the velocity curves of the right eye to that of the head (30). The VOR gains were measured for individual trials as the ratio of the mean eye velocity divided by the mean head velocity during a 40-ms window centered at the time of peak head acceleration (31). We defined abnormal HIT findings when the mean VOR gain was less than the mean minus 2 SDs of the control data (i.e., <0.88 for the HC, <0.75 for the AC, and <0.77 for the PC).

Cervical vestibular-evoked myogenic potentials (cVEMP) were recorded with the subject supine on a bed with the head raised ∼30° from the horizontal and rotated contralaterally in order to activate the sternocleidomastoid (SCM) muscles. The surface EMG activity was measured from an active electrode placed over the belly of the contracted SCM after subtracting activity from a reference electrode located on medial clavicle. A ground electrode was attached to the forehead. cVEMP were recorded using a Nicolet Viking Select unit (Nicolet-Biomedical, Madison, WI, USA). A short burst of alternating tone (110 dB nHL, 123.5 dB SPL, 500 Hz, rise time = 2 ms, plateau = 3 ms, fall time = 2 ms) was applied at 2.1 Hz monaurally via a headphone. The analysis time for each stimulus was 50 ms and responses elicited by up to 80 stimuli were averaged for each test. The signal was bandpass filtered at 30–1,500 Hz, and the mean values of at least two trials were obtained from each ear for all participants. During each recording, the amplified EMG activities of the SCM were also monitored and digitized at 1 kHz using an analog-todigital converter (NI PCI-4461, National Instruments, Austin, TX, USA). The LabVIEW program (National Instruments, Austin, Texas, USA) was used to analyze the peak to peak amplitudes and calculate the mean tonic activation during the recording. The absolute cVEMP amplitude was then normalized against the mean tonic activation of the SCM during the recording. To compare the normalized p1 – n1 amplitudes of the cVEMP between the sides, the interaural difference ratio of the normalized amplitudes (IAD, %) was also calculated as [(AR – AL) / (AR + AL) × 100], where AR and AL are the normalized p1-n1 amplitude on the right and left sides, respectively. Both the p1 and n1 peak latencies were also calculated (32). In this study, we defined normal range of cVEMP when the IAD ratio was less than 22.5%.

Unilateral vestibular hypofunction (UVH) was diagnosed if catch-up saccades in a single direction were evident on HIT; and if the canal paresis was >25% or the sum of the maximum SPV on a single side (R44+R30 or L44+L30) was <10°/s. Bilateral vestibular hypofunction (BVH) was diagnosed when the sum of the maximum SPVs under four conditions (R44+R30+L44+L30) was <12°/s, or if no VOR was evident on the rotation chair test.

Radiologic Evaluation

Magnetic resonance imaging (MRI) was performed using a 3-T MRI scanner (Achieva and Ingenia; Philips, Best, the Netherlands) with a 32-channel SENSE head coil (Philips Healthcare). All subjects underwent brain MRI with T2-weighted imaging (TR, 3,000 ms; TE, 80 ms; FOV, 185 × 230 mm^2; acquisition matrix, 420 × 375; slice thickness, 5 mm; slice gap, 1 mm; flip angle, 90°) and/or $T2^*$-gradient recalled-echo (GRE) imaging (TR, 800 ms; TE, 18 ms; FOV, 185 × 230 mm^2; acquisition matrix, 256 × 256; slice thickness, 5 mm; slice gap, 1 mm; flip angle, 23°). Thin-section internal auditory canal imaging was additionally performed in 4 subjects using T2-weighted volume isotropic turbo spin-echo acquisition (VISTA) (TR, 2,000 ms; TE, 250 ms; FOV, 160 × 160 mm^2; acquisition matrix, 228 × 228; slice thickness, 0.7 mm; overlapping, 0.35 mm; flip angle, 90°) and balanced turbo field-echo (bTFE) (TR, 8.5 ms; TE, 4.3 ms; FOV, 150 × 150 mm^2; acquisition matrix, 224 × 336; slice thickness, 1.4 mm; overlapping, 0.7 mm; flip angle, 50°) sequence. A neuroradiologist blinded to the clinical information assessed the extent and the location of hemosiderin deposits including cerebellum, brainstem, and CN VIII.

RESULTS

Case Reviews

The clinical characteristics, clinical courses, neurotological evaluations, and laboratory data of our six SS subjects are summarized in **Tables 1–4**.

Subject 1 (F/78)

A 78-year-old female patient presented with cerebellar ataxia without hearing loss 11 years prior to her initial neurotological evaluation. Four years later, symmetrical mild hearing loss in both ears was observed on PTA. Speech discrimination (SD) also showed 92% on both ears. However, her hearing did not deteriorate further during follow-up PTA (**Figure 1A**). On VNG examination, spontaneous down-beating nystagmus (DBN) and right-beating nystagmus were documented, the intensities of which increased upon head-shaking, reflecting perverted DBN. Also, GEN, characterized by DBN augmentation during lateral- and up-gazing, was evident during the most recent examination. The ocular motor test revealed hypometric saccades with low-pursuit gain. The bithermal caloric test result was normal at initial evaluation; however, the test results deteriorated bilaterally during follow-up. During her most recent evaluation, the rotator chair test was compatible with BVH. Similarly, cVEMP

TABLE 1 | Clinical characteristics and clinical course in our subjects with superficial siderosis.

Subject	Sex	Age	Etiology of SS (onset, ago)	Initial neuro-otologic symptoms	Duration: From event to initial symptoms	Sequential symptoms (Time duration from initial symptom)	Audiologic manifestations	
							Characteristics	Duration of progression
1	F	78	Idiopathic	CA	-	B) HL (4years) Oscillopsia (9years)	Non-progressive symmetric SNHL	Not affected
2	M	38	Head trauma (14 years ago)	B) HL, disequilibrium	2 years	Hyposmia (1year)	Progressive asymmetric SNHL	1 year
3	F	42	Brain surgery due to chordoma (18 years ago)	CA	10 years	B) HL (3 years) B) dysesthesia (5 years)	Progressive asymmetric SNHL	8 months
4	F	52	Brain hemorrhage due to cavernous hemangioma (20 years ago)	L)HL	8 years	CA, disequilibrium (1 year)	Progressive asymmetric SNHL	5 years
5	F	53	Subarachnoid bleeding in sacrum level (6 years ago)	CA, B) HL	2 years	Diplopia (3 months)	Progressive symmetric SNHL	2 years
6	M	65	CNS surgery due to lumbar cystic tumor (20 years ago)	CA	10 years	R) HL (7 years)	Progressive asymmetric SNHL	1 year

M, male; F, female; B, bilateral; R, right; L, left; CA, cerebellar ataxia; HL, hearing loss; SNHL, sensorineural hearing loss.

TABLE 2 | Neurotologic evaluations in our subjects with superficial siderosis[†].

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
VIDEO NYSTAGMOGRAPHY						
Spontaneous	DB, RB	–	subtle DB	–	–	subtle DB
Gaze-evoked	DB	–	DB, RB/ DB, LB	–	RB/LB	–
Vibration	–	–	DB, RB	LB	LB	DB, RB
Head shaking	DB, RB	–	DB	LB	-	DB
Head thrust	–	BCU	BCU	-	BCU	BCU
OCULAR MOTOR TEST						
Pursuit gain	BD	Normal	BD	BD	BD	Normal
Saccade	Hypometria	Normal	Hypermetria	Normal	Hypometria	Hypermetria

[†] *If positive signs of each variables were identified at least once during several neurotologic evaluations, we documented the positive findings in* ***Table 2****. DB, down beating; RB, right beating; LB, left beating; BCU, bilateral catch up saccade; BD, bilaterally decreased.*

test showed normal symmetric response on first examination; however, IAD (the right value was 47.3% that of the left) suggestive of right-sided saccular dysfunction were evident at the 2-year follow-up evaluation. She began to experience oscillopsia recently. T2-weighted and GRE images revealed superficial siderosis around the cerebellum and brainstem, additionally, both CN VIII were shown based on bTFE images of internal auditory canals (**Figure 2A**).

Subject 2 (M/38)

Fourteen years ago, this patient suffered severe head trauma while engaging in whitewater rafting. Two years thereafter, he developed sudden hearing loss in the left ear and disequilibrium. Subsequently, he started to have hyposmia 3 years after trauma. Initial PTA revealed total deafness in the left ear and mild SNHL of 30 dB HLin the right ear. Hearing of the right ear also deteriorated to profound deafness over the following year (**Figure 1B**). Cochlear implantation was eventually performed. Postoperative open-set speech perception improved compared with the preoperative results: sentence test, 76%; mono-syllabic word test, 60%; bi-syllabic word test, 50%. On an exhaustive VNG examination, no definite nystagmus was documented. In addition, the ocular motor test revealed normal saccade amplitude and latency. Bithermal caloric tests revealed bilateral canal paresis, and the direction of nystagmus on supine and prone position was not changed during the ice-water test. Notably, VEMP elicited responses from both ears but the left was 52.1% smaller than that of the right on amplitude. At the 6-year follow-up, cVEMP response was not evident on either side. T2-weighted and GRE images revealed superficial siderosis around

TABLE 3 | Laboratory evaluations in our subjects with superficial siderosis.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
CALORIC TEST (INITIAL)						
SPV(RW+RC), deg/sec	37	4	1	32	9	38
SPV(LW+LC), deg/sec	34	0	1	31	0	36
Ice water test		NR	NR		NR	
CALORIC TEST (LAST F/U)						
SPV(RW+RC), deg/sec	4			2		N/A
SPV(LW+LC), deg/sec	4			0		N/A
Ice water test	NR			NR		N/A
ROTATOR CHAIR TEST (LAST F/U)						
Gain	Decrease	Decrease	Decrease	Decrease	Decrease	N/A
Phase	Lead	Lead	Lead	Lead	Lead	N/A
Symmetry	Symmetry	Symmetry	Symmetry	Symmetry	Symmetry	N/A
STEP VELOCITY TEST						
CW Tc (sec)	4.58	1.22	–	4.67	2.37	N/A
CCW Tc (sec)	4.16	1.74	–	5.55	2.39	N/A
VEMP (INITIAL)						
Response (Rt/Lt)	(+/+)	(+/weak)	(+/+)	(+/+)	(+/+)	(+/+)
IAD (%)	5.8	52.1	12.1	4.6	18.3	36.5
VEMP (LAST F/U)						
Response (Rt/Lt)	(weak/+)	(–/–)	N/A	(weak/+)	(–/–)	N/A
IAD (%)	47.3	–	N/A	47.8	–	N/A
VIDEO HIT						
LHC gain	N/A	N/A	N/A	N/A	0.25	1.08
RHC gain	N/A	N/A	N/A	N/A	0.27	1.21
LAC gain	N/A	N/A	N/A	N/A	0.15	0.82
RAC gain	N/A	N/A	N/A	N/A	0.15	1.02
LPC gain	N/A	N/A	N/A	N/A	0.13	0.84
RPC gain	N/A	N/A	N/A	N/A	0.24	0.89

SPV, slow-phase velocity; RW, right warm; RC, right cold; LW, left warm; LC, left cold; F/U, follow-up; CW Tc, clockwise time constant; CCW Tc, counter-clockwise time constant; VEMP, vestibular-evoked myogenic potentials; HIT, head impulse test; LHC, left horizontal canal; RHC, right horizontal canal; LAC, left anterior canal; RAC, right anterior canal; LPC, left posterior canal; RPC, right posterior canal; N/A, not available; NR, no response

the cerebellum and brainstem, additionally, both CN VIII were shown based on bTFE images of internal auditory canal.

Subject 3 (F/42)

This patient was diagnosed with a cervical spine chordoma 16 years ago and underwent several operations for tumor resection over the next 3 years. Seven years after her surgeries concluded, she presented with cerebellar ataxia. Over the following 3 years, she had developed bilateral hearing loss. She subsequently reported dysesthesia after bilateral hearing loss. The initial PTA revealed asymmetric SNHL (deafness and 0% SD in the right ear and 65 dB HL threshold and 4% SD in the left ear, **Figure 1C**). During an exhaustive VNG examination, subtle spontaneous DBN, and GEN, characterized by DBN with ipsilateral horizontal nystagmus during lateral gaze, were documented. The ocular motor test revealed a hypermetric saccade with a low pursuit gain. The bithermal caloric test revealed bilateral caloric paresis at initial evaluation, and the direction of nystagmus did not change during the ice-water test. The cVEMP responses were normal and the IAD was within the normal range on initial evaluationT2-weighted and GRE images revealed SS in the lining of the cerebellum, brainstem, and both CN VIIIs probably suspected by severe hemosiderin deposition surrounding internal auditory canal (**Figure 2B**).

Subject 4 (F/52)

This patient had a history of brain hemorrhage caused by a cavernous hemangioma in the right temporal lobe. Left side hemiparesis developed after a decompressive craniotomy. Eight years later, she initially presented with left-side hearing loss. One year later, she complained of cerebellar ataxia and disequilibrium. Initial PTA revealed unilateral SNHL (Rt:10dB HL and 100% SD, Lt: 60 dB HL and 36% SD). She then developed bilateral deafness over the following 5 years (**Figure 1D**). Cochlear implantation was eventually performed. Postoperative open-set speech perception improved compared with the preoperative results: sentence test, 70%; mono-syllabic word test, 60%; multi-syllabic word test, 50%. No specific nystagmus was noted on SN, GEN, HSN, and VIN test. The ocular motor test revealed

TABLE 4 | The patterns of vestibulopathy, presence and characteristics of hearing impairment, and radiologic assessment.

Subject	Patterns of vestibulopathy (initial)	Patterns of vestibulopathy (F/U)	Hearing impairment		MRI finding (hemosiderosis deposition)		
			SNHL[†] (R/L)	OAE	Cerebellum	Brainstem	CN VIII
1	Central	B) combined	M/M	N/A	Yes	Yes	Yes
2	B) peripheral	B) peripheral	P/P	NR	Yes	Yes	Yes
3	B) combined	B) combined	MS/P	N/A	Yes	Yes	Yes
4	B) combined	B) combined	P/P	NR	Yes	Yes	Yes
5	B) combined	B) combined	P/P	N/A	Yes	Yes	unclear
6	Central	Central	m/P	NR	Yes	No	No

[†] *We described final follow-up status based on pure tone audiogram. B, bilateral; R, right; L, left; F/U, follow-up; CN VIII, vestibulocochlear nerve; m, mild; M, moderate; MS, moderate to severe; P, profound; N/A, not available; NR, no response.*

bilaterally decreased pursuit gain without saccades. Both ears responded normally to bithermal caloric irrigation; however, right caloric paresis developed over the years and bilateral caloric paresis was evident at the most recent examination (**Figure 3**), at which time the rotator chair test indicated a phase lead, a decreased gain, but no definite asymmetry, compatible with BVH. Similarly, initial cVEMP indicated that the amplitude and latency of both ears were normal on initial evaluation; however, at the 3-year follow-up, the right-side IAD was 47.8% that of the left side. T2-weighted and GRE images revealed diffuse hemosiderin depositions around the cerebellum, brainstem, midbrain, and both CN VIII but the cavernous hemangioma exhibited no interval change over the years.

Subject 5 (F/53)

This patient had a history of spinal cord bleeding 6 years prior to her first visit. Two years later, she began to complain of cerebellar ataxia and bilateral hearing loss. Initial PTA revealed symmetrical SNHL (threshold: 60 dB HL, SD: 16%). Profound bilateral SNHL developed over the next 2 years (**Figure 1E**). She recently began to suffer from intermittent diplopia. On VNG examination, SN was absent, but GEN was evident during lateral gaze. The ocular motor test revealed hypsometric saccades and a low pursuit gain. The bithermal caloric test revealed bilateral caloric paresis, and no change in the direction of nystagmus was evident during the ice-water test. Moreover, video HIT revealed both overt and covert saccadic movements, and the VOR gains of all six semicircular canals were reduced (**Figure 4**). Notably, the cVEMP test was normal at initial evaluation, but was absent at the 2-year follow-up. T2-weighted and GRE images revealed diffuse hemosiderin deposition in the brain, particularly the cerebellum and brainstem. Additionally, T-spine MRI showed that the entire spinal cord exhibited SS.

Subject 6 (M/65)

This patient was diagnosed with a cystic lumbar tumor 20 years ago and underwent several surgeries for tumor resection. He presented with cerebellar ataxia 10 years after the last operation. Seven years later, he developed right-side hearing loss. PTA revealed asymmetric SNHL (80 dB HL and 12% SD on the right, 30 dB HL and 100% SD on the left side; **Figure 1F**). During exhaustive VNG examination, subtle spontaneous DBN with left-beating nystagmus was documented. The ocular motor test indicated a hypermetric saccade without a pathological pursuit gain. At initial evaluation, his responses to bithermal caloric irrigation were within the normal range, and video HIT revealed normal VOR gains in all six semicircular canals. In addition, the cVEMP test demonstrated that the hearing thresholds and latencies were normal There were no additional abnormal neurologic findings. T2-weighted and GRE images revealed SS only in the superior cerebellum (**Figure 2C**).

Patterns of Vestibular Presentation

We list the patterns of vestibulopathy found during follow-up in **Table 4**. When hearing impairment was evident on the most recent vestibular work-up, bilateral combined central and peripheral vestibulopathy was the most common vestibular presentation; four of the six cases (subjects 1, 3, 4, and 5) presented with cerebellar ataxia, neuropathy, and vestibular areflexia syndrome(CANVAS) due to combined central and peripheral vestibulopathy on both sides. Of the remaining two patients, however, one exhibited bilateral vestibulopathy without central signs or cerebellar ataxia, and the other showed cerebellar ataxia and central signs without peripheral vestibular dysfunction, consistent with isolated central vestibulopathy.

Of note, the patterns of vestibulopathy had evolved in two patients during the follow-up (subjects 1 and 4). For example, the subject 1 with spontaneous DBN, GEN and progressive cerebellar ataxia, but normal caloric test and cVEMP initially showed an isolated central vestibulopathy, but later conversion into bilateral combined central and peripheral vestibulopathy.

Radiological Manifestations

Radiologically, hypo-intense lesions surrounding the cerebellum and brainstem were evident on T2-weighted and GRE MRIs of all patients, but one patient lacked such lesions around the brainstem. The hypo-intense lesions were visualized along both CN VIII on bTFE images of the internal auditory canal in two patients and were suspected on T2-weighted and GRE images in another two patients. Although cochleo-vestibular dysfunction usually progressed asymmetrically, asymmetry of the MRI lesions

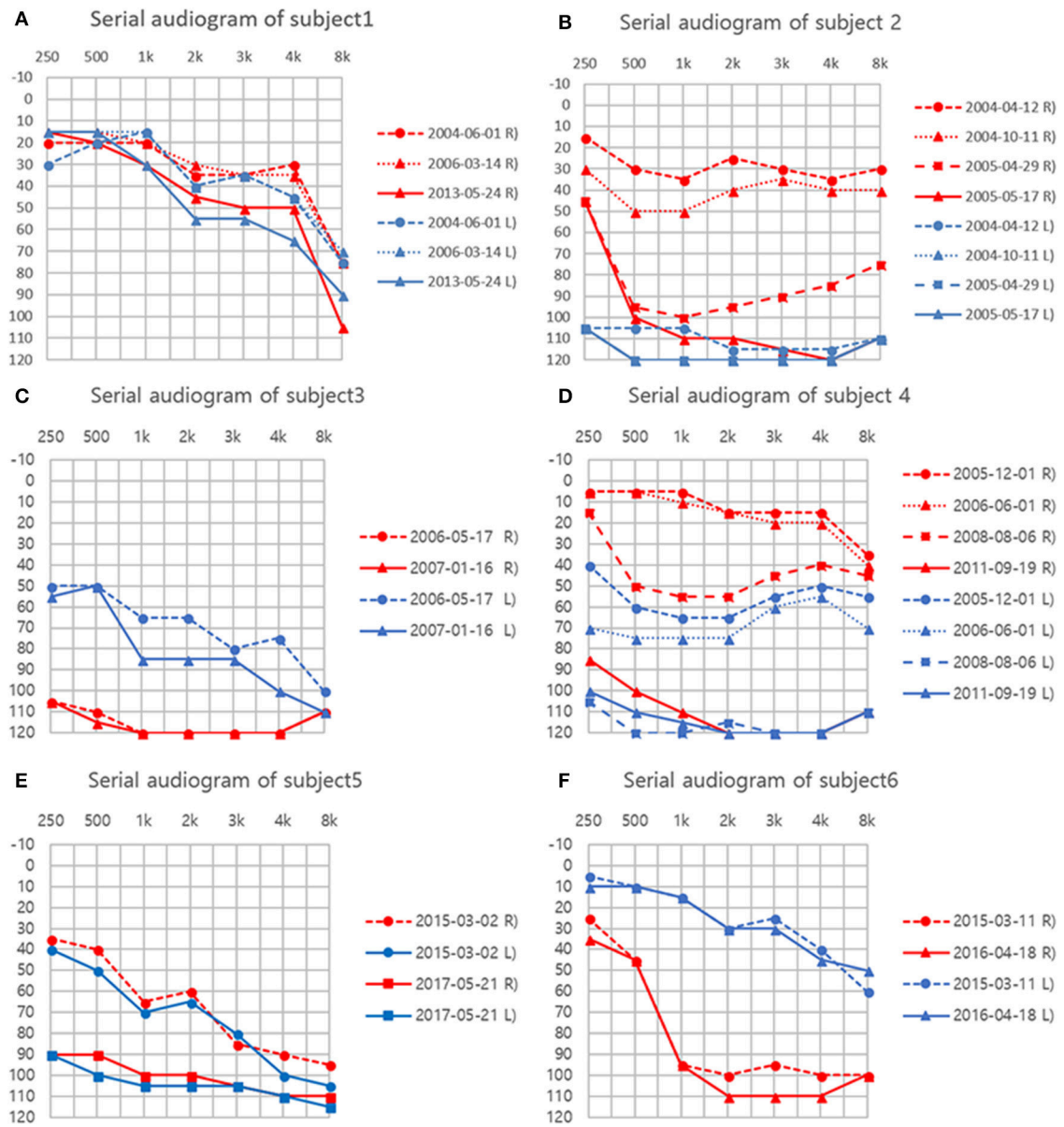

FIGURE 1 | (A–F) Serial audiograms in individual patients. Air conduction thresholds (dB HL) at each frequency (Hz) are plotted for both ears.

was not evident. **Table 4** summarize the radiological extents and locations of hemosiderin deposits.

DISCUSSION

All patients exhibited SNHL, which progressed over the years in five of the six patients. Similarly, heterogeneous vestibular patterns were observed during the disease process, but most patients exhibited combined bilateral peripheral and central vestibulopathy at their most recent evaluations. Also, although cochlea-vestibular dysfunction was mostly bilateral and progressed asymmetrically, no asymmetry of hemosiderin deposition was evident on MRIs. Thus, precise identification of cochlea-vestibular dysfunction and central signs is essential in SS, and patients with SS should undergo regular, comprehensive neurotological evaluation to optimize their treatments and prognosis.

Vestibular Characteristics and the Clinical Course of Superficial Siderosis

SS is associated with slow progressive deterioration (5), and vestibular status can vary over time. However, SS patients ultimately suffer from functional decline of either the central or peripheral vestibular system. Recently, a correlation between

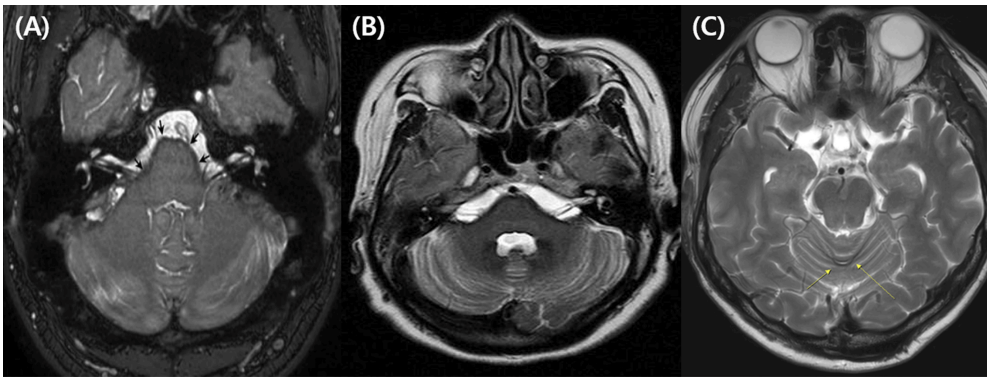

FIGURE 2 | Representative caloric test results obtained during the follow-ups in subject 4. The responses to bithermal caloric irrigation were normal in both ears at initial evaluation. **(A)** But, deteriorated asymmetrically over the years. **(B)** Finally, bilateral caloric paresis became evident at the most recent examination **(C)**.

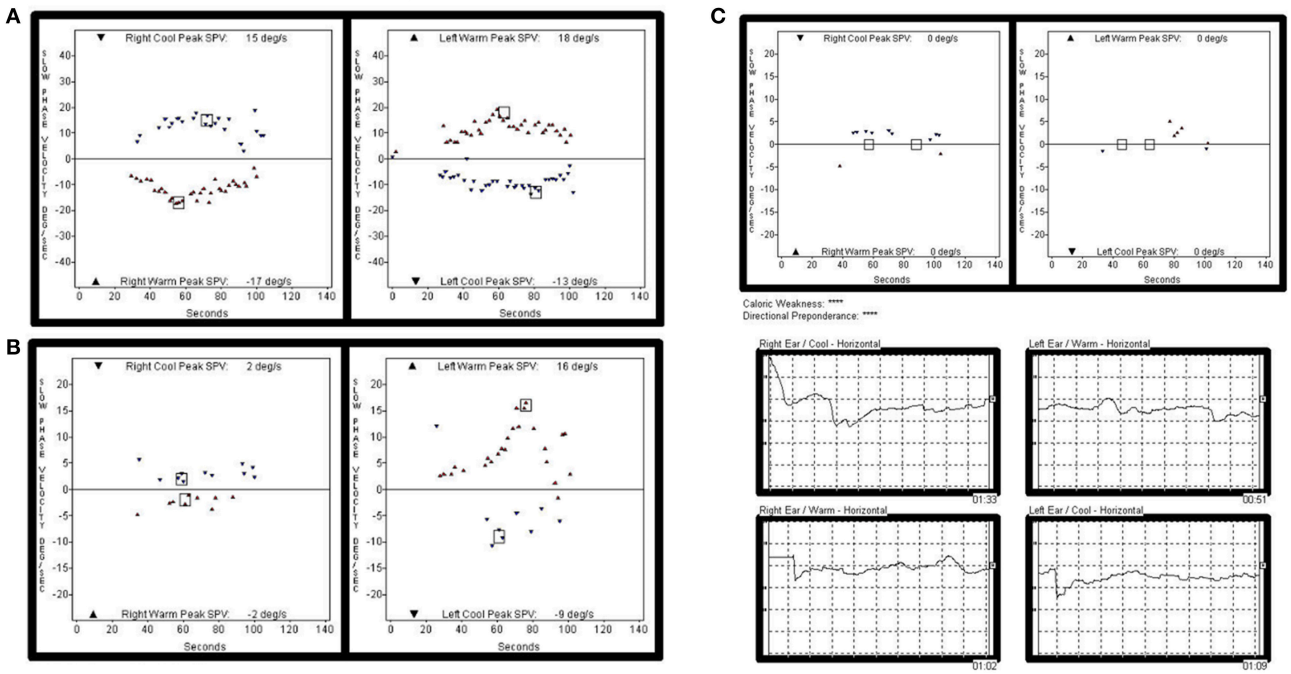

FIGURE 3 | Representative MRIs illustrating hemosiderin deposition. **(A)** Balanced turbo field-echo (bTFE) image shows hemosiderin deposition lining the cerebellum, brainstem, and both vestibulocochlear nerves (subject 2, The arrow indicates the surface of the pons.). **(B)** T2-weighted image shows hemosiderin deposition around the cerebellum, brainstem, and both vestibulocochlear nerves (subject 3). **(C)** T2-weighted image shows hemosiderin deposition on the posterior cerebellum (subject 6).

central ataxia and bilateral vestibulopathy has been noted (33). Also, recent reports have suggested that when chronic bilateral combined vestibulopathy is associated with hearing impairments, SS may be the most common cause (7, 9). In the present study, four of six patients exhibited bilateral combined central and peripheral vestibulopathy on their most recent evaluations. The other two patients exhibited bilateral peripheral vestibulopathy or isolated central vestibulopathy.

Several studies have reported various patterns of vestibulopathy, however, all were cross-sectional in nature (3, 5–9, 11–22). The median follow-up of our cases was 12 years (range, 3–15years). In this study, we showed that vestibulopathy is heterogeneous during follow-up. Notably, of four patients with bilateral combined vestibulopathy, evolution of the vestibular pattern from isolated central vestibulopathy into bilateral combined central and peripheral vestibulopathy was evident in two patients. The caloric function and cVEMP test results were normal at the initial evaluation, and then deteriorated asymmetrically during follow-up. However, the comparison of each side would be meaningless in markedly decreased response.

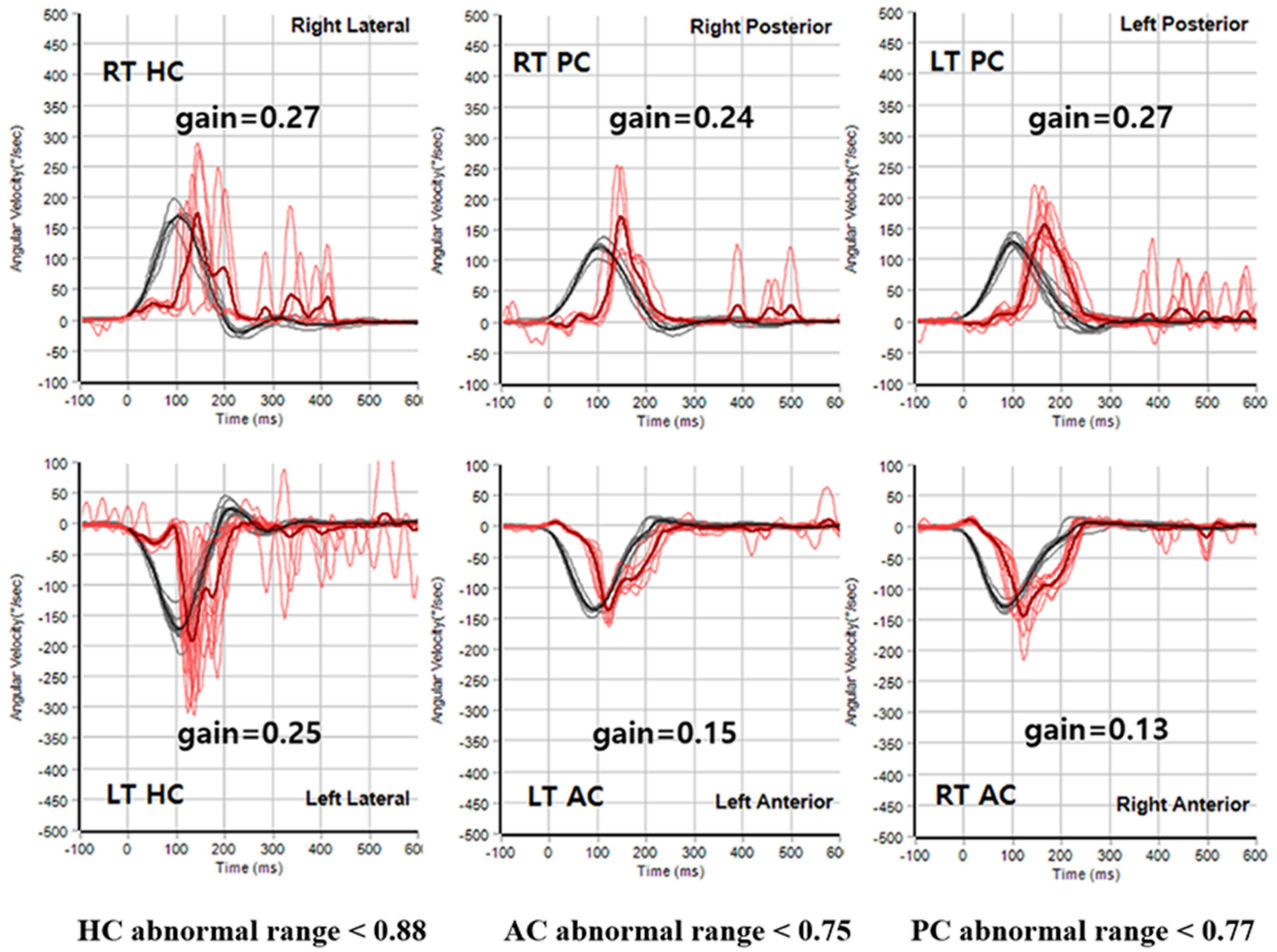

FIGURE 4 | Representative video HIT results obtained during the follow-ups in subject 5. The VOR gains were reduced for all six semicircular canals during the recording of video HIT.

In patients with chronic bilateral combined vestibulopathy, conspicuous cerebellar dysfunction may mask peripheral vestibular involvements (9). A previous study suggested that such patients would find it challenging to develop central adaptation for their imbalance because bilateral vestibulopathy weakens primary vestibular function (33). Thus, the progressive and bilateral nature of the pathology is important when planning treatment and predicting prognosis. Identification of the precise vestibular status and central signs via regular, comprehensive neurotological evaluation may be the key for optimization of both treatment and prognosis (9).

Moreover, all patients exhibited SNHL (mostly asymmetric and progressive), in line with the findings of a previous longitudinal study on the audiological characteristics of SS (6). Typically, SS presents bilateral, asymmetrically progressive, cochlea-vestibular dysfunction combined with cerebellar ataxia. However, although cochlea-vestibular dysfunction usually progresses asymmetrically, no asymmetry of hemosiderin deposition was evident on MRIs in the present study. Also, previous studies reported that the extent and distribution of deposits evident on MRI did not necessarily correlate with the severity of clinical manifestations (34, 35). Although this is an enigmatic finding, it has recently been suggested that certain physiological pathways protecting the CNS against intracranial iron overload may become activated in SS patients (36).

Specific Vestibular Signs in Superficial Siderosis

Neurotologically, DBN may constitute diagnostic vestibular evidence of SS. In the present study, DBN developing either spontaneously or after head-shaking was evident in three of the six patients. Although the mechanism of DBN remains unclear, asymmetry of the cerebellum-brainstem network and an imbalance between the downward and upward vestibular tracts, including the superior vestibular nucleus-ventral tegmental tract, may generate DBN (37, 38). Hemosiderin deposits in the cerebellum or brainstem were common radiological characteristics of our patients. Selective hemosiderin deposition in the cerebellum interferes with the cerebellum-brainstem network and compromises vertical vestibular-cerebellum neural

integration, causing DBN. In addition, hemosiderin deposition on the brainstem, which lies on the course of the superior vestibular nucleus-ventral tegmental tract (39), may compromise the normal functioning of that tract, inducing vertical nystagmus. Recently, a relationship between CANVAS and DBN was found in a large series of patients with DBN, which was associated with additional signs including bilateral vestibulopathy, cerebellar ataxia, and peripheral neuropathy (40, 41). The vestibular test batteries used in the present study showed that cerebellar ataxia was present in all three patients with DBN and bilateral vestibulopathy in two of them. Furthermore, bilaterally positive HIT, impaired pursuit gains, and GEN were documented in more than half of the patients. Similarly, a previous study on CANVAS patients suggested that impairment of the visually enhanced VOR was a typical sign of combined vestibulopathy because both smooth pursuit and the VOR were simultaneously affected in such patients (42).

The cVEMP test is regarded reliable when used to evaluate the integrity of the saccule, inferior vestibular nerve, and its central connections (43). All patients of the present study yielded normal cVEMP test results at their initial evaluations, supporting the findings of previous studies having shown that otolithic function is preserved in SS patients (3, 5). The cVEMP has contributions from different areas of the cerebellum. Hemosiderin deposition may initially target the cerebellar flocculus, which mostly modulate the angular VOR control, but not the cerebellar nodulus that is more closely related to the otolith reflexes (44). Furthermore, as hemosiderin deposition in CNS persists for at least several months (45), cVEMP responses tend to be impaired in patients who have suffered from SS for longer periods, and not in those with early-stage disease. The four patients who underwent follow-up cVEMP developed significant IAD or lost their cVEMP responses over the years.

Although both caloric function and the cVEMP deteriorated during follow-up, considerable differences were evident on initial evaluation. The caloric test, which evaluates the VOR (46), indicated vestibulopathy in four of the six patients, but cVEMPs were all normal. Thus, the superior vestibular nerve appears to be more affected by hemosiderin deposition than the inferior vestibular nerve. Anatomically, the superior vestibular nerve is longer than the inferior vestibular nerve, and traverses small, osseous neural canals (47). In addition, more of the surface area of the superior vestibular nerve is in contact with the cerebrospinal fluid (CSF). Thus, the superior vestibular nerve has a greater glial segment susceptible to iron impregnation (47).

Vestibular Pathophysiology in Superficial Siderosis

The clinical manifestations of SS depend on the sites and extents of hemosiderin deposition (1). We found that the cerebellum and brainstem were the most commonly affected regions, consistent with the previous studies. The cerebellum has a large, folded surface, which may make it susceptible to iron deposition. These sites are exposed to high levels of CSF (1, 4). Chronic bleeding into the subarachnoid space increases the CSF hemoglobin level, and heme oxygenase produced by glial or microglial cells cleaves free heme into biliverdin and iron. Thus, iron deposits in this region are common in patients exhibiting gliosis, neuronal loss, and demyelination (48). Also, iron deposition increases hydroxyl radical production, causing oxidative stress and tissue damage (49). Thus, oxidative cellular damage, accompanied by reactive gliosis, neuronal loss, and demyelination associated with hemosiderin deposition may weaken the pathways that must be active to counter any decline in VOR gain (50). Such a pathological cascade could cause the characteristic progressive cerebellar ataxia and progressive SNHL evident in the present study (51). Our findings are similar to those of a previous study; progressive SNHL and progressive cerebellar ataxia developed in 95 and 88% of cases, respectively.

In addition, hemosiderin can be deposited along the cranial nerves. In particular, the CN VIII running through the pontine cistern has a long glial segment and is exposed to high-level CSF flow, rendering the nerve particularly susceptible to iron deposition (52). Also, the inner ear structures can also be affected in SS (12). In support of these findings, an earlier histopathological study of the temporal bone showed that atrophy of CN VIII, the loss of hair cells (53), and subsequent fibrosis, contributed to impairment of peripheral blood flow in the inner ear (12). Moreover, a previous report suggested that chronic hemorrhage directly affected the inner ear structures, precipitating neurotological symptoms (54). Likewise, loss of smell sensation may be an initial feature of SS since the olfactory tract and bulb can also be affected during the earlier phase of this disorder (55).

Limitations and Future Perspectives

To the best of our knowledge, this is the first study to discuss vestibular manifestations over time in a relatively large SS cohort. Although our data will be useful in terms of diagnostic evaluation and will assist future clinical and basic studies on SS, some limitations of our work remain to be addressed. First, because our sample was relatively small, we cannot conclude that we encountered all possible vestibular manifestations; a prospective larger cohort study is necessary. Second, given the heterogeneity in vestibular function evident among the studies, it is difficult to describe associations between vestibular function and SS; a unified protocol for vestibular evaluation is required. Third, although the location and extent of hemosiderin deposition revealed by MRI can plausibly be used to explain the vestibular pathophysiology, the disease is multifactorial in nature; temporal bone histopathological data and more accurate neuroimages would be helpful. Lastly, we generally used caloric paresis as a marker of peripheral vestibular involvement, which is a well-known feature of SS. However, caloric paresis may reflect brainstem pathology involving the vestibular fascicle or the nuclei (56).

CONCLUSION

SS typically presents bilaterally asymmetric, progressive audiovestibular dysfunction with cerebellar ataxia. The most common pattern of vestibular dysfunction is bilateral

combined central and peripheral vestibulopathy. Thus, precise identification of audiovestibular dysfunction and central signs is essential in SS, and patients with SS should undergo regular, comprehensive neurotological evaluation to optimize their treatments and prognosis.

AUTHOR CONTRIBUTIONS

S-YL designed and performed experiments, analyzed data and wrote the paper; J-WK conceived the study and wrote the paper; D-HL, YB, and J-JS collected and analyzed data; J-WK, and JK revised the article critically for important intellectual content. All authors discussed the results and implications and commented on the manuscript at all stages.

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Susceptibility to Fear of Heights in Bilateral Vestibulopathy and Other Disorders of Vertigo and Balance

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Aims: To determine the susceptibility to visual height intolerance (vHI) in patients with acquired bilateral vestibulopathy (BVP). The question was whether postural instability in BVP, which is partially compensated for by visual substitution of the impaired vestibular control of balance, leads to an increased susceptibility. This is of particular importance since fear of heights is dependent on body posture, and visual control of balance at heights can no longer substitute vestibular input. For comparison susceptibility to vHI was determined in patients with other vestibular or functional disorders.

Methods: A total of 150 patients aged 18 or above who had been referred to the German Center for Vertigo and Balance Disorders and diagnosed to have BVP were surveyed with a standardized questionnaire by specifically trained neurological professionals. Further, 481 patients with other vestibular or functional disorders were included.

Results: Susceptibility to vHI was reported by 29% (32 % in females, 25% in males) of the patients with BVP. Patients with vHI were slightly younger (67 vs. 71 years). Seventy percent of those with vHI reported avoidance of climbing, hiking, stairs, darkness, cycling or swimming (84% of those without vHI). Mean age for onset of vHI was 40 years. Susceptibility to vHI was higher in patients with other vertigo disorders than in those with BVP: 64% in those with phobic postural vertigo, 61% in vestibular migraine, 56% in vestibular paroxysmia, 54% in benign paroxysmal positional vertigo, 49% in unilateral vestibulopathy and 48% in Menière's disease.

Conclusions: The susceptibility to vHI in BVP was not higher than that of the general population (28%).This allows two explanations that need not be alternatives but contribute to each other: (1) Patients with a bilateral peripheral vestibular deficit largely avoid exposure to heights because of their postural instability. (2) The irrational anxiety to fall from heights triggers increased susceptibility to vHI, not the objective postural instability. However, patients with BVP do not exhibit increased comorbid anxiety disorders. This view is supported by the significantly increased susceptibility to vHI in other vestibular syndromes, which are characterized by an increased comorbidity of anxiety disorders.

Keywords: bilateral vestibulopathy, vestibular migraine, Menière's disease, benign paroxysmal positional vertigo, phobic postural vertigo, visual height intolerance

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INTRODUCTION

Historical View on Mechanisms of Fear of Heights Associated With Postural Imbalance

A short historical excursus may be permitted here as to the dependence of fear of heights on posture, locomotion, and balance control, all of which are affected by bilateral vestibulopathy. There is phylogenetic evidence of an inborn behavioral pattern allowing us to perceive and avoid heights, the so-called "visual cliff" phenomenon. This broadly gene-linked avoidance of depths in order to prevent falls off cliffs was comprehensively studied by Walk et al. (1), Walk and Gibson (2). The innate ability of pre-walking and walking infants to visually avoid a brink (3, 4) was further supported by animal experiments in a number of other species including chicks, rats, kittens, and goats. There are two visual signs for perceiving height as a special case of distance: the drop-off increases in texture density beyond the edge, and the absolute and relative motion parallax cues differ during active locomotion and head movements. Both texture/density preferences (5, 6) and motion parallax cues are utilized and interact with each other.

Therefore, it is not surprising that our ancestors were well aware of visual height intolerance. There are numerous descriptions of provoking situations and typical symptoms in the Greek, Roman, and Chinese classics which suggest visual height intolerance and fear of heights (7). One example is found in Titus Livius's history on the second Punic war, where he describes how soldiers on high ladders plunged to the ground when attacking Carthago Nova because the heights "had veiled their eyes with dizziness." Another example is Hannibal's crossing of the Alps in the third century BC. Silius Italicus recounted this feat in *Punica,* describing how "the gaze became dizzy on the high rocks" (8). In the Chinese classic *Huangdi Neijing,* the Yellow Thearch is said to suffer from a confusion and to feel dizzy when he climbed up on to an observation platform (9). It is interesting that several historical sources report stance and gait being disturbed. Demokles, for example, experienced a "slackening of the muscles of the entire body" (Greek *Corpus Hippocraticum* fifth century BC) when walking along the edge of a precipice or over a bridge; however, he would dare to walk in the ditch itself. Similarly Phaeton turned pale while driving the sun chariot (Ovid's *Metamorphoses,* about 0–8 AD) and suddenly felt his knees trembling from fear (8). Later the main ouvre of Erasmus Darwin, *Zoonomia, or The Laws of Organic Life* in 1794 (10), also provided a detailed early concept of disturbed sensorimotor control when exposed to heights. The Yellow Thearch in ancient China intuitively found a treatment, namely kneeling on the ground: it alleviated the symptoms that had occurred at heights while he stood on an observation platform. This historical "antidote" corresponds to contemporary psychophysical experiments (11, 12).

The mechanism that explains a physiological postural imbalance at heights is separate and distinct from that caused by purely cognitive reasons or anxiety as earlier researchers like Purkinje in 1820 (13) emphasized. A geometrical consideration reveals the mechanism of physiological postural imbalance at heights. In order to be visually detected, body sway must increase with increasing distance between the eyes and the stationary contrasts in the environment, because angular displacement of the surroundings on the retina is smaller, the greater the distance to them (11, 12, 14). Head sway is no longer visually detected by retinal slip (which is subthreshold) when the distance between the eyes and stationary contrasts exceeds about 3 meters. Then head and body sway rely solely on vestibular and somatosensory input. Hence, visual stabilization of posture is impaired and instability increases in the fore-aft and lateral planes. This causes an unsteadiness that increases the danger of falling (11, 14) (**Figure 1**).

Further analyses were performed under real stimulus conditions while subjects with visual height intolerance stood on a force-measuring platform. Major results were that open-loop control was disturbed by a higher diffusion activity, and the sensory feedback threshold for closed-loop control was lowered. This was predominantly associated with increased co-contraction of the leg muscles (15, 16). Walking in these subjects is slow and cautious, broad-based, and consists of small, flat-footed steps with less dynamic vertical oscillations of the body and head (12, 17).

The non-medical Anglo-American community uses a single term "fear of heights" to refer to a more-or-less severe visual height intolerance that, however, does not generally fulfill the criteria of the specific phobia "acrophobia." On the basis of the above-described findings we proposed in an earlier study to distinguish between three terms in order to resolve possible confusion about physiological and pathological (psychiatric) mechanisms active during exposure to heights (18): (1) An imbalance of stance and gait at heights caused by impaired visual control. This is physiological and has no clinical relevance; (2) A visual height intolerance, which is more or less distressing and has clinical relevance for about one half of those susceptible; (3) Fear of heights or acrophobia, defined as a specific phobia in psychiatry (19, 20) which requires psychotherapy (7). In our study which was based on a questionnaire we did not differentiate between visual height intolerance and acrophobia, instead used visual height intolerance (vHI) as the umbrella term.

Why Investigate Susceptibility to vHI in Bilateral Vestibulopathy and Other Vestibular Disorders?

The major question of the current study, i.e., whether bilateral vestibulopathy (BVP) is a trigger of vHI (7), is related to an impaired balance in both conditions. Thus, postural instability in BVP could act as a trigger of vHI. More specifically, there were three reasons which prompted us to investigate a potential increase in susceptibility of patients with BVP to vHI:

1) The loss of vestibular function causes not only oscillopsia during locomotion, but also unsteadiness of stance and gait. This unsteadiness is partially compensated for by visual substitution of the impaired vestibular control of postural balance.

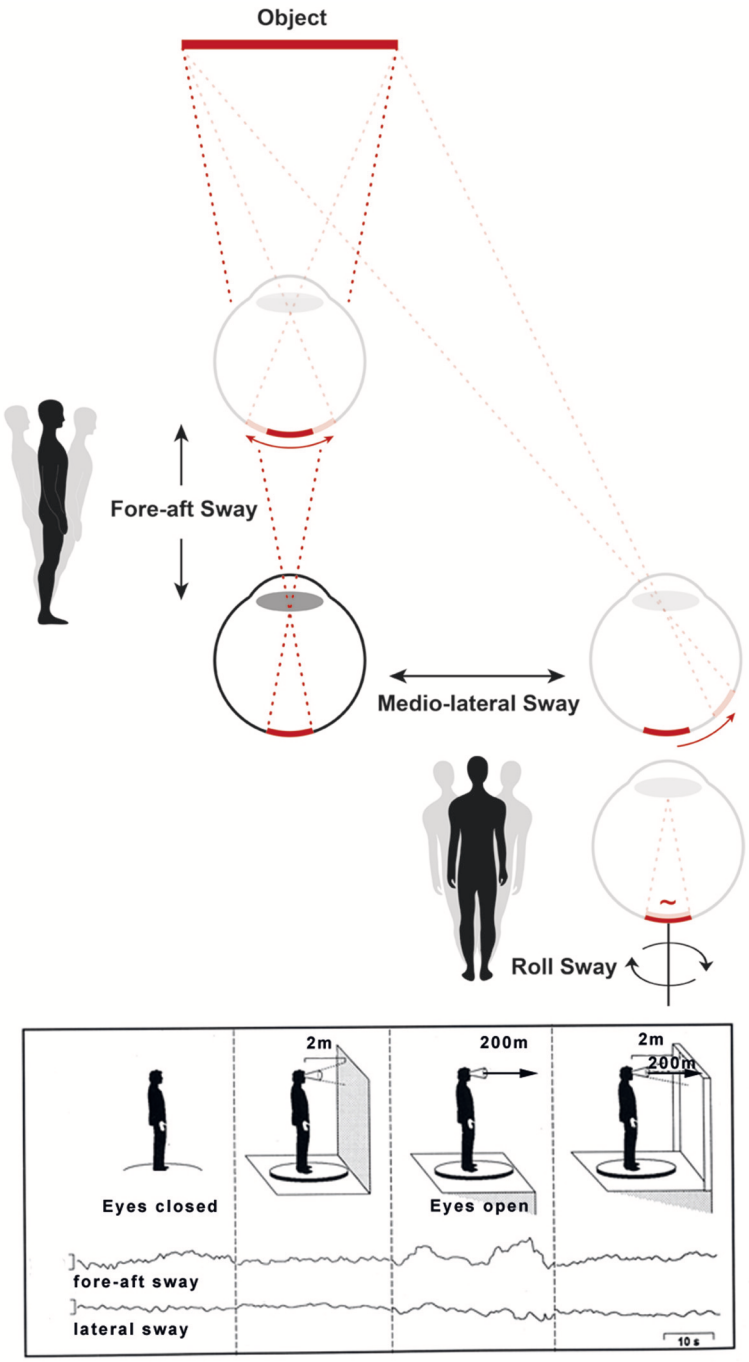

FIGURE 1 | The mechanism of a physiological postural imbalance at visual heights can be explained by the dependence of the retinal slip of viewed objects on their distance. This is depicted schematically **(Top)**. Visual control of body sway in fore-aft, lateral, and roll planes shows that angular displacement on the retina caused by fore-aft and lateral head displacements are smaller, the greater the distance is to the object. Therefore, when exposed to heights, the head sway goes visually undetected (the retinal slip is below the threshold value for detecting motion) and thus impairs visual stabilization of posture. This is different for head and body sway in the roll plane **(Bottom** right of the **Top** figure). In this plane, the distance between eyes and fixated objects has no influence on the net retinal slip. Original traces of the fore-aft and lateral body sway with the eyes closed, eyes open in front of a wall shows the stabilizing effect of posture **(Bottom**, figure left). Viewing from a balcony with the eyes open impairs fore-aft and lateral body sway since the retinal slip of the viewed environment is subthreshold. However, with additional stationary contours of the balcony in the peripheral visual field the visual stabilization of posture is restored **(Bottom**, figure right). The influence of head movements in the frontal roll plane on postural control was not measured in the experiment. However, as stated above, retinal slip is independent of the viewing distance for head and eye movements in roll [modified from (15, 16)].

2) Visual control of balance, however, is impaired at substantial heights. When stationary targets are viewed from distant/remote heights, the retinal slip of the image falls below the threshold value at which head and body sway can no longer be detected (**Figure 1**).
3) Balance is further impaired by an associated sensory polyneuropathy, which is found in about 25% of the mostly elderly patients with BVP. It also occurs with associated cerebellar symptoms in 25% of these patients, (21), in part overlapping. It has been shown that the combination of BVP and polyneuropathy particularly increases instability of stance and gait, which leads to frequent falls in darkness and/or on uneven ground (22).

All three reasons make it likely that patients with BVP adjust their behavior in order to avoid experiencing visual heights, since balance control puts special demands on this condition.

The occurrence of vHI is clearly related to body position. It is strongest during erect stance, when maintaining balance is most difficult, less severe when kneeling down or sitting, and minimal or absent when the subject is lying while looking down (11). This is supported by the experiences of airplane passengers, who do not complain about having vHI.

The current study on the effects of BVP and other vestibular and functional disorders of vertigo and balance on the susceptibility to vHI is based on a standardized questionnaire applied to patients who were examined as outpatients in the German Centre for Vertigo and Balance Disorders (DSGZ).

METHODS

Patients and Data Collection

A total of 150 patients with complete or asymmetrically incomplete loss of peripheral vestibular function were surveyed. Further, 481 patients with other vestibular or somatoform/functional disorders were included for comparison: vestibular migraine ($n = 51$), Menière's disease ($n = 112$), benign paroxysmal positional vertigo ($n = 97$), vestibular paroxysmia ($n = 25$), unilateral vestibulopathy ($n = 94$), and phobic postural vertigo (functional dizzines) ($n = 102$). Patients were included if they were aged 18 or above and had been referred to the DSGZ. All patients received a complete neurological, neuro-ophthalmological, and neuro-otological examination by experts in neuro-otology. Data were extracted from clinical patient records and the specific questionnaires.

Inclusion Criteria

The diagnosis of BVP was based on the patient history as well as bedside and laboratory examinations. Patients complained of unsteadiness when walking or standing, which worsened in darkness and/or on uneven ground, but had no such symptoms while sitting or lying down under static conditions. Laboratory examinations revealed a bilaterally reduced or absent angular vestibulo-ocular reflex (VOR; VOR gain <0.6 on both sides) (indicating a high frequency deficit of the VOR) and bilaterally diminished (mean peak slow-phase velocity <5 deg/s on both sides) or absent nystagmus responses to caloric irrigation (indicating a low frequency deficit). These criteria largely correspond to the recently published Consensus Document of the Classification Committee of the Bárány Society (23). The diagnosis of the other vestibular and functional disorders of vertigo and balance was also based on the criteria of the classification committee of the Bárány Society (24–29). All patients had given their informed consent.

Exclusion Criteria

Exclusion criteria were other disorders of stance and gait, cognitive impairment, psychiatric disorders, severe visual loss, chronic medication with sedatives or drug/substance abuse.

Questionnaires

Susceptibility and characteristics of vHI were ascertained by a questionnaire containing questions to symptoms, triggers, course of the condition, and compensational behavior (30). It had been adapted and extended to include patients with BVP and other vestibular and functional disorders by adding questions on quality of life, physical and sporting activities, social functioning, avoidance behavior, and motion sickness susceptibility.

The German version of the Dizziness Handicap Inventory (DHI) was used in 49 of the 150 patients with BVP to evaluate vertigo-specific functioning (31). The DHI consists of 25 items that can be grouped into three domains representing functional, emotional and physical aspects. A total score is obtained by summing each ordinal scaled response. The total score ranges from 0-100 points; higher scores indicate a more severe handicap. The sub-domains consist of seven physical items, nine functional items, and nine emotional items.

Statistics

Differences were tested using Student's *t*-Tests for numerical and Chi-Square Tests for categorical variables on an explorative testwise alpha level of 0.05. SAS V9.4 for Windows 10 was used for all analyses.

RESULTS

Of the 150 patients with a verified diagnosis of BVP (mean age 70.0, 47% females, 31% academics) vHI was reported by 29% (females 32%, males 25%; see **Table 1**). Of those with vHI 70% reported avoidance of climbing, hiking, stairs, darkness, cycling, swimming, or skiing (84% of those without vHI). Patients with vHI were not significantly younger (67 vs. 71 years, $p = 0.165$) and had had a significantly earlier lifetime onset of BVP (58 vs. 64 years, $p = 0.031$). Mean age for onset of vHI was 40 years.

Among persons with polyneuropathy, 21% had vHI (31% of those without polyneuropathy had vHI); among persons with migraine, 32% reported vHI (28% without migraine); among persons with motion sickness, 45% reported vHI (26% without motion sickness).

Sixteen percent of all BVP patients had one or more family members with vHI (3—parents, 3—siblings, 1—children). Anxiety, panic attacks, or any phobia was present in 11% of all BVP patients. Among those with anxiety, vHI was reported by 41%. Climbing a tower was the most frequent first trigger for vHI, followed by climbing a ladder or looking out of the window of a high building; 35% (15/43) reported they avoid

TABLE 1 | Frequency of vHI, migraine, motion sickness, anxiety, polyneuropathy, and fear or panic in patients with BVP.

	Total	Visual height intolerance in those with BVP			
		No		Yes	
	N	*N*	%	*N*	%
AGE GROUP					
<30	2	2	100.0	0	0
30–39	2	1	50.0	1	50.0
40–49	5	2	40.0	3	60.0
50–59	21	14	66.7	7	33.3
60–69	29	20	69.0	9	31.0
70–79	56	40	71.4	16	28.6
80+	35	28	80.0	7	20.0
SEX					
Male	79	59	74.7	20	25.3
Female	71	48	67.6	23	32.4
MIGRAINE					
No	125	90	72.0	35	28.0
Yes	25	17	68.0	8	32.0
MOTION SICKNESS					
No	130	96	73.8	34	26.2
Yes	20	11	55.0	9	45.0
PHOBIA/ANXIETY					
No	141	100	70.9	41	29.1
Yes	9	7	77.8	2	22.2
POLYNEUROPATHY					
No	59	41	69.5	18	30.5
Yes	33	26	78.8	7	21.2
Total	150	107	71.3	43	28.7

TABLE 2 | Frequency of vHI in benign paroxysmal positional vertigo (BPPV), bilateral vestibulopathy (BVP), functional dizziness/phobic postural vertigo, Menière's disease, unilateral vestibulopathy (UVP), vestibular migraine, and vestibular paroxysmia.

	Total	Visual height intolerance			
		No		Yes	
	N	*N*	%	*N*	%
DIAGNOSIS					
BPPV	97	45	46.4	52	53.6
BVP	150	107	71.3	43	28.7
Functional dizziness	102	37	36.3	65	63.7
Menière's disease	112	58	51.8	54	48.2
UVP	94	48	51.1	46	48.9
Vest. migraine	51	20	39.2	31	60.8
Vest. paroxysmia	25	11	44.0	14	56.0
Total	631	326	51.7	305	48.3

TABLE 3 | Frequency of fear or panic in seven disoreders of vertigo and balance (benign paroxysmal positional vertigo (BPPV), bilateral vestibulopathy (BVP), functional dizziness/phobic postural vertigo, Menière's disease, unilateral vestibulopathy (UVP), vestibular migraine, and vestibular paroxysmia.

	Total	Fear or Panic			
		No		Yes	
	N	*N*	%	*N*	%
DIAGNOSIS					
BPPV	97	76	78.4	21	21.6
BVP	150	133	88.7	17	11.3
Functional dizziness	102	64	62.7	38	37.3
Menière's disease	112	91	81.3	21	18.8
UVP	94	73	77.7	21	22.3
Vest. migraine	51	36	70.6	15	29.4
Vest. paroxysmia	25	20	80.0	5	20.0
Total	631	493	78.1	138	21.9

hiking in the mountains (this was identical in BVP patients without vHI), 9% (4/43) avoid this because of vHI. Further details on specific symptoms (such as swaying vertigo, inner agitation, trembling, diffuse sweating) concerning vHI attacks and the manifestation of BVP as well as its time-course since then are not reported here for two reasons: first, the limitation of the reliability of these details collected in a printed questionnaire, and second, because most patients with BVP cannot determine the exact date and time-course of the bilateral vestibular failure.

Patients with vHI scored higher on the DHI total (46.8 vs. 39.7), but the difference was not significant. We did not see any significant differences in instrumental measures between patients with and without vHI.

Susceptibility to vHI was higher in patients with other disorders of vertigo and balance than in BVP patients (**Table 2**): Prevalence of vHI was 64% in patients with phobic postural vertigo, 61% in vestibular migraine, 56% in vestibular paroxysmia, 54% in benign paroxysmal positional vertigo, 49% in unilateral vestibulopathy, and 48% in Menière's disease. As depicted in **Table 3** these disorders were also associated with an increased frequency of fear or panic ranging from 20 to 37%, whereas in BVP it only amounted to 11%.

DISCUSSION

Visual Height Intolerance and Bilateral Vestibulopathy

The survey did not support our expectation that BVP patients would have a heightened susceptibility to vHI. We found that the overall susceptibility to visual height intolerance of varying severity including acrophobia was not significantly higher than that for the general German population.

Patients with BVP indicated a current susceptibility rate of 29% (in females 32%, in males 25%), whereas the life-time prevalence in the general population is 28% (in females 32%, in

TABLE 4 | Comparison of the life-time prevalence of visual height intolerance (vHI) drawn from a cross-sectional epidemiological study on 3,517 individuals (middle column, 15) and the reported susceptibility to vHI in patients with acquired BVP (right column) depicted for age groups from below 30 to above 60 years.

Age group	From Huppert et al. (32)	Patients with BVP
<30	29% (144/495)	0% (0/2)
30–39	28% (117/417)	50% (1/2)
40–49	31% (214/691)	60% (3/5)
50–59	33% (230/698)	33% (7/21)
>=60	25% (304/1216)	26% (32/121)

males 25%) (30). The value of comparing different age groups (**Table 4**) is limited because of the lower random sample of the current study.

The characteristics of the development and course of BVP did not allow us to correlate the pronounced variations in vHI susceptibility with disease onset and the severity of BVP. The onset of BVP may be abrupt as in meningitis or after intake of ototoxic antibiotics, or stepwise for each ear as in Menière's disease, or slowly progressive as in the majority of cases with degenerative or "idiopathic" etiology (21, 32). In the patients with associated polyneuropathy and/or cerebellar symptoms, conditions that further increase postural instability, we did not find an enhanced susceptibility to vHI. The specific triggers of vHI are the same in patients with and without BVP: climbing a tower was the most frequent first trigger for vHI, followed by climbing a ladder or looking out of the window of a high building.

These results are surprising, since the occurrence and severity of vHI and acrophobia critically depend on body position. Visual height intolerance is strongest during free upright stance at heights when the major concern and anxiety of the individual is to fall (11, 14). Several studies have focused on postural instability in patients with BVP, in particular if visual and/or proprioceptive substitution of the diminished/absent vestibular input is experimentally impaired (33) and also when virtual reality stimulation is used (34). Gait analysis of BVP patients walking on a pressure-sensitive carpet revealed that especially increased gait fluctuations during slow walking are most predictive of an increased fall risk (22). This study also found that a sensory polyneuropathy further critically impairs postural instability. A controlled cross-sectional study reported that the rate of recurrent fallers was 30% in patients with BVP and associated polyneuropathy (35). This increases fear of falling, deteriorates quality of life and negatively impacts on physical and social functioning (36). Our study showed that a considerable percentage avoided potentially dangerous situations, e.g., cycling, walking in the dark and hiking. Thus, contrary to our expectations patients with BVP did not exhibit an increased susceptibility to vHI. Possible explanations are discussed below in the Conclusions.

Another finding of our survey was that some patients with BVP may still experience motion sickness: 10% in BVP patients and 21% in patients with BVP and vHI. This seemingly disagrees with findings of various animal experiments in dogs and monkeys and observations in humans: namely, that motion sickness no longer occurred in any species following bilateral vestibular loss (37–39). It is conceivable that residual vestibular function in incomplete BVP may be responsible for the preserved susceptibility to motion sickness (40).

Limitations

A study just based on filling out a printed questionnaire has several limitations as to the reliability of the data on triggers, symptoms, and time-course of vHI. The used questionnaire does not allow us to differentiate between vHI and the specific phobia fear of heights. In the meantime such a questionnaire has been developed (41) which was not available at the time of the study. Furthermore, the onset of BVP remains particularly unclear for most patients since it may be abrupt (i.e., secondary to ototoxic antibiotics) or slowly progressive and asymmetric, involving one ear in the beginning with subsequent involvement of the second ear. Therefore we concentrated on the overall frequency of vHI rather than trying to statistically correlate detailed statements provided by the questionnaire. Experimental ideas initiated by the study results would be systematic quantitative analyses of posture and gait in patients with BVP with and without vHI under natural stimulus conditions at heights at which vision can no longer substitute for the lack of vestibular information for balance control.

CONCLUSIONS

Our finding that BVP does not increase susceptibility to vHI can be interpreted in two ways. First, one could argue that patients with this sensory deficit actively avoid exposure to heights (84% of BVP patients without vHI and 70% with vHI avoid climbing, hiking, stairs, darkness, cycling, swimming, or skiing). It is, however, very difficult to avoid stimuli when they are ubiquitous, e.g., staircases, balconies, bridges. Second, the objective postural instability is not the major trigger of an increased susceptibility to heights, but rather the irrational subjective anxiety at heights is the major trigger. It is well known that there are links between vestibular disorders, balance control, and anxiety. Based on pathways that mediate vestibular-autonomic interactions and anxiety, these links involve the parabrachial nucleus and its reciprocal interconnections with the amygdaloid nucleus, infralimbic cortex, and the hypothalamus (42). Several experiments have supported this, showing that susceptible subjects walk in a cautious way, both when visually exposed to heights as well as when only aware of heights but not visually exposed (17, 43) or during virtual reality stimulation [used in acrophobia research and treatment; (44)]. In a case-control study a representative sample of 2,012 individuals was surveyed in which acrophobia was associated with high rates of comorbid, anxious, and depressive disorders; migraine was also a significant predictor of acrophobia (45). With respect to our current study, the argument that increased anxiety is a trigger of vHI in patients with BVP is not supported by the findings of a study on psychiatric comorbidity in patients with various vestibular disorders. It revealed that

anxiety/phobic disorders were less in BVP than in vestibular migraine, Menière's disease, vestibular paroxysmia, or benign paroxysmal positional vertigo (46). Our data confirm this psychiatric comorbidity (**Table 3**). Obviously in BVP anxiety is low because vestibular-autonomic interaction is reduced due to the lack of vestibular input. Both above-described interpretations need not be alternative explanations but may contribute to each other.

ETHICS STATEMENT

The questionnaire used in our study was part of a clinical routine assessment made after obtaining the prior written informed consent of the outpatients who presented at the dizziness unit. The evaluation of the data was completely anonymized. Ethical approval was not required for this study according to the ethical standards laid down in the 1964 Declaration of Helsinki.

AUTHOR CONTRIBUTORS

DH, TB, and MS conceived and designed the study, examined the patients, interpreted the data, and wrote the manuscript. EG statistically analyzed and interpreted the data, and wrote the manuscript.

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The remaining authors declare that there are no conflicts of interest, there exist no financial or other relationships that have influenced the work.

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Acute Bilateral Superior Branch Vestibular Neuropathy

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The rapid onset of a bilateral vestibular hypofunction (BVH) is often attributed to vestibular ototoxicity. However, without any prior exposure to ototoxins, the idiopathic form of BVH is most common. Although sequential bilateral vestibular neuritis (VN) is described as a cause of BVH, clinical evidence for simultaneous and acute onset bilateral VN is unknown. We describe a patient with an acute onset of severe gait ataxia and oscillopsia with features compatible with acute BVH putatively due to a bilateral VN, which we serially evaluated with clinical and laboratory vestibular function testing over the course of 1 year. Initially, bilateral superior and horizontal semicircular canals and bilateral utricles were impaired, consistent with damage to both superior branches of each vestibular nerve. Hearing was spared. Only modest results were obtained following 6 months of vestibular rehabilitation. At a 1-year follow-up, only the utricular function of one side recovered. This case is the first evidence supporting an acute presentation of bilateral VN as a cause for BVH, which would not have been observed without critical assessment of each of the 10 vestibular end organs.

Keywords: vestibular neuritis, vestibulo-ocular reflex, head impulse test, bilateral vestibular hypofunction, acute gait ataxia

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INTRODUCTION

Acute vestibular syndrome (AVS) is a clinical condition characterized by sudden, severe, and prolonged vertigo that develops over seconds, minutes, or hours. AVS of peripheral origin is a result of the asymmetric vestibular nerve input due to acute unilateral vestibular nerve or labyrinthine damage (1). Patients often have a presumed viral or immune related cause for their symptoms of AVS. Vestibular neuritis (VN) is the most accepted etiology when hearing is spared, with the lesion presumed to be localized to the vestibular nerve (vestibular neuropathy) (2). While rare, a separate lesion to the contralateral nerve has been described in 1–4% of patients (2, 3). Such cases usually occur in a sequential pattern, after a long period (months to years) following the initial nerve damage (2, 4). To our knowledge and experience, simultaneous bilateral and acute involvement of each vestibular nerve due to a putative VN is undocumented (5).

Acute bilateral vestibular damage is rare and has generally been associated with the iatrogenic effect of ototoxic drugs such as gentamicin (5). Typical symptoms include blurred vision induced by head movement (oscillopsia) and gait ataxia. In these cases, the ototoxicity of the hair cells is diffuse,

causing a global loss of function easily identified using vestibular function tests (6). Here, we report a case of acute bilateral vestibular hypofunction (BVH) with selective damage to each superior vestibular nerve branch. We propose the mechanism is a bilateral simultaneous VN, unreported to date in the literature.

CASE REPORT

A 68-year-old man with a 7-day history of upper respiratory tract infection had no prior history of vertigo, gait, or hearing disorder. He began to suffer from vertigo that developed over minutes. The following day, he reported his vertigo resolved but required help with walking due to a severe ataxia. Furthermore, he reported that images of the visual environment appeared blurry during head motion. He did not suffer any subjective changes in hearing. The patient was seen in the emergency room where he had no limb ataxia or other motor or sensory abnormalities. A 1.5 T MRI (1.5 T Achieva; Philips, Eindhoven, Netherlands) with 3D FLAIR sequence of the brain stem and cerebellum revealed non-specific isolated cerebral white matter lesions. Diffusion weighted sequences (DW1) and T1 with contrast was normal. A more detailed neuro-otologic exam with Video Frenzel goggles was performed on the third day from onset. No bedside ocular-motor abnormalities were observed (no nystagmus, normal pursuit, and saccades). With fixation removed, the patient had a spontaneous upbeating nystagmus. The Dix–Hallpike test induced an increase in the intensity of the spontaneous nystagmus without positional vertigo. The clinical head impulse test (HIT) was abnormal bilaterally in the horizontal semicircular canal plane. The dynamic visual acuity test showed a loss from baseline of eight lines for horizontal head rotation. In the Romberg test, the patient fell backward with his eyes closed and during head motion. He was unable to walk without falling.

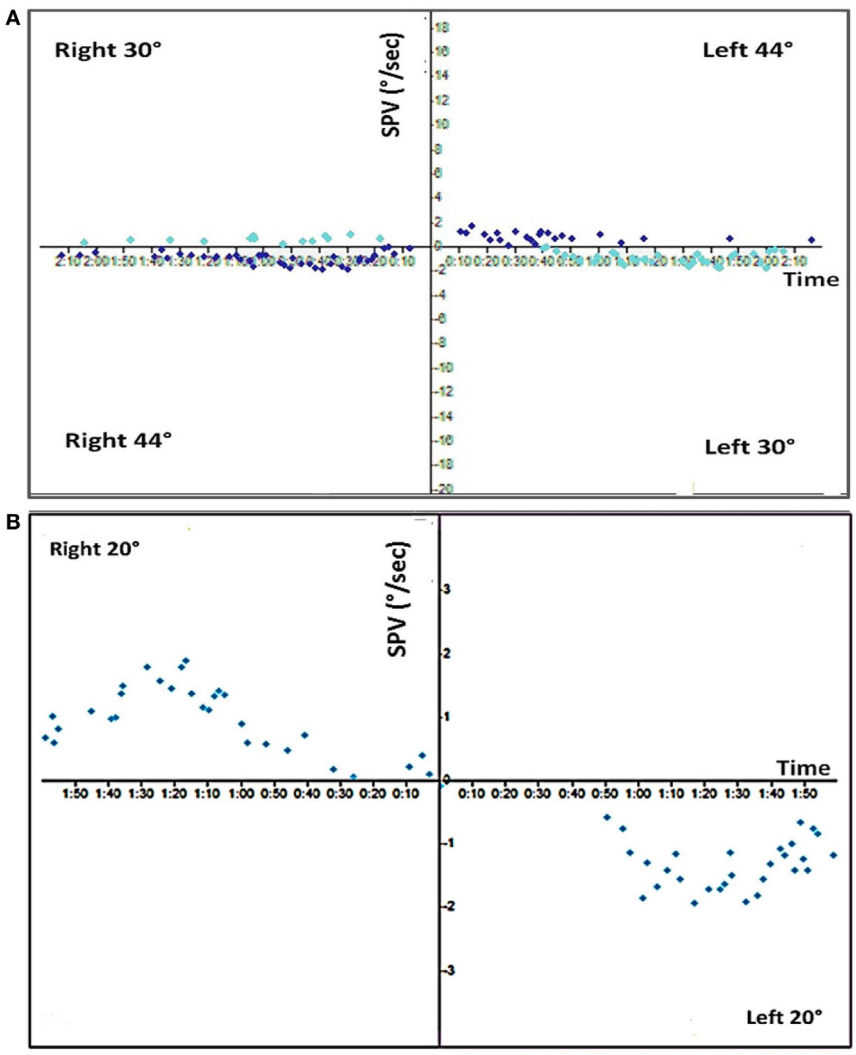

FIGURE 1 | Caloric exam. **(A)** Top, the standard bithermal caloric test showed no response to either temperature irrigation from either ear. **(B)** Bottom, ice water irrigation (20°C) shows only a minor residual response (total response = 4°/s).

Standard video-nystagmography (VO425-Interacoustics; Middelfart, Denmark) revealed normal smooth pursuit, saccades, and optokinetic nystagmus. However, bithermal caloric testing with water irrigation revealed a bilateral vestibular areflexia, with very weak, though residual responses to ice water irrigation (**Figure 1**). Video head impulse test (vHIT) (EyeSeeCam—Interacoustics, Middelfart, Denmark) showed a severe reduction in each horizontal and superior semicircular canal gains but a normal response in both posterior semicircular canal gains (**Figure 2**). The patient was started on a steroid taper over 2 weeks.

In a follow-up consultation 2 weeks later, air-conducted cervical and ocular vestibular evoked myogenic potential (cVEMP and oVEMP) (Eclipse-Interacoustics, Middelfart, Denmark) showed an absence of both oVEMP responses but normal cVEMP responses (**Figure 3**). The audiogram showed a mild, symmetrical (left–right) high frequency hearing loss with normal auditory evoked potentials. Extensive serological studies testing for paraneoplastic syndromes, auto-immunological panel including anti-cochlear antibody, viral hepatitis (A, B, C), Epstein–Barr virus, herpes simplex virus 1 and 2, varicella-zoster virus, HIV, human cytomegalovirus, venereal disease research laboratory test, and mycoplasma pneumonia were all negative. A second MRI 3 tesla (3 T Discovery 750, General Electrics, Milwaukee, WI, USA) did not show any changes within the auditory canal or of the brain structures (**Figure 4**).

The patient was seen again 30 days from initial examination with report of a positional vertigo. The Dix–Hallpike maneuver confirmed a posterior semicircular canal benign paroxysmal positional vertigo (PC-BPPV) on the right side. A repositioning maneuver (Modified Epley) resolved the PC-BPPV.

The patient completed a 5-month vestibular rehabilitation program including home exercises focused on vestibulo-ocular reflex (VOR) and balance exercises with only modest results (**Table 1**). At 6 months, the spontaneous upbeating nystagmus without visual fixation had disappeared. However, a new left-sided PC-BPPV was diagnosed, treated, and resolved. At 1-year follow-up, the patient was symptom-free at rest and low-velocity walking but reported oscillopsia during running or high-velocity head movement. Repeat vHIT did not show any change compared to earlier studies (**Table 1**). An improvement in the left oVEMP was documented (**Figure 3**).

Written informed consent was obtained from the participant for publication of this case report.

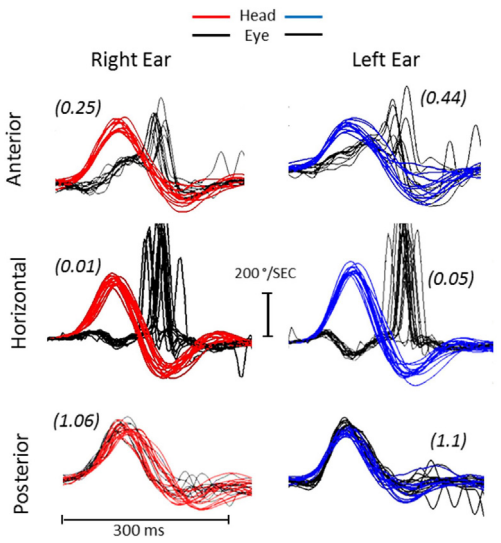

FIGURE 2 | Video head impulse test (vHIT). The vHIT shows severe and reduced vestibulo-ocular reflex (VOR) gain in the horizontal and superior semicircular canals with corrective compensatory saccades. Both posterior semicircular canals (RP, right posterior; LP, left posterior) show normal VOR gain (parenthesis) without compensatory saccades.

DISCUSSION

Bilateral vestibular hypofunction is characterized by unsteadiness of posture and gait with a disabling oscillopsia during head movements. Objective testing of the VOR using laboratory vestibular function tests confirms the BVH (7). Our case presents a clinical picture most compatible with acute BVH with preservation of hearing given the absence of a central nervous system lesion, hearing loss, or history of ototoxicity exposure. VN is typically unilateral and damages the superior vestibular nerve much more frequently than the inferior vestibular nerve (8). We propose our case is best explained as a bilateral VN, given that the pattern of damage has clearly damaged both superior vestibular nerves—as evidence from the reduction of VOR gain from each horizontal and superior semicircular canals and the utricle, with preservation of function in the posterior semicircular canal and saccule.

Substantial clinical features rule out a sequential VN as the first diagnostic: it is highly unlikely that the patient had a previous unilateral VN for three main reasons. First, there was no previous history of vertigo, dizziness, or any ancillary related symptoms like hearing disorders, gait unsteadiness, or BPPV as would be expected in the case of a prior unilateral reduction of vestibular function. Second, the symptoms of an acute unilateral vestibular hypofunction are accompanied with a mixed horizontal and torsional nystagmus that beats toward the more active labyrinth, which reduces once the asymmetrical vestibular tone is restored by central compensation. In a sequential VN, the second assault then causes the nystagmus to beat in the contralateral direction due to central decompensation (9) [known as Bechterew's phenomenon (10)]. Although our patient did experience a brief vertigo, likely signifying a brief asymmetric involvement as both systems were suffering impairment at different rates, our patient instead had a spontaneous upbeating nystagmus. In a bilateral superior vestibular neuropathy, a severe reduction of input from the horizontal and superior semicircular canals along with the utricles creates a bias in the neural resting activity of the residual posterior semicircular canals and saccule. This pattern of symmetric and unopposed vertical semicircular canal excitation results in an upbeat spontaneous nystagmus without a torsional component due to the roll components canceling, as described in the case of bilateral posterior canal stimulation (11). Finally, our patient developed BPPV, a common complication (16%) of VN of the superior branch given the spared posterior semicircular canal (3). This

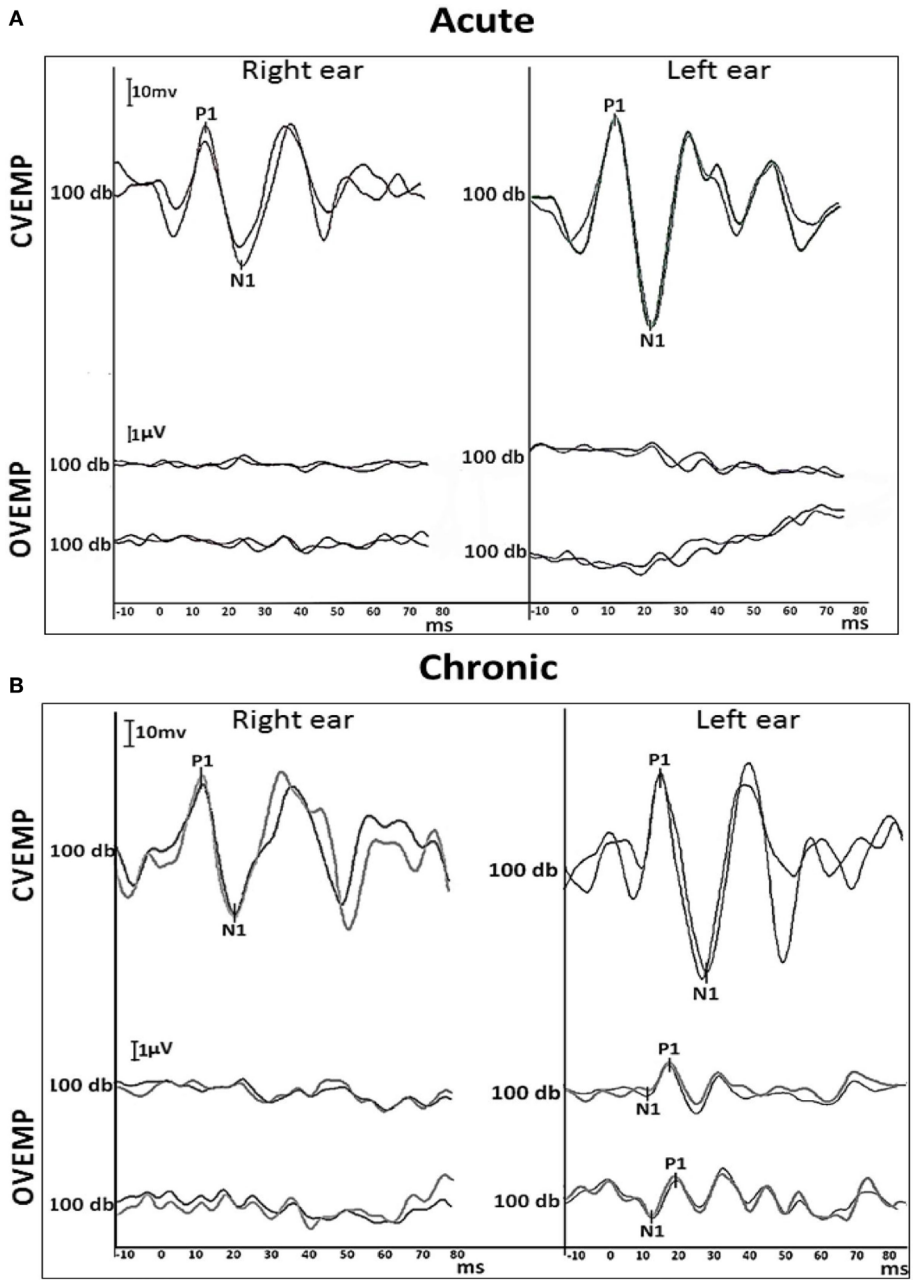

FIGURE 3 | Air-conducted VEMP traces. **(A)** Acute cervical (top) and ocular (bottom) VEMP responses recorded 2 weeks from the onset of symptoms. **(B)** Chronic cervical (top) and ocular (bottom) VEMP recorded again at 12 months. The cVEMP responses were reproduced bilaterally at the acute and chronic stages with latency, amplitude and asymmetry within the normal range. The cVEMP amplitudes [normalized to background electromyography (EMG) activation (EMG scaling)], showed <20% asymmetry, suggesting bilaterally spared inferior vestibular nerves. In contrast, the acute oVEMP showed no reproducible responses bilaterally. At 1 year, a reproducible oVEMP was observed only on the left side. Two trials were conducted in order to confirm results (two traces). Cervical and ocular VEMP waves of respective potentials (positive and negative deflections—P1/N1) were analyzed. Stimuli was a 100 db air-conducted 500 Hz tone burst.

is attributed to utricular damage that causes detached otolithic debris to fall into the neutrally active and ipsilateral posterior semicircular canal (12). Our patient had BPPV of both posterior semicircular canals during the follow-up, which provides additional evidence of damage to the superior branch without inferior branch involvement of the vestibular nerves.

Vestibular rehabilitation is known to help patients with BVH, though the range of meaningful change is highly variable and their quality of life often remains impaired (13, 14). Our patient did not have much improvement in the outcome measures we examined, matching prior report of stable function and highlighting the need for different forms of rehabilitation (15, 16).

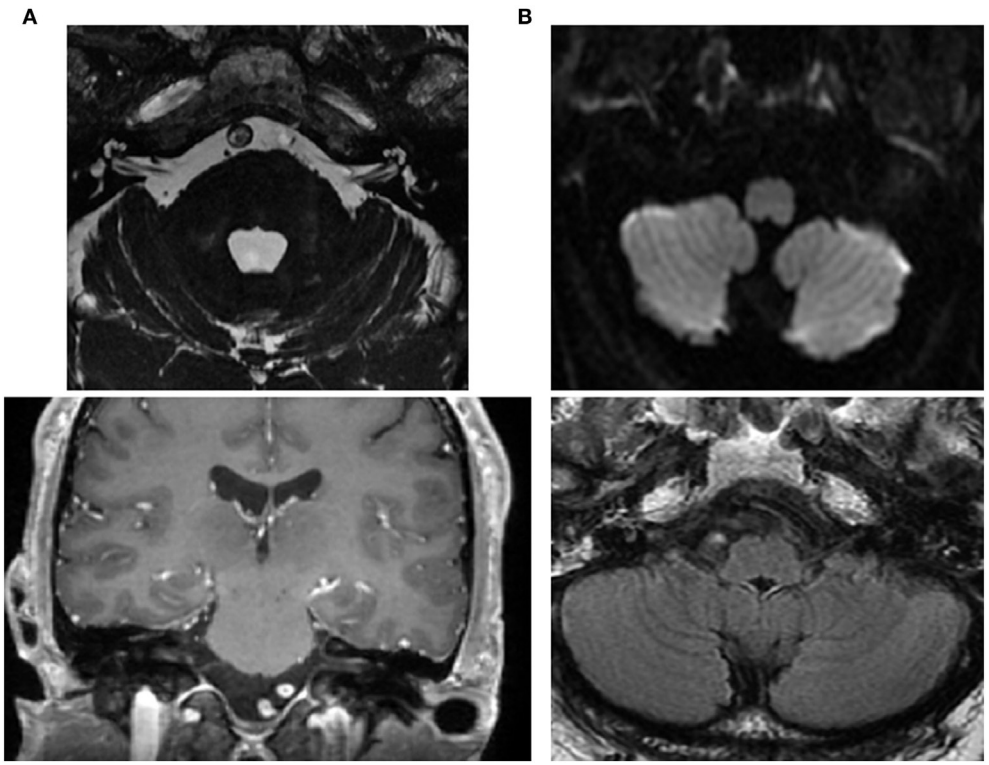

FIGURE 4 | Brain MRI. **(A)** Normal internal auditory canals as visualized *via* axial FIESTA (upper) and coronal T1 with contrast (lower). **(B)** Normal inferior and medial vestibular nuclei at the level of the medulla (axial diffusion—upper) and FLAIR (lower).

TABLE 1 | Comparison between pre- and post-vestibular rehabilitation program.

Evaluation	Pre	Post
Dizziness handicap inventory (DHI)		
– Total	64	48
– Emotional	18	12
– Functional	22	18
– Physical	24	18
Activities-specific balance confidence scale (ABC)	85%	88.12%
Oscillopsia visual analog scale (oVAS) while walking (0–10)	8.20	7.50
Modified clinical test for sensory interaction in balance (CSTIB)	90/120 s	90/120 s
Clinical vestibular dynamic visual acuity (DVA)—4 m		
– Difference from static acuity yaw plane	8 lines	7 lines
– Difference from static acuity pitch plane	5 lines	4 lines
Gait speed (comfortable) m/s	1.10	1.14
Functional gait assessment (FGA)	22/30	23/30
Vestibulo-ocular reflex Gain (vHIT)		
– aSCC (right/left)	0.25/0.44	0.36/0.42
– hSCC (right/left)	0.01/0.05	0.03/0.04
– pSCC (right/left)	1.06/1.10	1.03/1.12

Pre and 6-month post outcome measures of vestibular physical therapy. Modified CSTIB results reflect duration of time in standing on firm and foam surface with eyes open and closed (120 s is normal). VHIT gain results of all 6 canals did not change. aSCC, anterior semicircular canal; hSCC, horizontal semicircular canal; pSCC, posterior semicircular canal.

CONCLUSION

Our case report suggests that (1) VN can present bilaterally and suddenly; (2) in patients with acute onset of severe ataxia and oscillopsia, the clinician should rule out acute bilateral VN; (3) loss of caloric function by itself is insufficient to diagnose bilateral VN given its limit in identifying the spared vestibular function; and (4) therefore, examining each of the 10 vestibular end organs with VHIT and VEMPs in acute case presentations of BVH is the only way to identity of bilateral vestibular neuropathy as an independent condition.

ETHICS STATEMENT

This study was carried out in accordance with the University of Maimónides ethical standards. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

DY, VUJ, and DV oversaw the patient and collection of data. DY, JF, DV, and MS wrote and critically revised the manuscript.

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frontiers in Neurology

CASE REPORT
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Bilateral Vestibular Dysfunction Associated With Chronic Exposure to Military Jet Propellant Type-Eight Jet Fuel

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We describe three patients diagnosed with bilateral vestibular dysfunction associated with the jet propellant type-eight (JP-8) fuel exposure. Chronic exposure to aromatic and aliphatic hydrocarbons, which are the main constituents of JP-8 military aircraft jet fuel, occurred over 3–5 years' duration while working on or near the flight line. Exposure to toxic hydrocarbons was substantiated by the presence of JP-8 metabolite *n*-hexane in the blood of one of the cases. The presenting symptoms were dizziness, headache, fatigue, and imbalance. Rotational chair testing confirmed bilateral vestibular dysfunction in all the three patients. Vestibular function improved over time once the exposure was removed. Bilateral vestibular dysfunction has been associated with hydrocarbon exposure in humans, but only recently has emphasis been placed specifically on the detrimental effects of JP-8 jet fuel and its numerous hydrocarbon constituents. Data are limited on the mechanism of JP-8-induced vestibular dysfunction or ototoxicity. Early recognition of JP-8 toxicity risk, cessation of exposure, and customized vestibular therapy offer the best chance for improved balance. Bilateral vestibular impairment is under-recognized in those chronically exposed to all forms of jet fuel.

Keywords: JP-8, jet propulsion fuel-8, JP-8 jet fuel, bilateral vestibular dysfunction, ototoxicity, vestibulotoxicity, rotational chair, hydrocarbons

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INTRODUCTION

The primary jet fuel used in the United States Air Force and NATO military operations is jet propellant type-eight (JP-8). JP-8 is a kerosene-based fuel comprised of over 228 aromatic and aliphatic hydrocarbons (1). During 1992–1996, the Air Force transitioned from using JP-4 to JP-8 due to the improved safety profile of the latter. JP-8 is also used as a multipurpose fuel for ground vehicles, generators, tent heaters and air conditioners, lamps, and cooking stoves allowing for an array of exposure opportunities. JP-8 typically contains 18% aromatic hydrocarbons and 82% aliphatic hydrocarbons, in particular, 9% C8–C9, 65% C10–C14, and 7% C15–C17 (2). JP-8 differs from commercial airline fuel due to its military additives including static electricity/corrosion/icing inhibitors, thermal stability enhancers, and antioxidants.

Vestibulotoxicity from JP-8 has been suggested but not well-documented in previous studies. Several studies indicate an association with impaired balance (3, 4), hearing, and central auditory processing (5–8).

We present a case study of three patients who had chronic complaints of dizziness, headache, fatigue, and imbalance. One patient performed fuel-tank maintenance for the Air National Guard

for over a decade, while the other two worked 4–6 years in administrative positions in a small under-ventilated building proximate to the flight line. Each developed documented-bilateral vestibular dysfunction most probably related to chronic inhaled JP-8 fumes over a long period of time.

CASE REPORTS

Case 1: Military Flight Refueler

A 37-year-old woman presented with several years of progressively worsening continuous dizziness, headache, and fatigue. The dizziness consisted of sensations of spinning, tilting, disequilibrium, and head fullness. She did not report tinnitus or hearing loss. She was employed as a military flight refueler and exposed to JP-8 vapors and exhaust while working full-time on and around a KC-135E tanker aircraft, a plane used for performing in-flight refueling missions. She worked in a large enclosed hangar that housed all but the tail section of the tanker aircraft. During inspection and maintenance of the aircraft, up to 9,750 gallons of fuel would be loaded. Jet fuel vapors were always present in the hangar due to venting, small leaks, and fuel residue. Fuel vapor concentrations were even greater when engine maintenance necessitated removal of fuel filters and fuel components, draining of fuel into buckets, and opening of fuel lines. She worked in engine maintenance with over 4 years of inhalational and dermal exposure to JP-4 and JP-8.

Her examination showed moderately impaired equilibrium to walk only three steps in tandem before taking a sidestep. Romberg testing revealed more sway during eye closure but no falling. Her medical and neurological examinations were normal. There was no spontaneous, gaze, or positional nystagmus. Qualitative head impulse test was not performed at that time.

A brain SPECT study at an outside facility revealed mild-right frontal hypoperfusion that persisted on a repeated study the following year. Neurocognitive examination showed overall memory function in the 97th percentile. An MRI brain without gadolinium and an EEG were normal. An initial hydrocarbon assay revealed the presence of 3-methylpentane and *n*-hexane in the blood at concentrations of 27 and 15.7 ng/ml (parts per billion), respectively (none should be measurable in normal individuals). Ten months later, 3-methylpentane and *n*-hexane remained present although at significantly lower concentrations. Eighteen months after presentation, 3-methylpentane and *n*-hexane persisted in the blood and had only diminished an additional 20%. Rotational chair, more so than caloric vestibular testing, demonstrated bilateral vestibular dysfunction (**Figures 1** and **2**) with reduced gain values on step velocity along with a reduced time constant. Gain was also reduced on all sinusoidal rotations with increase phase lead at 0.01, 0.02, and 0.04 Hz rotations. The patient reported that her headaches, dizziness, fatigue, and mild unsteadiness improved somewhat following a transfer to the finance department where no JP-8 exposure existed. There was a long interval of 15 years since her initial visit when she was lost to follow up. Now, 16 years after her initial presentation, she reports that the dizziness is mild but headaches and severe fatigue persist. She has continued to work but plans to retire earlier than originally anticipated due to the ongoing symptoms. Recently, cervical and ocular vestibular-evoked myogenic potential (cVEMP and oVEMP, respectively) and video head impulst testing for each canal were performed and all results were normal.

Cases 2 and 3

The following two patients were employees in a small-purchasing warehouse, located 75 feet south of the flight path, which was separated from the blast and heat emissions from jet aircraft engines by a metal-coated and chain-link fence. Neither air conditioning vents nor carpet had not been cleaned or replaced for over a decade. On inspection, the vents were found to be malfunctioning such that air was able to enter the building but unable to escape. Subsequent inspection by the U. S. Occupational Safety and Health Administration (OSHA) confirmed poor ventilation evidenced by carbon dioxide concentrations >1,500 ppm (normal <1,000 ppm according to the U.S. Department of Labor). Hydrocarbons discovered in the carpet *via* an independent analysis using gas chromatography/mass spectrometry included

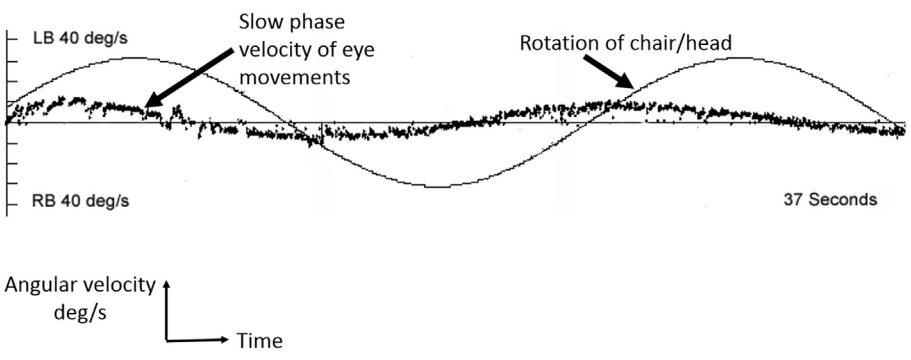

FIGURE 1 | Example of vestibular hypofunction seen across all frequencies for Case 1. A sinusoidal rotation at 0.04 Hz, 60 deg/s by rotational chair testing. The smooth sinusoid is the chair/head rotation at 0.04 Hz, and the scatter line represents the slow phases of compensatory nystagmus in response to the sinusoidal head (and chair) rotations. The abscissa is time measured in seconds. LB, left beating nystagmus; RB, right beating nystagmus. Performed using Micromedical Technologies (Chatham, IL, USA).

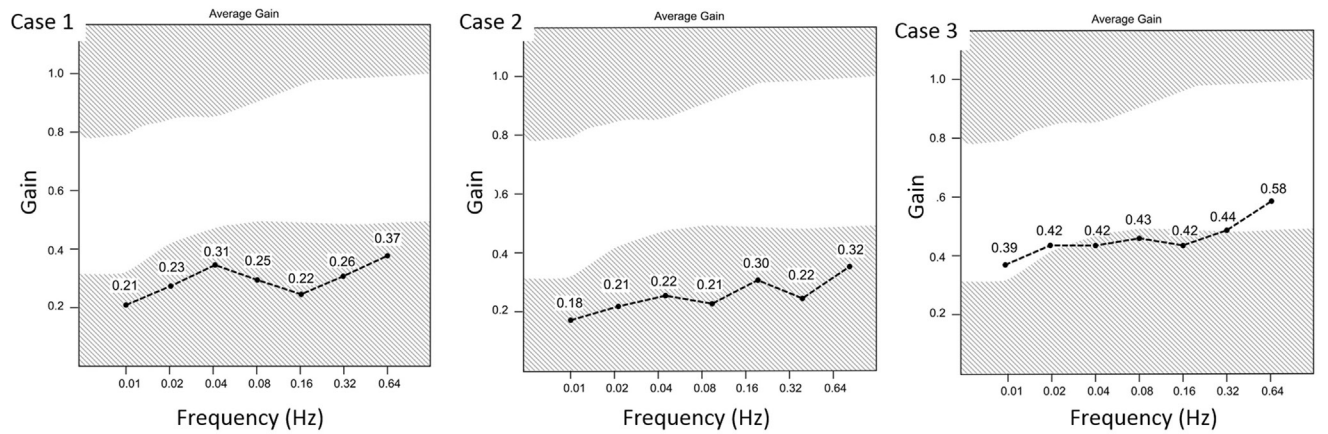

FIGURE 2 | The summary of average gain values at frequencies between 0.01 and 0.64 Hz sinusoidal rotations. The gain values were below normal for all frequencies tested for Cases 1 and 2 and were reduced at most frequencies for Case 3.

undecane (C11), dodecane (C12), tridecane (C13), tetradecane (C14), and toluene (C8)—all known JP-8 constituents (2). The chemicals present in the office carpet likely reflected poor indoor air quality. Vapor, aerosol, dermal, and eye absorption of JP-8 are presumed.

Case 2: Warehouse Employe 1

A 45-year-old female contracting officer for the National Guard reported several years of imbalance, headache, fatigue, eye and skin irritation, coughing, sinus congestion, recurrent urinary tract infections, chest tightness, irritability, depression, shortness of breath, palpitations, and numbness. She described her dizziness as an intermittent floating and a rightward tilting sensation with imbalance lasting minutes to hours without any particular pattern. She had a history of asthma and allergies including reaction to aspirin causing urticaria and airway obstruction. In 1998, she developed syncope and dizziness though no specific cause was found. She started working in the building in 1994 and worked there full-time for 5 years.

Her examination was normal except that she fell on Romberg testing and could only walk a few steps in tandem. Brain MRI, EEG, audiogram, and pulmonary function tests were normal. Quantitative rotational chair and caloric vestibular tests revealed bilateral peripheral vestibular dysfunction (**Table 1**; **Figure 2**). Her caloric responses improved following removal from the under-ventilated environment (**Table 1**).

Case 3: Warehouse Employe 2

A 54-year-old female National Guard contract specialist presented with 2 years of intermittent dizziness, blurred vision, and occasional palpitations. Dizziness was experienced at least 3 days a week. She reported intermittent problems with erratic heart beats, cough, sneezing, headaches, fatigue, recurrent sinus infections, upper respiratory tract, and bladder infections. She worked in the purchasing warehouse full-time for 3 years. When away from the workplace her symptoms were improved. After moving with her colleagues into a new building, the frequency of dizziness was lessened.

TABLE 1 | Caloric vestibular test results of each case.

	Timing[b]	RC[a]	RW[a]	LC[a]	LW[a]	VR%	DP%
Case 1	0	16	12	14	20	9 Right	16 Left
Case 2	0	5	7	6	8	7 Right	0
Case 2	16 Months	19	32	30	21	0	22 Right
Case 3	0	23	17	11	10	31 Left	8 Right
Case 3	7 Months	20	32	20	36	3 Right	3 Left

All studies performed with water caloric irrigation using ICS Chartr VNG, now GN Otometric (Schaumburg, IL).

[a]Peak slow phase velocity in degrees/second of caloric-induced nystagmus.

[b]Time 0 = initial presentation. Subsequent studies designated as months subsequent to presentation.

RC, right cool irrigation, LC, left cool irrigation, RW, right warm irrigation, LW, left warm irrigation; VR, vestibular response asymmetry as a percentage using Jongkees formula; DP, directional preponderance which reflects the direction (rightward versus leftward) of the bithermal caloric-induced nystagmus expressed as a percentage using Jongkees formula.

Her medical, neurological, and oto-neurological examinations were normal. Electronystagmography revealed somewhat reduced caloric vestibular responses for age and a 33% reduced vestibular response on the left. Rotational testing showed reduced gain with sinusoidal rotational stimuli at frequencies from 0.02 to 0.16 Hz (**Figure 2**). Her caloric responses improved following removal from the "sick-building" environment (**Table 1**). Computerized dynamic posturography showed falls on conditions 4, 5 and 6 indicating some general impairment of equilibrium and a predominant vestibular deficit pattern. Audiometric tests were normal except for mild-sensorineural hearing loss in the right ear from 250 to 8,000 Hz and borderline normal left-sided hearing from 250 to 2,000 Hz sloping to a moderate loss between 3,000 and 8,000 Hz.

DISCUSSION

These case reports describe three women working in close proximity to JP-8 jet fuel who developed bilateral vestibulopathy after 3–5 years of exposure. Serum studies in one of the patients (Case 1) demonstrated JP-8 fuel metabolites 3-methylpentane

and *n*-hexane (1). These compounds are not present in human blood normally. The levels of these metabolites diminish over time once the individual is removed from repeated exposure. Quantitative vestibular testing revealed bilateral vestibular dysfunction in all three patients after JP-8 exposure. There was no other probable identifiable explanation for the vestibular dysfunction. Although causal relationship cannot be definitively proven yet, this collection of data suggests a relationship between prolonged exposure to JP-8 fuel and development of bilateral vestibular dysfunction which has not previously been documented in humans.

The presence of bilateral vestibular dysfunction in these cases may be due to a process localizing to the vestibular nerves, the vestibular end-organs, or a combination of both. However, the constituent hydrocarbons in JP-8 are lipophilic and have been shown to affect the CNS so a peripheral vestibular mechanism is assumed but not assured. Indeed, for Case 1 on whom we have long-term follow up, headaches and severe fatigue have persisted for years, which are symptoms associated with CNS hydrocarbon toxicity. A CNS toxicity contribution might also explain the chronicity of symptoms and lackluster response to vestibular rehabilitative efforts. The relative preservation of caloric vestibular responses (**Table 1**) in the presence of prominent pan-frequency vestibular dysfunction on rotational chair testing raises the possibility of some degree of frequency-specific ototoxicity (9). Furthermore, improvement in the caloric responses with removal from continued exposure implies the possibility of some degree of reversibility of vestibular dysfunction. Dedicated occupational studies in humans on the vestibular effects of chronic JP-8 exposure are limited and data are still sparse on the direct mechanisms of ototoxicity due to jet fuel.

Human Studies

A study of the effects of low-level exposure to JP-8 fuel vapor in U.S. Air Force aircraft maintenance personnel found a correlation between solvent exposure (benzene, toluene, xylene) and increased postural sway implying vestibular or proprioceptive impairment (3). Another study of 37 Air Force personnel with short-term work day exposure to JP-8 did not identify increases in postural sway (4). Long-term exposure to jet fuel in a subset of eight subjects assessed by vestibular testing found minor vestibular abnormalities but those patients actually reported more cognitive symptoms than vestibular findings (10).

Liquid hydrocarbon fractions are distilled from petroleum based on density. Although there may be variations in composition, these hydrocarbon mixtures have toxic effects on the human body similar to jet fuels (11). Some organic solvents commonly used in commercial industries are also hydrocarbon mixtures and would be expected to have similar toxicities. Indeed, dizziness, sometimes but not always resulting in vestibular test abnormalities, is a common symptom among individuals exposed to organic solvents (12). Workers exposed chronically to toluene and ethanol for many years exhibited reduced pursuit tracking and increased postural sway; and the latter suggests possible impairment of vestibular function (13). A study of three welders with short-term exposure to hydrocarbons found vestibular nystagmus and vestibular abnormalities that persisted for 3–18+ months after exposure (14).

It has been suggested that aliphatic and aromatic hydrocarbon toxicity may be associated with bilateral vestibular dysfunction, dizziness, and abnormal performance on posturography testing (3, 15). Although, organic solvents may have toxic effects on peripheral vestibular function or brainstem vestibular pathways (16), most of the data simply suggest increased sway in those exposed, which is not necessarily a specific indicator of vestibular dysfunction. A small study of 18 individuals with exposure to organic solvents found a significantly greater number with abnormal vestibular function including oVEMP and cVEMP, and caloric testing when compared to unexposed controls. The authors suggest that organic solvent toxicity may adversely affect the function of the utricle and saccule to a greater degree than hearing or semicircular canal function (17).

Animal Studies

Studies in rats exposed to JP-8 vapor for 6 h per day, 5 days per week for a total of 1 month showed that pure-tone hearing thresholds, outer hair cell function, and hair cell numbers remained unaffected with exposure of 1,500 mg/m^3. However, when rats were exposed to JP-8 plus noise, marked decreases in distortion produce otoacoustic emissions amplitude, increases in pure-tone auditory threshold along with a small reduction (<1%) in the number of cochlear outer hair cells were detected (18, 19). A study of 26 pigmented rats exposed to toluene in a prosptective cross-over control study found a dose-related reduction in VOR suppression and reduced VOR gain and time constants (20). Another study in rats exposed to 1,000 mg/m^3 of JP-8 found impaired encoding of stimulus intensity both in rats exposed only to JP-8 and in those exposed to JP-8 and noise. There were no changes in auditory thresholds and no loss of cochlear outer hair cells; however, there was impaired brainstem encoding of stimulus intensity indicating dysfunction of central auditory processing (6, 8).

There are no studies of the long-term effects of JP-8 specifically on peripheral vestibular function in humans. This may be in part because many exposed personnel tolerate limited exposure well, and those that do have symptoms have not been evaluated and reported in published literature. Bilateral vestibular dysfunction, regardless of cause, is probably under-recognized in clinical medicine (21). Hence, the true incidence of vestibulopathy from jet fuel exposure is unknown.

Human Exposure and Absorption of Jet Fuel

Military duties such as fuel transportation, aircraft fueling and defueling, aircraft maintenance, cold aircraft engine starts, maintenance of equipment and machinery, use of tent heaters, and cleaning or degreasing with fuel may result in jet fuel exposure. Fuel handlers, mechanics, flight line personnel, especially crew chiefs, and even incidental workers remain at risk for developing illness secondary to chronic JP-8 fuel exposure in aerosol, vapor or liquid form. JP-8 is one of the most common occupational chemical exposures in the US military (1). The Air

Force has set recommended exposure limits for JP-8 at 63 ppm (447 mg/m^3 as an 8-h time-weighted average) (22).

In addition to exposure by JP-8 vapor inhalation, toxicity may also occur by absorption through the skin, which is proportional to the amount of skin exposed and the duration of exposure (23, 24). In addition to the standard operating procedure and safety guidelines, double gloving, immediate onsite laundering of contaminated/soiled jumpsuits, regular washing of safety goggles and masks, reduced foam handling time, smoking cessation, adequate cross ventilation, and frequent shift breaks may reduce the overall risk of JP-8 induced illness (1, 2). At this time, OSHA has not determined a legal limit for jet fuels in workroom air. The U.S. National Institute of Occupational Safety and Health set a recommended limit of 100 mg/m^3 for kerosene in air averaged over a 10-h work day. Multi-organ toxicity has been documented from JP-8 exposure in animal experiments over the past 15 years. More recently, toxicology researchers are investigating the adverse tissue effects of JP-8 jet fuel in concentrations *well below* permissible exposure limits. Ultimately, the new data may help us to better understand the emerging genetic, metabolic and inflammatory mechanisms underpinning JP-8 cellular toxicity—including auditory and vestibular toxicity—and lead to a reassessment of the safe JP-8 exposure limits (25, 26). In the meantime, bedside vestibular screening for vestibular dysfunction can be performed by dynamic visual acuity testing or by head impulse testing.

Are there any known JP-8 biomarkers? Yes. Breath, blood, urine, and microRNA tissue biomarkers have been studied and aid in confirming JP-8 exposure. Self-reported JP-8 exposure in the workplace is a reliable indicator and a stronger predictor of measured exposure than job title (27). After controlling for work shift smoking, measurements of blood volatile organic compounds (ethylbenzene, toluene, xylene) are higher among US Air Force personnel self-reporting JP-8 exposure in association with elevated hydrocarbons in the breathing zone (28). Urinary biomarkers 1- and 2-naphthol, the metabolites of naphthalene, are the most sensitive and useful short-term surrogates of JP-8 exposure due to their strong correlation with breathing zone naphthalene, greater abundance, and slower elimination kinetics (29, 30). Blood microRNAs (miRNAs) may be unique biomarkers for volatile organic compounds and have been compared recently to urinary biomarkers in human dockyard workers found to have toluene, xylene, and ethylbenzene in whole blood. Fifty subjects underwent miRNA microarray analysis and 211–695 mRNAs were identified for toluene, xylene, and ethylbenzene suggesting higher sensitivity, specificity, and accuracy than urinary biomarkers (31). The analysis of circulating miRNAs in the blood of military veterans exposed to JP-8 is worthy of future research.

CONCLUSION

Bilateral vestibular dysfunction in these three patients with prolonged vapor and dermal JP-8 fuel exposure should raise awareness in people with occupations that expose them to jet fuels, liquid hydrocarbons, or organic solvents. Dizziness and mild imbalance may be the main initial symptoms. Early recognition and limiting further exposure as well as treatment with vestibular therapy (32) may improve their function and quality of life.

ETHICS STATEMENT

Written informed consent to publish the report was obtained from each patient. This report was approved by the local Institutional Review Board at Barrow Neurological Institute/DignityHealth, Inc., case series tracking number Case Series 18-004.

AUTHOR CONTRIBUTIONS

TF attended to the three patients in oto-neurological consultation, contributed to project conception, data collection and analysis, critical revision, and final approval of the manuscript. MR contributed to project conception, scientific poster presentation, data collection and analysis, drafting of the article and critical revision, and final approval of the manuscript. KriS contributed to drafting of the article and critical revision and final approval of the manuscript. KaS contributed to critical revision and final approval of the manuscript.

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Vestibular Dysfunction in Wernicke's Encephalopathy: Predominant Impairment of the Horizontal Semicircular Canals

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Background: Wernicke's encephalopathy (WE), a metabolic disorder due to thiamine deficiency, manifests with various neurological symptoms and signs. It has been known as a cause of vestibular dysfunction. Preliminary reports have proposed predominant involvement of the horizontal semicircular canals (HSCs).

Objective: To better characterize the pattern of vestibular impairment in patients with WE using quantitative video head-impulse testing and to review the literature regarding this topic.

Method: From January 2014 to December 2016, we retrospectively enrolled five cases of WE that received quantitative video-head-impulse testing (vHIT). We retrieved the clinical features from the medical records and reviewed quantitative head-impulse testing (qHIT) and caloric irrigation. Based on the gain and the number of corrective saccades, the function (normal vs. impaired) of each semicircular canal was rated. In addition, we conducted a MEDLINE and EMBASE search to identify other published cases of WE that had received qHIT. Neuro-otologic and neuro-ophthalmologic findings and vestibular testing results were extracted.

Results: A total of 17 patients (own series = 5; published cases = 12) aged 54.6 ± 11 years were included. Key neurologic findings were ataxia of stance and gait (13/13, 100%), spontaneous nystagmus (7/14, 50%), gaze-evoked nystagmus (GEN) (17/17, 100%), positive bedside head-impulse testing for the horizontal canals (16/17, 94%), and memory impairment and mental changes (6/11, 54.5%). Regarding vestibular testing, qHIT (either video based or search-coil based) documented selective bilateral horizontal canal dysfunction with normal or minimal vertical canal impairment (14/14, 100%). On caloric irrigation, bilateral horizontal canal paresis was noted in most cases (10/11, 91%).

Conclusion: In WE, signs of both peripheral and central vestibular dysfunction (i.e., GEN, ataxia of stance and gait, abnormal head-impulse testing) were common. Selective or predominant impairment of the HSCs seems to be the most common finding of WE likely related to enhanced vulnerability of the medial vestibular nuclei neurons to thiamine deficiency. Quantitative vHIT of all six semicircular canals is therefore a useful tool for the diagnosis and should be applied in all patients with suspected WE.

Keywords: vestibulo-ocular reflex, Wernicke encephalopathy, thiamine deficiency, head-impulse test, bilateral vestibulopathy

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INTRODUCTION

Wernicke's encephalopathy (WE) was first described in 1881, and later the disease was named after a German doctor, Carl Wernicke (1, 2). At that time, the cause of WE was unknown, and it took another 50 years to link thiamine deficiency with the disease (3). Various medical conditions associated with nutritional deprivation such as hyperemesis gravidarum, intestinal obstruction, malignancy, and alcoholism may result in WE (4). WE is a potentially fatal disease that is still underdiagnosed in both adults and children. In adults, prevalence of WE lesions (0.8–2.8%) were higher than expected by clinical studies (0.04–0.13%) (5, 6). WE is more common in males (male-to-female ratio: 1.7 to 1) and the estimated mortality is 17% (2, 5). These numbers emphasize the need for improved diagnostic testing.

The classic symptom triad of WE consists of mental status changes, ophthalmoplegia, and gait ataxia (2, 4). However, the complete triad may be present in as few as 16–19% of cases (6, 7). For diagnostic purposes, therefore, requiring all three findings will result in low sensitivity. This is taken into account by published diagnostic guidelines such as the EFNS guidelines (8), requiring only two out of four signs (dietary deficiencies, eye signs, cerebellar dysfunction, and either an altered mental state or mild memory impairment).

Both horizontal, vertical, and gaze-evoked nystagmus (GEN) (unilateral or bilateral) abducens palsy (eventually progressing to complete external ophthalmoplegia) and internuclear ophthalmoplegia may be found (9). In a large case series with 232 WE patients, nystagmus was the most commonly (85%) described neuro-ophthalmologic finding, whereas other findings including ophthalmoplegia were less often reported (5). For detecting vestibular impairment, the angular vestibulo-ocular reflex (aVOR) can be assessed. This can be achieved by the horizontal head-impulse test at the bedside (10) or by quantitative aVOR measurements. Bilateral and often severe impairment of the horizontal aVOR is characteristic of WE and has been quantified using caloric irrigation and rotational chair testing in the past (11, 12). However, these studies were limited in the assessment of peripheral-vestibular function, as no testing of the vertical canals was possible. With the recently developed video-head-impulse testing (vHIT), quantitative assessment of all six semicircular canals became available to the clinician (13, 14). Its reliability and value in the emergency setting has been demonstrated before (15). As WE is a potentially reversible vestibulopathy if thiamine replacement is initiated in a proper and rapid manner, using the vHIT on the ED may provide very useful in assessing any vestibular impairment (16).

These considerations have fueled research interest in vestibular dysfunctions of WE, potentially supporting the diagnosis by providing a specific pattern of semicircular canal impairment. However, so far only few studies with small sample sizes have been published on this topic. Based on preliminary data from small case series and single case studies, relative sparing of the vertical canals seems to be a typical feature of vestibular impairment in WE. To increase the number of published cases and to further advance on this topic, we screened our own vHIT-database for WE patients and assessed the pattern of semicircular canal impairment. In addition, we will review and summarize the literature regarding this topic.

MATERIALS AND METHODS

Patient Selection

We searched the electrical medical recording system for patients presenting to the emergency department or the outpatient clinic of the Department of Neurology, Chonnam National University Hospital, Gwangju, South Korea that received a diagnosis of WE. Between January 2014 and December 2016, we retrospectively identified 11 WE patients who received quantitative vestibular testing. Five consecutive patients were eligible. Six patients had to be excluded because of incomplete data (missing vHIT, $n = 5$) or completely resolved symptoms and signs at the time of testing ($n = 1$). Eventually, five patients with WE with typical history (i.e., chronic alcohol abuse, poor feeding due to gastrointestinal surgery) and laboratory (i.e., low thiamine levels), neurologic (i.e., spontaneous or GEN or ophthalmoplegia, ataxia, impaired memory or mental change), and radiologic [brainstem, mammillary body and/or thalamic lesions on T2, fluid-attenuated inversion recovery (FLAIR) or diffusion-weighted imaging (DWI) on magnetic resonance image (MRI)] findings were enrolled. As this was a retrospective case series, no pre-defined diagnostic criteria for inclusion were available and we had to rely on the treating physicians' final diagnosis.

Video-oculography (VOG; SLMed, Seoul, South Korea) was performed in a sitting position for the detection of spontaneous (horizontal or vertical) nystagmus and GEN. All subjects received a detailed neurologic examination and vHIT and did not show evidence of central or peripheral vestibulopathy. This study was carried out in accordance with the recommendations of the Institutional Review Board of the Chonnam National University Hospital (Gwangju, South Korea) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the Chonnam National University Hospital (Gwangju, South Korea).

Caloric Testing

The caloric stimuli comprised alternating irrigation for 60 s with cold and hot air (24 and 50°C; 8 L/min). Nystagmus was recorded binocularly using VOG. Bilateral vestibulopathy was defined as an overall absolute slow-phase velocity of the nystagmus of less than 20°/s for all four stimulation conditions together (17).

Video-Head-Impulse Testing

A structured bedside neuro-otologic examination was obtained from all patients at the emergency department or in the dizziness clinic of the Chonnam National University Hospital. Quantitative vHIT was obtained by use of a lightweight, portable VOG device (ICS Impulse; Otometrics, Taastrup, Denmark). Therefore, patients were asked to look at a distant target (~1.5 m away) while seated. For calibration of eye position, laser targets projected from the goggles were used. Afterward, the examiner applied a series of horizontal head-impulses to the left and right

in random order. Vertical head-impulses were applied along the left-anterior–right-posterior canal plane and along the right-anterior–left-posterior canal plane (13). We aimed for head velocities between 150 and 200°/s and head displacements of 10–20°. For each canal, 20 valid head-impulses were required. Gains of the vHIT recordings were analyzed using OtosuiteV 4.0 (Otometrics). The VOR gain was calculated as the ratio of cumulative slow-phase eye velocity over cumulative head velocity from the onset of the head impulse to the moment when head velocity returned to 0 (13). This software visualizes all compensatory saccades to ensure accurate characterization. Overt saccades were defined as saccades that occurred in the opposite direction of the head rotation and that reached peak acceleration after the head had stopped moving. Covert saccades, on the other hand, reached peak acceleration before the head had stopped moving (18). Traces with artifacts (e.g., blinks during the head-impulse) were removed interactively (19). If spontaneous nystagmus (SN) was present, OtosuiteV 4.0 was operated in the nystagmus-adjusted interpretation mode. Thereby filtering algorithms for determining inadequate impulses are adjusted and traces with SN otherwise removed because of high velocity saccades will be considered as well. This makes the algorithm more robust in the presence of SN, but at the same time bears the risk of slightly less accurate aVOR gain calculations if saccades occur during the aVOR. Noteworthy, a distinction from early (covert) catch-up saccades (CS) is usually readily possible. Therefore, visual inspection as done for all traces as part of the overall rating of vHIT will ensure inappropriate traces may still be removed. All vHIT traces were independently reviewed by two experienced neuro-otologists (Seung-Han Lee and Alexander Andrea Tarnutzer). Reviewers were blinded to the clinical findings and the results from MR imaging. We used the cutoff values in VOR gains as proposed by the manufacturer of the video-goggles (Otometrics), i.e., 0.8 for the horizontal canals and 0.7 for the vertical canals. These values were also in agreement with normative values for a wide range of ages reported (20). The video-head impulse traces were evaluated by the reviewers for reduced VOR gain, increased corrective saccades, or a combination of both (21) and rated as either normal or impaired.

Neuroimaging

According to the imaging protocol of the Chonnam National University Hospital, all patients suspected to have WE underwent MR imaging at the emergency department or the dizziness clinic of the Department of Neurology. The MRI protocol consisted of axial DWI, axial FLAIR, axial gradient-echo sequences, and time-of-flight MR angiography in a sequential manner. MR-sequences were analyzed independently by two neurologists (Seung-Han Lee and Sang-Hoon Kim), who were blinded to the clinical data. Discrepancies were resolved by consensus.

Review of the Literature

We conducted a review of the literature on WE. We searched MEDLINE (*via* PubMed) and EMBASE using the following terms: WE, thiamine deficiency, Wernicke–Korsakoff syndrome, vestibular, dizziness, vertigo, ataxia, and nystagmus. This literature search was conducted in November 2017. Articles were selected using predetermined criteria. These criteria excluded reports that were not written in English language, did not include human subjects, lacked original patient data, did not provide a description of vestibular symptoms, or did not indicate vestibular function testing. For inclusion, thiamin-deficiency and confirmed bilateral vestibulopathy (either by caloric irrigation or head-impulse-testing) were required. From suitable cases, we extracted both clinical data and results from vestibular testing [caloric irrigation and/or quantitative head-impulse testing (qHIT)].

We identified 13 articles (out of 1,167), 8 of which were excluded due to either the presence of only descriptive vestibular symptoms and/or tests (i.e., caloric irrigation) without reporting head-impulse data ($n = 7$) or duplicated data ($n = 1$). After a full-text review, we found 5 manuscripts reporting on a total of 12 cases with WE that included head-impulse testing of both the horizontal and the vertical canals (16, 22–25). From one publication, two cases were excluded due to the lack of head-impulse testing of the vertical canals (16), whereas from another publication, one case was excluded due to duplicity (24).

RESULTS

Representative Case

In June 2011, a patient in the early 60s (patient #2) was referred to the dizziness clinic of the Department of Neurology, Chonnam National University Hospital, due to gait disturbance and oscillopsia. In May 2010, he had a laparoscopic colectomy due to suspected colon cancer. About 1 month after the colectomy, an entero-cutaneous fistula developed as a complication. For about 50 days, total parenteral nutrition (TPN) and antibiotic treatment were performed. Fistulectomy and extended right hemicolectomy were performed in August 2010 and TPN was stopped again. In January 2011, the caregivers noted an impairment of memory. However, at that time no further evaluations were performed. When referred to the dizziness clinic 5 months later, the initial neurologic examination revealed a recent memory impairment with normal mental status, GEN and gait ataxia. Also, the bedside head-impulse test for the horizontal canals showed bilateral CS, and bithermal caloric irrigation demonstrated bilateral canal paresis (see **Tables 1** and **2**). Brain MRI demonstrated atrophy of the mammillary bodies, with increased signal intensity on FLAIR imaging, suggestive of chronic WE. From the time, the diagnosis of WE was established, one of the authors (Seung-Han Lee) followed-up the patient and regularly assessed vestibular function. Whereas the patient received ambulatory vestibular rehabilitation, the bedside head-impulse test remained abnormal bilaterally. In October 2014, vHIT was performed, demonstrating low gains and clear CS (overt and covert) in both horizontal canals. In February 2016, the vHIT was repeated, indicating persistent impairment of the horizontal canals.

Clinical and Laboratory Findings in Our Patients

A total of five patients (four men and one woman) with a mean age of 58.2 years (SD = 14.7 years) were included in this retrospective data analysis. The causes of thiamine deficiency were alcoholism

TABLE 1 | Demographical and clinical findings of five patients with WE.

#	Age range (years)	Cause of WE	D/V	M/M	Op	G/S	SN	GEN	bHIT for HC	Thiamine (initial)[b]	Abnormalities on brain MRI	Thiamine replacement	Recovery
1	66–70	Alcohol	Y	Y[a]	Partial bilateral 6th palsy	Y	UB	Y	CS/CS	33.78	T2/FLAIR lesions in MVN, PAG, MB, HT, medial thalamus	IV (1,500 mg/day for 3 days, then 250 mg/day for 4 days) followed by PO (thiamine HCL 30 mg/day for 22 months)	All symptoms resolved after 6 months (22 months F/U in total)
2	66–70	Gut OP/TPN	Y	Y	N	Y	N	Y	CS/CS	NA	FLAIR lesions in MB and atrophy of MB	PO (thiamine HCL 20 mg/day + benfotiamine 138.3 mg/day for ~5 years)	Not improved (~6 years F/U in total)
3	36–40	Alcohol	N	N	N	Y	N	Y	CS/CS	NA	FLAIR lesions in MB and PAG	IV (1,500 mg/day for 7 days), followed by PO (thiamine HCL 30 mg + benfotiamine 138.3 mg/day for 21 days), then (thiamine HCL 20 mg/day + fursultiamine 54.57 mg/day for 20 months)	G/S—persistent (2.5 years F/U in total); others—improved
4	66–70	Alcohol	N	Y	N	Y	N	Y	CS/CS	56.17	T2/FLAIR lesions in PAG, medial thalamus, MB; atrophy of MB	IV (750 mg for 7 days) → PO (thiamine HCL 90 mg + benfotiamine 138.3 mg for 3 months) → (thiamine HCL 40 mg/day + benfotiamine 138.3 mg/day for 7 months)	Mental, G/S—improved; memory, HIT—persisted during 9 months F/U
5	46–50	Alcohol	N	N	N	Y	UB	Y	CS/CS	51.23	NS	IV (600 mg/day for 10 days), followed by PO (thiamine HCL 90 mg/day + benfotiamine 138.3 mg/day for 1 month)	Complete
All	58.2 (±15)	Alcohol (n = 4), TPN (n = 1)	2/5	3/5	1/5	5/5	2/5	5/5	5/5	47 (±11.7)	4/5	IV + PO (n = 4), PO only (n = 1)	Complete (n = 2), partial (n = 2), none (n = 1)

[a]*Mild memory impairment.*

[b]*Normal range of total serum thiamine levels for this study was 66–200 nmol/L.*

bHIT, bedside head-impulse testing; CS, catch-up saccades; D/V, dizziness and/or vertigo; F, female, FLAIR, fluid-attenuated inversion recovery; GEN, gaze-evoked nystagmus; G/S, gait and station impair; HT, hypothalamus; IV, intravenous; M, male, M/M, memory impairment or mental change; MB, mammillary body; MVN, medial vestibular nucleus; N, no; NA, not available; NS, non-specific; Op, ophthalmoplegia; PAG, periaqueductal gray matter; PO, per oral; SN, spontaneous nystagmus; TPN, total parenteral nutrition; UB, upbeat nystagmus; WE, Wernicke's encephalopathy; Y, yes; MRI, magnetic resonance image.

TABLE 2 | Findings of caloric irrigation and video-head-impulse testing (vHIT) in five patients with Wernicke's encephalopathy.

#	bHIT for HC	O-to-A (d)	T-to-C (d)	T-to-vHIT (d)	SPV on caloric irrigation (°/s)				vHIT[a] (gains and CS)							
					RC	RW	LC	LW	RH	LH	RA	LA	RP	LP	CS (RH/LH)[b]	CS (RA/LA)	CS (RP/LP)
1	CS/CS	8	4	4[c]	4.3	−3.0	−4.6	1.6	***0.66***	***0.67***	0.82	0.83	0.76	0.86	+/+	−/−	−/−
2	CS/CS	240	78	78	4.2	−3.6	−5.1	2.8	***0.55***	***0.68***	0.81	0.93	1.09	0.81	+/+	−/−	−/−
3	CS/CS	90	2	2	7.7	−5.4	−10	9.1	***0.49***	***0.67***	0.88	0.90	1.08	1.00	+/+	−/−	−/−
4	CS/CS	30	4	4	4.9	−2.9	−3.2	6.7	***0.77***	***0.79***	0.53	0.67	0.66	0.53	+/+	−/−	+/−
5	CS/CS	1	NA	8	NA	NA	NA	NA	0.89	***0.63***	0.73	0.71	0.93	0.81	−/+	−/−	−/−
Avg	NA	73.8 ± 99.3	22.0 ± 37.3	19.2 ± 32.9					***0.67 ± 0.16***	***0.69 ± 0.06***	0.75 ± 0.14	0.81 ± 0.11	0.90 ± 0.19	0.80 ± 0.17	NA	NA	NA

[a]*Gain values in bold and italics refer to those semicircular canals that were rated as overall abnormal by the reviewers (Seung-Han Lee and Alexander Andrea Tarnutzer).*

[b]*CS were either present (+) or absent (−).*

[c]*Note that at the time of vHIT the patient had recovered mostly from the bilateral sixth nerve palsy.*

bHIT, bedside head-impulse testing; CS, catch-up saccades; d, days; LA, limb ataxia; LC, left cold; LH, left horizontal canal; LP, left posterior canal; LW, left warm; NA, not available; O-to-A, onset to admission; RC, right cold; RW, right warm; RA, right anterior canal; RH, right horizontal canal; RP, right posterior canal; SPV, slow-phase velocity; T-to-C, treatment to caloric testing; T-to-vHIT, treatment to video-head-impulse testing.

(four out of five) and history of gut surgery with TPN (one out of five).

Neurologic examination showed memory impairment and/or mental changes (three out of five, 60%), gait ataxia (five out of five, 100%), partial bilateral sixth nerve palsy (one out of five, 20%), GEN (five out of five, 100%), spontaneous upbeat nystagmus (two out of five, 40%), and positive bedside head-impulse testing for the horizontal canals (five out of five, 100%). Hearing was normal in all patients and none of them reported previous audio-vestibular symptoms (dizziness, tinnitus, etc.).

In three patients, the initial serum total thiamine levels were checked and found to be below normative values. Brain MRI was performed in all patients. Except patient 5, all patients showed typical imaging abnormalities linked to WE (see **Table 1** for details). The MRI of patient 1 had typical lesions including the medial vestibular nucleus (MVN) (**Figure 1**).

Bithermal Caloric Irrigation

Bithermal caloric irrigation was obtained in four out of five patients, whereas one patient (#5) was not tested. In three patients, the sum of nystagmus slow-phase velocities was below 20°/s, whereas in patient 3 the value was above 20°/s (**Table 2**).

Quantitative vHIT

Analysis of VOR Gains and Compensatory Saccades

Based on the analysis of VOR gains and compensatory saccades (**Table 2**), vHIT demonstrated preferential impairment of the horizontal semicircular canals (HSCs), as shown for a single patient in **Figure 2**. The VOR gains of HSCs were decreased (i.e., were below 0.8) in all five patients except for the right HSC in patient 5 (see **Table 2** for average values and **Figure 3** for individual measurements). The VOR gains of the vertical canals were mostly normal (i.e., above 0.7) except for patient 4 who showed subnormal VOR gains in the vertical canals (**Table 2**). Compensatory CS were observed in all HSCs except for the right HSC in patient 5. For the vertical canals, no CS were noted. This was true also for patient 4 who showed slightly reduced vertical canal VOR gains. Note that vHIT was obtained between 3 and 6 days *after* diagnosis of WE and treatment initiation with thiamine in all our patients except for patient 2 who received testing about 3 years after diagnosis.

Overall Function of Individual Semicircular Canals

The reviewers rated each canal function as normal or impaired without knowledge of the clinical findings and the results from MR imaging. Inter-rater agreement for individual canal function (normal vs. abnormal) in all five subjects was 0.94 (Cohen's kappa) (26). After resolving discrepancies, both horizontal canals were rated as abnormal in four out five patients, while in one patient (#5) the right horizontal canal was spared. The vertical canals were rated as normal in all patients (see **Table 1** for details).

Literature Review

We identified five papers that reported on detailed vestibular function testing in WE patients. We excluded the duplicate data and then finally extracted data from 12 patients (53.2 ± 9.7, 6 males, 6 females) from five papers. Details are shown in **Tables 3**

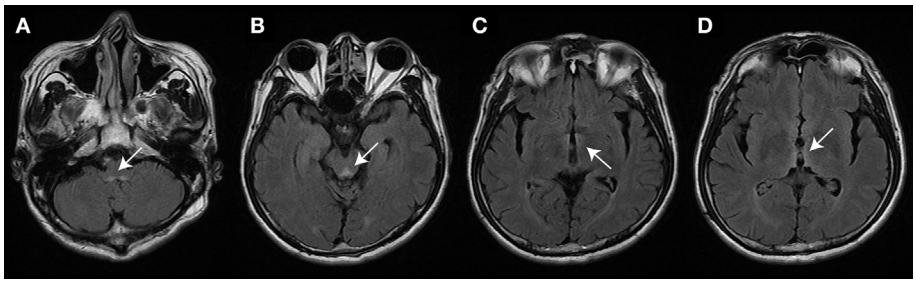

FIGURE 1 | Brain magnetic resonance image (patient #1) studies (fluid-attenuated inversion recovery images) show bilateral symmetrical lesions (as marked by white arrows) in the medial vestibular nucleus **(A)**, the periaqueductal region **(B)**, around the hypothalamus and mammillary bodies **(C)**, and the periventricular regions of the thalamus **(D)**.

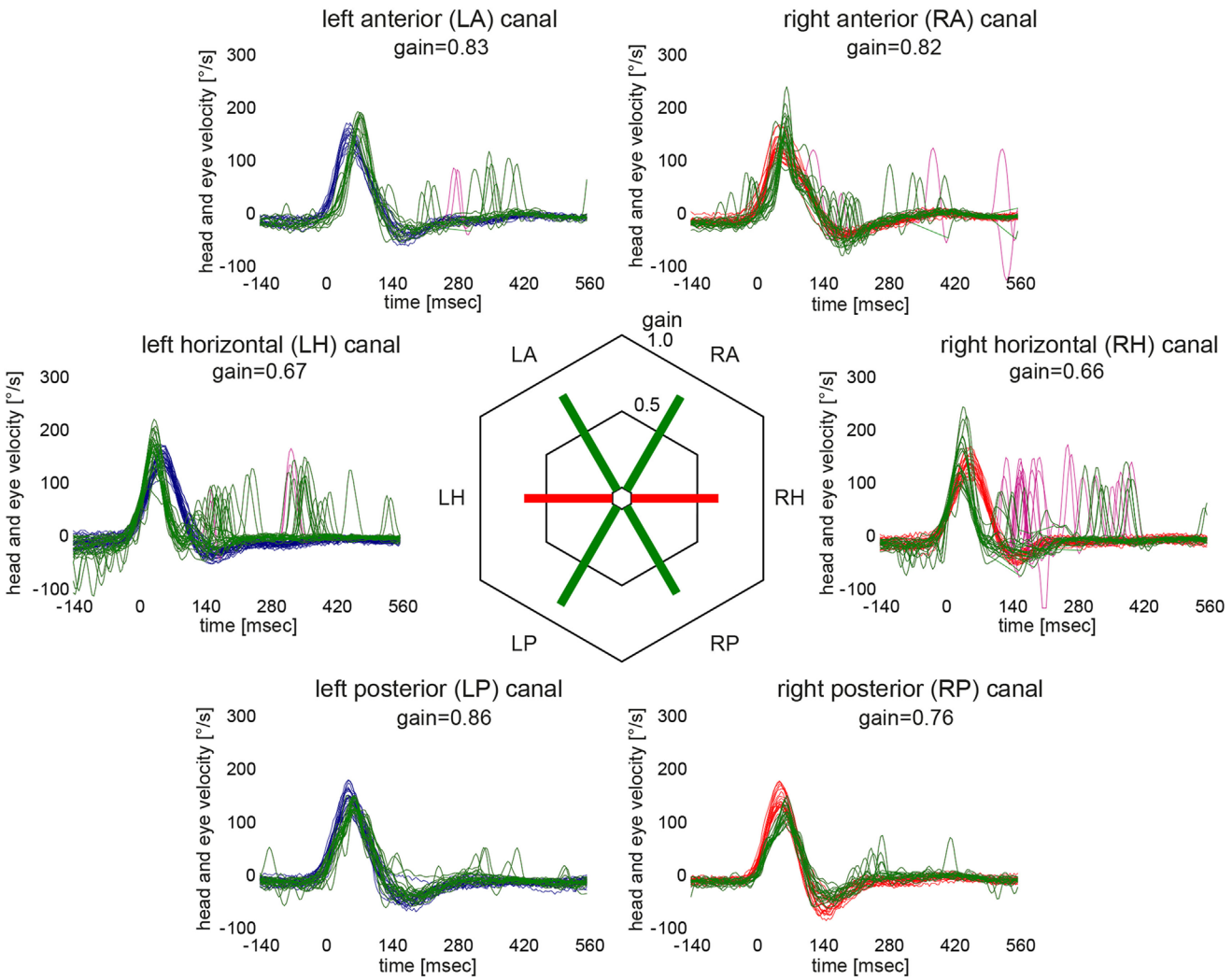

FIGURE 2 | Video head-impulse testing from the same patient as in **Figure 1** (patient #1) 12 days after symptom onset illustrating semicircular canal impairment restricted to the horizontal canals. For each semicircular canal, individual eye velocity traces (in green) and head velocity traces (in red for assessing the right vestibular organ and in blue for assessing the left vestibular organ) are plotted against time (20 trials per canal were recorded). Note that eye velocity traces are inverted to allow for better visualization and comparison with the head velocity traces. Mean gain values (eye velocity/head velocity) are shown in the hexagonal plot in the center of the figure. Whereas green bars indicate normal gains, red bars refer to reduced gains.

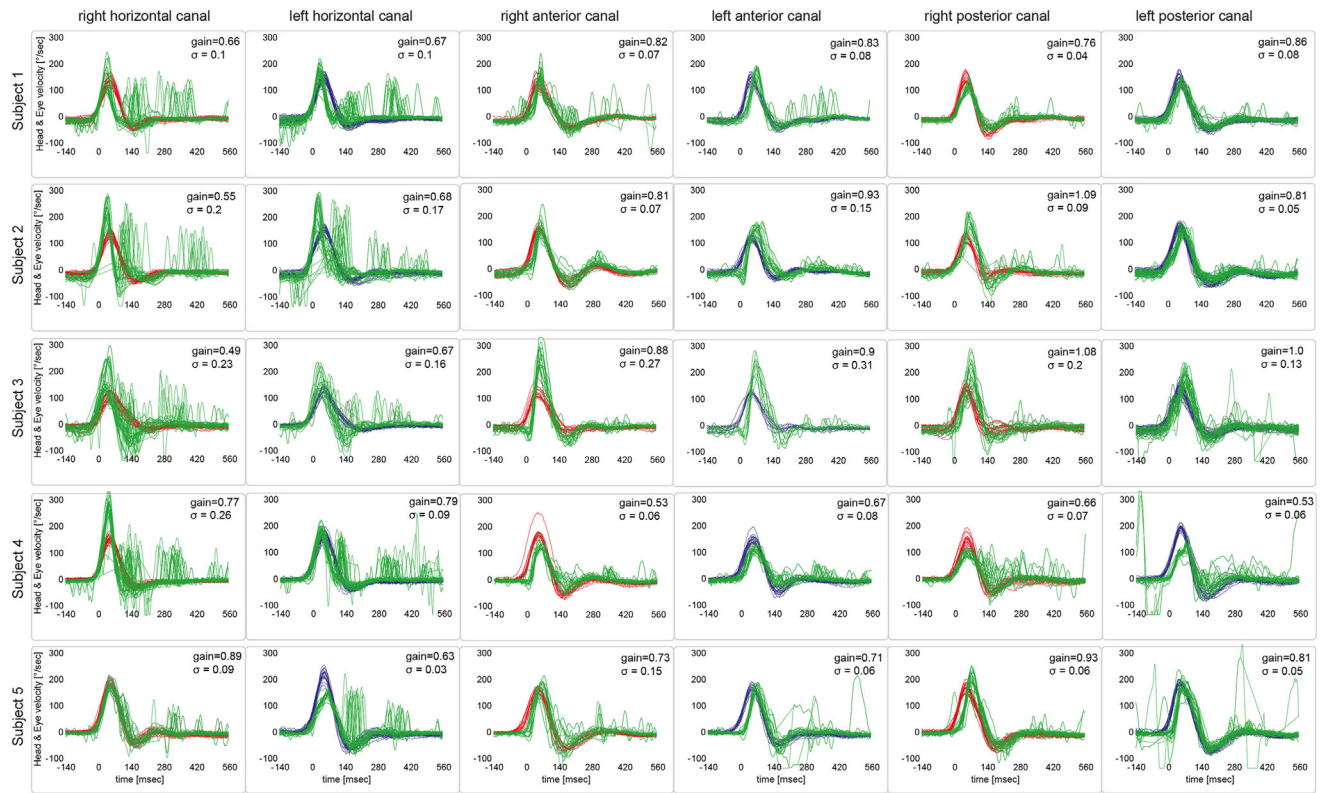

FIGURE 3 | Video head-impulse testing from all five patients, showing the results from a single subject in one row. For each semicircular canal, individual eye velocity traces (in green) and head velocity traces (in red for assessing the right vestibular organ and in blue for assessing the left vestibular organ) are plotted against time. Note that eye velocity traces are inverted to allow for better visualization and comparison with the head velocity traces. While upbeat nystagmus was present at the time of vHIT recordings in patients #1 and #5, this did not result in an increased number of saccades on the traces or reduced gains.

and **4**. In all 12 patients, bilateral vestibulopathy was confirmed by abnormal bithermal caloric tests (n = 7/7) and/or bedside horizontal head-impulse-testing (n = 11/12). GEN (12 of 12), difficulties in stance and/or gait (8 of 8), and diplopia (3 of 5) were common symptoms and signs of WE with bilateral vestibulopathy. qHIT (vHIT or magnetic search-coil testing) was available in 9 patients and revealed selective HSC impairments (n = 6) or predominant HSC impairment with minimally reduced vertical canal function (n = 3) (**Tables 3** and **4**). The timepoint of vHIT relative to treatment initiation could be retrieved only from three patients besides our five patients (see **Table 4**).

DISCUSSION

Contrary to common wisdom, vestibular dysfunction in WE is rather common, even though numbers on its incidence are lacking. More importantly, there seems to be a characteristic pattern of vestibular impairment in WE, with preferential loss of function of the HSCs and sparing of the vertical canals, as confirmed both in our patients and in those cases identified in the literature. With respect to previous studies reporting on the clinical findings in WE, we think that vestibular dysfunction may have been missed for several reasons. In the study of Victor and co-workers, reporting on 245 patients with WE, the authors noticed that ataxia of stance and gait was common (87%), whereas ataxia of the lower extremities was present in only 20% of the patients (5). To explain the ataxia of stance and gait, the authors therefore proposed loss of function of midline cerebellar structures including the vermis, while peripheral-vestibular function was not assessed. This has led to the perception that in WE rather co-existing cerebellar lesions caused disturbances in gait and stance than a vestibulopathy.

However, both previous studies as identified in our literature review and our own cases indicate that ataxia of gait and stance could be linked to vestibular dysfunction as well. While previous studies applied caloric irrigation or rotatory chair testing for the evaluation of vestibular function in WE (11, 12), it is head-impulse testing that has contributed to the early detection of these symptoms more recently. As vestibular disturbances can be reversible, showing rapid improvement after thiamine replacement (16, 25), this underlines the importance of testing the aVOR in these patients acutely, either at the bedside or if available quantitatively by vHIT. In case of delayed vHIT (after treatment initiation), there is a risk of missing the acute impairment of the aVOR due to recovery. Furthermore, while vertigo/dizziness and acute motion intolerance, which are common in acute unilateral vestibular loss such as vestibular neuritis or cerebellar stroke (27), are less common in WE, some WE cases presented with vertigo

TABLE 3 | Clinical and neuro-otologic findings in selected cases with Wernicke's encephalopathy reporting vestibular function (data from literature review).

#	Age (years), sex	Cause	V	D	H	M/M	Op[a]	G/S	LA	SN	GEN	CPN	bHIT	Pur	Sac	CP	qHIT		B1 nmol/L	MRI	Replacement therapy	Recovery
																	Hor	Ver				
Choi et al. (22)																						
1	63, F	TPN	Y	NA	N	Y	Y	Y	Y	NA	Y	NA	CS	Ab	Ab	Y	Ab	Ab[b]	NA	Ab	IV (100 mg/day)	Par
2	40, M	Alcohol	Y	NA	N	Y	Y	Y	Y	NA	Y	NA	CS	Ab	Ab	Y	Ab	Nr	NA	Nr	IV (dose NA)	Par
Kattah et al. (16)																						
3	50, F	Alcohol	N	NA	NA	N	N	Y	N	N	Y	NA	CS	NA	NA	Y	Ab	Nr	88	Nr	PO (100 mg/day)	NA
4	60, M	G.byp/ Vo	Y	Y	NA	N	Y	Y	N	N	Y	NA	CS	NA	NA	NA	Ab	Nr	21	Nr	IV (500 mg/day), then PO (100 mg/day)	N
5	37, F	G.byp/ Vo	N	NA	NA	N	N	Y	N	DB	Y	NA	CS	NA	NA	NA	Ab	Ab[b]	55	NS	IV (500 mg/day), then PO (100 mg/day)	Par
Choi et al. (24)																						
6	53, M	NA	Y	N	N	NA	NA	NA	Y	UB	Y	NA	CS	Ab	Ab	Y	NA	NA	NA	NA	NA	NA
7	64, M	NA	Y	Y	N	NA	NA	NA	N	UB	Y	Y	CS	Ab	Ab	Y	Ab	Nr	NA	Ab	NA	NA
8	45, F	NA	Y	Y	N	NA	NA	NA	N	N	Y	N	CS	NA	NA	Y	NA	NA	NA	NA	NA	NA
9	62, M	NA	Y	N	N	NA	NA	NA	N	N	Y	N	Nr	Nr	Ab	Y	NA	NA	NA	NA	NA	NA
Akdal et al. (23)																						
10	55, F	Alcohol	N	NA	N	NA	Y	Y	NA	UB	Y	NA	CS	Ab	Ab	NA	Ab	Nr	NA	Ab	IV (dose NA)	NA
11	64, M	TPN	Y	NA	N	NA	Y	Y	NA	NA	Y	NA	CS	NA	Ab	NA	Ab	Nr	NA	Ab	IV (600 mg for 3 days, then 200 mg for 5 days), then PO (100 mg/day)	Par
Kattah et al. (25)																						
12	45, F	Alcohol/ Vo	NA	NA	NA	Y	NA	Y	NA	UB	Y	NA	CS	NA	NA	NA	Ab	Ab[b]	~30	Ab	IV(500 mg/day)	Par
All	53.2 (±9.7)		8/11	3/5	0/8	3/6	5/7	8/8	3/9	5/9	12/12	1/3	11/12	5/6 Ab	7/7 Ab	7/7	9/9 Ab	3/9 Ab	48.5 (±30)	5/9 Ab	7/8 IV	5/6 Par

[a]*The extent of ophthalmoparesis varied. While "limited ocular motor range" in the horizontal plane was reported in cases 1 and 2 being suggestive of partial bilateral sixth nerve palsy, case 4 had "8-prism diopter esotropia in left gaze during cross-cover testing," "almost total loss of horizontal eye movements" in case 10 is consistent with severe bilateral sixth nerve palsy and "bilaterally limited horizontal gaze" in case 11 likely reflects partial bilateral sixth nerve palsy.*

[b]*In these patients, vertical canals were rated as borderline abnormal.*

Ab, abnormal; ap, apogeotropic nystagmus; bHIT, bedside head-impulse testing; B1, thiamine; CP, canal paresis tested by caloric test; CPN, central positional nystagmus; CS, catch-up saccades; D, diplopia; DB, downbeat; F, female; G. byp, gastric bypass; GEN, gaze-evoked nystagmus; G/S, gait or standing impair; H, hearing loss; Hor, horizontal canal; IV, intravenous; LA, limb ataxia; M, male; M/M, memory impair or mental change; MRI, magnetic resonance image; N, no; NA, not available; Nr, normal; NS, non-specific; Op, ophthalmoplegia; Par, partial recovery; PO, per oral; Pur, pursuit; qHIT, quantitative head-impulse testing (either video based or search-coil based); Sac, saccades; SN, spontaneous nystagmus; TPN, total parenteral nutrition; UB, upbeat; Ver, vertical canal; V, vertigo; Vo, vomiting; Y, yes.

TABLE 4 | VOR gains obtained by head-impulse testing (video-oculography or search-coils) in 11 patients (5 from our series and 6 from the literature review) with Wernicke's encephalopathy.

	Test time relative to Tx	Method	VOR gains[a]					
			RH	LH	RA	LA	RP	LP
Own cases								
# 1	Post-Tx ~72 h	vHIT	***0.66***	***0.67***	0.82	0.83	0.76	0.86
# 2	Post-Tx ~3 y	vHIT	***0.55***	***0.68***	0.81	0.93	1.09	0.81
# 3	Post-Tx ~72 h	vHIT	***0.49***	***0.67***	0.88	0.90	1.08	1.00
# 4	Post-Tx ~72 h	vHIT	***0.77***	***0.79***	0.53	0.67	0.66	0.53
# 5	Post-Tx ~144 h	vHIT	0.89	***0.63***	0.73	0.71	0.93	0.81
Choi et al. (22)								
# 1	NA	Search coils	***0.38***	***0.31***	0.84	0.66	0.72	0.8
# 2	NA	Search coils	***0.44***	***0.53***	0.76	0.7	0.85	0.86
Choi et al. (24)								
# 7	NA	Search coils	***0***	***0.1***	0.91	0.93	0.67	0.67
Akdal et al. (23)								
# 10	Post-Tx ~24 h	Search coils	***0.18***	***0.13***	0.81	0.72	0.99	1.16
# 11	Post-Tx ~4 m	vHIT	***0.27***	***0.12***	0.86	0.84	0.82	0.84
Kattah et al. (25)								
# 12	Pre-Tx	vHIT	***0.43***	***0.26***	***0.51***	0.75	0.55	0.13
# 12	Post-Tx 72 h	vHIT	***0.60***	***0.51***	0.93	0.51	0.78	0.95

[a]*Gain values in bold and italics refer to those semicircular canals that were rated as overall abnormal.*

h, hours; LA, limb ataxia; LH, left horizontal canal; LP, left posterior canal; m, months; NA, not available; RA, right anterior canal; RH, right horizontal canal; RP, right posterior canal; Tx, treatment; vHIT, video-head-impulse testing; y, years.

and/or dizziness (16, 22). This was probably due to an asymmetric or sequential impairment of vestibular function. Therefore, also in asymmetric aVOR deficits and acute vertigo/dizziness, WE should be considered.

Vestibular Testing—Comparison of Different Tests and Limitations

Although gait disturbance and oscillopsia are frequently encountered in WE patients, deficits in the aVOR may be difficult to be detected in the acute phase since other symptoms such as ophthalmoplegia or nystagmus and limb ataxia are potential confounders, and other conditions such mental changes restrict history taking and the neurologic examination. Indeed, ocular motor palsies, either affecting a single nerve or presenting as complete external ophthalmoplegia, may limit the use of (video) head-impulse testing. While in a case series of 17 unselected WE patients (i.e., not included based on the presence of vestibular complaints such as vertigo or dizziness) vestibular impairment was reported in all patients (11), 11 patients had bilateral abducens palsy and 1 patient had total external ophthalmoplegia. In another case series, one out of two patients had bilateral sixth nerve palsy as well (12). These ocular motor deficits may have led to false abnormal caloric irrigation and rotatory chair testing results. From the 17 cases included here (own data and previously published cases), information on extraocular muscle palsies was available only in 12. Partial sixth nerve palsies were found in six patients, complete horizontal ophthalmoplegia was noted in one case. In these cases, the interpretation of vHIT and caloric irrigation must be made with caution and these tests will become useless in case of total external ophthalmoplegia as, e.g., in case 10 from **Table 3**. Note that in the single case from our own case series with initial partial bilateral abducens palsy ocular motor function had normalized at the time of vHIT on day four after admission.

In four out of five patients from our own data, horizontal canal impairment as assessed by caloric irrigation and by vHIT was consistent, whereas in one case (#3) a discrepancy between these two tests was noted. Such discrepancies might point to selective high-frequency aVOR impairment due to damage of the vestibular nuclei (VN) secondary to thiamine deficiency. In the paper by Choi and co-authors, one patient showed marked improvement on caloric irrigation, whereas the responses of rotatory chair testing and head-impulse testing remained unchanged (22). Similar to this report, in our patient #3, the caloric responses were near normal, whereas vHIT still showed bilateral horizontal canal impairment. This finding may be explained by the fact that caloric irrigation and vHIT were performed in the recovery period after thiamine replacement (usually within 3–6 days, but sometimes delayed by months or years). MVN neurons responsible for high acceleration horizontal aVOR may be the most vulnerable to thiamine deficiency, and this selective susceptibility may occur due to high metabolic demands of the neurons responsible for the high acceleration aVOR as proposed by Choi et al. (22).

Comparing bedside and video HIT findings in our case series, results were consistent in all but one patient (#5). While in this patient, the bedside HIT showed bilateral CS, vHIT demonstrated only unilateral CS. Noteworthy, the bedside HIT was performed at admission 1 day after symptom onset, whereas the vHIT was obtained 1 week later. Thus, in this patient the vHIT reflects partially improved vestibular function after thiamine supplementation. Obviously, prognosis depends on the

delay of treatment initiation. Recovery without neurological sequelae after prompt treatment was described in four out of five patients with acute/subacute symptom onset by Kattah and colleagues (16), whereas in our case series complete recovery was noted in two out of five cases only. Noteworthy, delay from symptom onset to diagnosis was 30 days or more in three of our five patients. Permanent vestibular injury persisting more than 5 years was noted in patient 2 due to delayed diagnosis and treatment.

MR Imaging in WE

Magnetic resonance image studies typically show bilateral symmetrical lesions in the periventricular regions of the thalamus, the hypothalamus, the mammillary bodies, the periaqueductal region, the floor of fourth ventricle, and the midline cerebellar structures (2). In our case series, abnormal MRI findings compatible with WE were found in four out of five cases (80%). However, in the pooled data analysis, only 9 of 14 WE cases who received MRI (64%) showed typical MR abnormalities. According to the literature, MRI has a moderate sensitivity (53%) only for detecting WE, while its specificity is high (93%) (28, 29). MR imaging may therefore be used to rule out WE, but a negative MRI does not exclude WE (2). Even though our series is retrospective and numbers from the literature reporting on the HIT in WE, the vHIT is likely more sensitive for the diagnosis of WE than MR imaging.

Explanations for Vertical Semicircular Canal Sparing in WE

Consistently with the literature, we noted selective impairment of the horizontal canals. Thus, such sparing of the vertical canals in the presence of bilateral horizontal canal impairment seems to be a pattern suggestive for WE. According to previous histopathologic studies, vestibular paresis in WE may be accounted for by loss of function of the VN (12). Neuropathologic examinations of patients with WE have revealed lesions in the VN, especially in the MVN, the nucleus prepositus hypoglossi, the nodulus, and the uvula (25). The MVN was most vulnerable to thiamine deprivation (30), and histological abnormalities in the labyrinthine cristae and vestibular nerves were relatively minor in thiamine deficient pigeons (31).

The vestibular neurons receiving different primary afferent input have a topographic distribution within the VN (32). The neurons activated by the saccule, utricle, and anterior and posterior canals are located mainly in the lateral VN (LVN) and the descending VN, while the neurons activated by the lateral canal were found mainly in the MVN and the LVN. Thus, vertical canal sparing and the distinct susceptibility of the vestibular end organs in WE may result from selective vulnerability of the neurons in the MVN to thiamine deficiency (5, 22, 33). In our case series, only 4 out of 13 cases who had received structural MR imaging (one from our series and three from the literature review) showed involvement of the MVN. However, all patients had selective or predominantly horizontal canal dysfunction in head-impulse testing. Low sensitivity of MRI and functional impairment rather than structural lesion may explain this discrepancy between the results of MRI and head-impulse testing. This is also supported by the notion that supplementation of thiamine in the acute stage may result in rapid clinical improvement and normalization of the HIT (25).

Limitations

Our paper has several limitations. This is a retrospective data analysis and therefore no prospectively defined diagnostic criteria for WE were available. Furthermore, due to relative rarity of WE, both our sample size and those from the literature were small. Also, data published were sometime incomplete (e.g., lacking raw data of search-coil or video head-impulse testing, thiamine levels or MRI). Practically, it was the combination of patient history, acute/subacute ocular motor and gait impairment, and either low thiamine levels or characteristic findings on MR imaging that led the treating physicians to a diagnosis of WE.

Importantly, ocular motor palsies as a confounder for abnormal results on HIT, caloric irrigation and rotatory chair testing were not taken into account in some cases. Vestibular dysfunction can be reversible after thiamine replacements. Therefore, timing of vestibular testing is crucial and recovery after treatment initiation may result in false negative results. Furthermore, we used an overall, reviewer-based rating of semicircular canal function as previously proposed by Tarnutzer and colleagues (21, 34), whereas in previous studies gain values were the single most important parameter for assessing vestibular function. In some of our patients, we noted artifacts on vHIT with peak eye velocities exceeding peak head velocities in predominantly the horizontal canals. This most likely reflects slippage of the vHIT-goggles and may result in false high (i.e., normal) gain values. Nonetheless, both the actual gain values in these patients and the CS clearly indicated impairment of the horizontal canals in these patients.

CONCLUSION

In conclusion, bedside or video HIT is valuable tools for the diagnosis of WE especially in the emergency department because MR imaging has a relatively low sensitivity in WE and may not be readily available. In case of acute to subacute bilateral vestibulopathy, WE should be in the list of differential diagnoses. In cases with early (i.e., covert) CS, vHIT will be superior compared to bedside HIT. Furthermore, with relative sparing of vertical canal function in the presence of profound bilateral horizontal canal impairment being the most common pattern, vHIT may facilitate the diagnosis of WE and accelerate thiamine supplementation, eventually improving the clinical outcome in these patients.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of the Chonnam National University Hospital (Gwangju, South Korea) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

The protocol was approved by the Institutional Review Board of the Chonnam National University Hospital (Gwangju, South Korea).

AUTHOR CONTRIBUTIONS

S-HL drafted the manuscript, performed the data collection, analyzed the data, and conceived of the study. S-HK analyzed the data and conducted the statistical analysis. J-MK performed the data collection, interpreted neuro-images, and analyzed the data. AT was involved in the design of the study, participated in the data analysis and the statistical analysis, and critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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BRIEF RESEARCH REPORT
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Head-Movement-Emphasized Rehabilitation in Bilateral Vestibulopathy

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Objective: Although there is evidence that vestibular rehabilitation is useful for treating chronic bilateral vestibular hypofunction (BVH), the mechanisms for improvement, and the reasons why only some patients improve are still unclear. Clinical rehabilitation results and evidence from eye-head control in vestibular deficiency suggest that head movement is a crucial element of vestibular rehabilitation. In this study, we assess the effects of a specifically designed head-movement-based rehabilitation program on dynamic vision, and explore underlying mechanisms.

Methods: Two adult patients (patients 1 and 2) with chronic BVH underwent two 4-week interventions: (1) head-movement-emphasized rehabilitation (HME) with exercises based on active head movements, and (2) eye-movement-only rehabilitation (EMO), a control intervention with sham exercises without head movement. In a double-blind crossover design, the patients were randomized to first undergo EMO (patient 1) and—after a 4-week washout—HME, and vice-versa (patient 2). Before each intervention and after a 4-week follow-up patients' dynamic vision, vestibulo-ocular reflex (VOR) gain, as well as re-fixation saccade behavior during passive head motion were assessed with the head impulse testing device—functional test (HITD-FT).

Results: HME, not EMO, markedly improved perception with dynamic vision during passive head motion (HITD-FT score) increasing from 0 to 60% (patient 1) and 75% (patient 2). There was a combination of enhanced VOR, as well as improved saccadic compensation.

Conclusion: Head movement seems to be an important element of rehabilitation for BVH. It improves dynamic vision with a combined VOR and compensatory saccade enhancement.

Keywords: vestibular rehabilitation, bilateral vestibular hypofunction, re-fixation saccades, vestibulo-ocular reflex, HITD-FT, dynamic vision

INTRODUCTION

Bilateral vestibular hypofunction (BVH) significantly affects quality of life (1). Patients suffer from symptoms like oscillopsia with head movement and postural instability, leading to difficulties with activities of daily living like driving and a 31-fold increased risk of falls with considerate morbidity (1). Mostly due to ototoxic aminoglycosides, Menière's disease or meningitis (2), BVH has an unfavorable prognosis with no improvement of peripheral vestibular function over several years in more than 80% of patients (3).

At variance with its clinical importance, and compared to most other vestibular disorders (including unilateral vestibular dysfunction), prospective therapeutic clinical trials in patients with BVH are sparse (4, 5). Treatment mostly relies on physical therapy. While it is consensus that vestibular rehabilitation is beneficial [(6–9), for review see (5), for clinical practice guideline see (4)], the mechanisms for improvement, their relative importance and the reasons why only some patients improve are still unclear (6–10).

Clinical rehabilitation results (4–9) and evidence from eye-head control in vestibular deficiency (11–14) suggest that head movement is a crucial element of vestibular rehabilitation. Head motion may improve vestibulo-ocular reflex (VOR) function in BVH (8, 9). Residual vestibular input during head movements is essential for triggering compensatory short-latency re-fixation saccades during passive head movements (12), which, in turn may improve dynamic visual function (13, 14).

In this case study, we assessed whether a specifically designed rehabilitation program based on head motion improves dynamic vision in BVH, and explore underlying mechanisms.

MATERIALS AND METHODS

Patients

Two patients (patient 1 and 2, 45–60 years old, gender and exact age have been removed on request of the journal) with chronic BVH were included. They were the only patients who completed the entire proposed program of the study "Eye-Head Movement in Bilateral Vestibulopathy: Translating Optimal Control Modeling and Neurophysiology to Rehabilitation," a completed translational pilot randomized controlled trial (for details on the study program, see study design below and supplement). In both cases, BVH was due to therapy with ototoxic aminoglycosides while being treated for endocarditis. Clinical BVH symptoms (visual blurring with head movement, and difficulties walking in darkness or on unsteady surfaces) had been present for 9 and 4 months for patients 1 and 2, respectively, slow phase eye movement response on bi-thermal water caloric testing was smaller than 5°/s bilaterally, and there was bilateral vestibular dysfunction in video head impulse testing. There was no clinical manifestation of cerebellar syndrome, polyneuropathy, anxiety or mood disorder in history or clinical neurological and psychiatric examination. Uncompensated vision of the better eye was better than 20% (4/20). None of the patients previously participated in vestibular rehabilitation. The patients did not experience any other changes in activity such as new exercises during the intervention or follow-up.

Abbreviations: BVH, bilateral vestibular hypofunction; EMO, eye-movement-only rehabilitation; HITD-FT, head impulse testing device—functional test; HME, head-movement-emphasized rehabilitation; MDC, minimal detectable change; VOR, vestibulo-ocular reflex.

Ethics Statement

The ethics committee of the Medical Faculty of Ludwig Maximilians University of Munich approved the study, which was conducted in accordance with the principles expressed in the Declaration of Helsinki. All patients gave their written informed consent prior to participation, and were free to withdraw from the study at any time.

Study Design

There was a therapeutic randomized controlled double-blind (examiner) crossover design (**Figure 1**), consisting of two 4-week interventions [Supplement 1, in analogy to (7)]: (1) head-movement-emphasized rehabilitation (HME) with exercises based on active head movements, both during active combined eye-head gaze shifts to a target and during fixation, thereby including a gaze stability task, and (2) eye-movement-only rehabilitation (EMO), a control intervention with eye movement exercises without head movement. Additional information regarding the specifics of each exercise protocol is detailed in the supplement. The crossover design was chosen to avoid possible influencing factors, in particular spontaneous recovery. Patients were randomized to first undergo EMO (patient 1) and—after a 4-week washout—HME, and vice-versa (patient 2). Before each intervention and after a 4-week follow-up dynamic vision, head impulse gain, as well as re-fixation saccade behavior during passive head motion were assessed with the head impulse testing device—functional test (HITD-FT).

Head Impulse Testing Device—Functional Test (HITD-FT)

An experienced examiner standing behind the patients performed passive, high-acceleration (3,500–5,000°/s^2), small amplitude (13–25°) head rotations to the left and right in the plane of the horizontal semicircular canals while patients fixated a standard Landolt ring on a screen 2 m straight ahead [HITD-FT testing in analogy to (13, 15, 16)]. Impulses were delivered with random timing and direction, to prevent anticipation. The size of the Landolt ring during the HITD-FT test was 0.6 logMAR bigger than the static visual acuity test [in analogy to (13)] and remained unchanged during the HITD-FT test. The Landolt ring had a gap measuring ⅕ of the ring diameter with eight possible gap positions at 45° increments. It appeared on the screen 58 ± 2 ms (mean ± SD) after head velocity reached 20°/s. Display duration was 173 ± 6 ms. Patients had to identify the position of the gap. They provided answers using an external computer keypad consisting of buttons for each gap position. Patients pressed a special "x" button if they had low confidence in their answer to further reduce the possibility of random correct answers. The answer was rated as correct or incorrect (including button x) for each trial. During the HITD-FT, eye

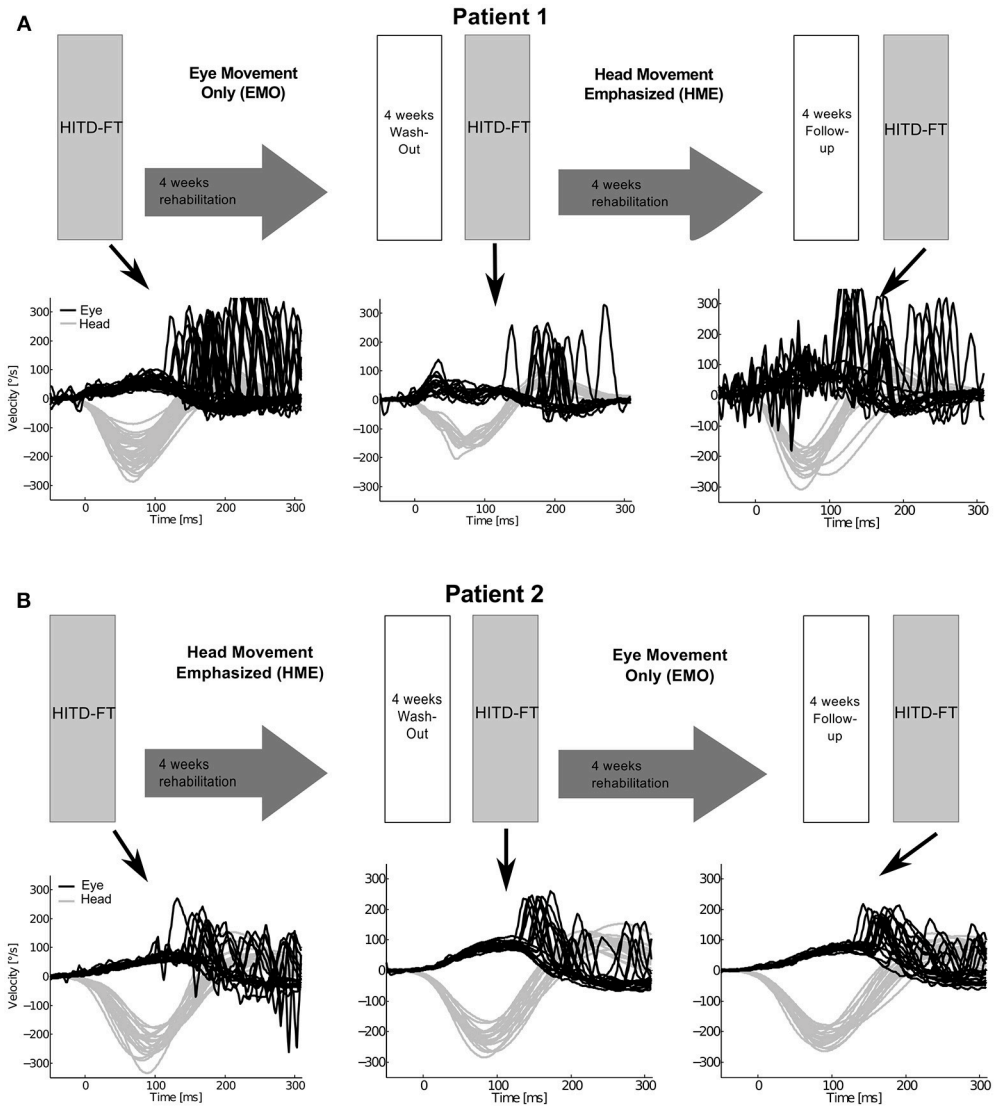

FIGURE 1 | Study design and eye and head movement recordings during head impulse testing device—functional testing (HITD-FT). The upper parts of this figure show the crossover study design for both patients. Patient 1 **(A)** was first treated with eye-movement-only rehabilitation (EMO), and, after a 4-week washout, with head-movement-emphasized rehabilitation (HME), patient 2 **(B)** first with HME, then with EMO. The lower parts of this figure display the corresponding recorded eye and head velocity data during HITD-FT testing with pooled head motion directions. During this test, patients were asked to determine the orientation of a Landolt ring on a screen 2 m straight ahead while their head was passively moved. The head movement is shown in gray, the eye movement in black. Note that vestibulo-ocular reflex (head impulse) gain, i.e., the ratio of median eye and head velocity within a 10-ms-window between 55 and 65 ms after head impulse onset, and compensatory saccade amplitude (integration of the area under the saccade(s) deviating from VOR slow phase velocity) improve after HME, not EMO.

movements were recorded by video-oculography of the left eye, head movements by inertial sensors (EyeSeeCam system with a sampling rate of 220 Hz, in analogy to (13, 17).

Data Analysis

Data were analyzed offline using MATLAB (MathWorks, Natick, MA) software. Head impulses and saccades were automatically detected using velocity and acceleration criteria with the possibility for manual correction. Head impulse started when head velocity exceeded 20°/s. Head impulse gain was calculated as the ratio between median eye and head velocity within a 10-ms-window between 55 and 65 ms after head impulse onset. There was no side difference in gain (Wilcoxon sign test, $p > 0.05$), so data from both sides was pooled. On average 22 ± 9 (mean ± SD) trials were considered for analysis. Eye movements within 300 ms after head impulse start characterized by an acceleration higher than 2,000°/s^2 were considered as re-fixation saccades. An acceleration threshold of 2,000°/s^2 was used to determine saccade onset, while an acceleration threshold of −2,000°/s^2 was used to determine saccade offset. Compensatory saccade amplitude deviation from the VOR slow phase velocity was computed by integrating the area under the saccade(s).

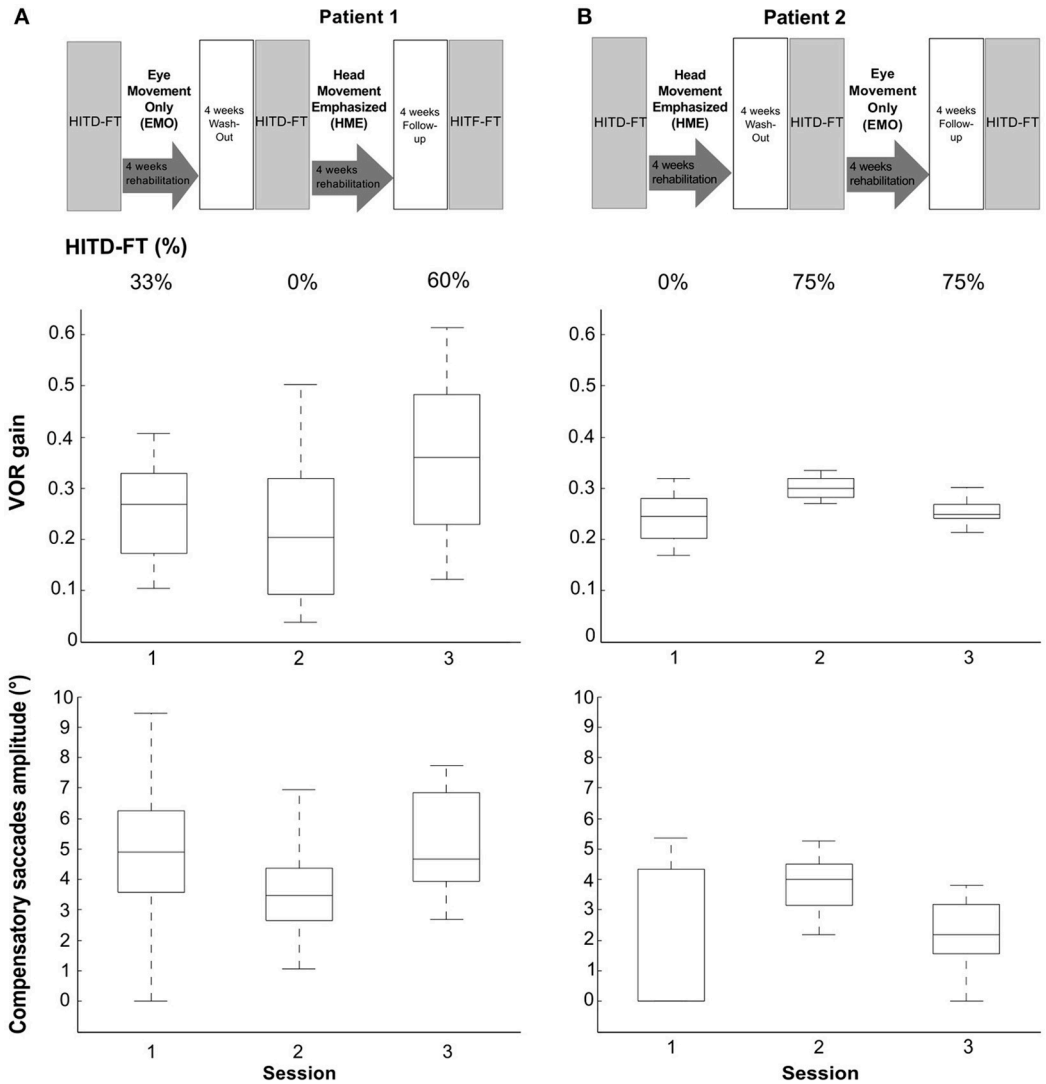

FIGURE 2 | Rehabilitation effects on head impulse testing device—functional testing (HITD-FT) scores, head impulse gain, and compensatory saccade amplitude. This figure shows HITD-FT scores (top), head impulse gain (middle), and compensatory saccade amplitude (bottom) in the course of the rehabilitation program sketched on top for patients 1 **(A)** and 2 **(B)**. In a crossover design, patient 1 was first treated with eye-movement-only rehabilitation (EMO), and, after a 4-week washout, with head-movement-emphasized rehabilitation (HME), patient 2 first with HME, then with EMO. During HITD-FT testing, patients were asked to determine the orientation of a Landolt ring on a screen two meters straight ahead while their head was passively moved. HITD-FT score was calculated as the rate (percentage) of correct answers from all trials of one patient in one session. From simultaneous recordings of eye and head movement, vestibulo-ocular reflex (VOR) gain (ratio of median eye and head velocity within a 10 ms window between 55 and 65 ms after head impulse onset) and saccade amplitude (integration of the area under the saccade(s) deviating from VOR slow phase velocity) were calculated. Gain and saccade amplitude are visualized in box plots. On each box, the central mark is the median, the edges of the box are the 25 and 75th percentiles, the whiskers extend to the most extreme datapoints the algorithm considers to be not outliers. Note the marked increase in dynamic vision (HITD-FT score) after HME with a combined enhancement of the VOR gain and compensatory saccade amplitude in this crossover design in both patients. After EMO, dynamic vision decreased (patient 1) or stayed stable (patient 2) while VOR gain and compensatory saccade amplitude deteriorated in both patients.

HITD-FT score was calculated as the rate (percentage) of correct answers from all trials of one patient in one session.

Statistical Analysis

For statistics, not the average, but all the values were used. Normality was assessed by Shapiro-Wilk testing. Differences in head impulse gains between the different orders of treatment were assessed with an independent samples Mann-Whitney-U test, differences within time points (pre- and post-EMO, pre- and post-HME) of both patients were assessed with a related samples Friedman ANOVA-by-ranks. Pairwise comparisons before and after each intervention were assessed by related samples Wilcoxon signed rank testing. All statistical testing was performed on two-sided exploratory 5% significance levels.

Computations were conducted with SPSS (SPSS Statistics for Mac).

RESULTS

Vestibular rehabilitation based solely on head movement exercises (HME) improved dynamic vision, with HITD-FT scores increasing from 0% before HME to 60% (patient 1) and 75% (patient 2) afterwards (**Figure 2**). With the EMO protocol, dynamic vision decreased (from 33 to 0% in patient 1) or remained stable (75%, patient 2). **Figure 1** shows the underlying recorded eye movement behavior with passive head motion. EMO and HME had an effect on both head impulse gains [related samples Friedman ANOVA-by-ranks, patient 1: $\chi^2_{(2)} = 43.3$, $p = 0$; patient 2: $\chi^2_{(2)} = 28.7$, $p = 0$] and compensatory saccade amplitude [patient 1: $\chi^2_{(2)} = 21.8$, $p = 0$; patient 2: $\chi^2_{(2)} = 11$, $p = 0.004$]. Effects were dependent on the order of the treatments (independent samples Mann-Whitney-U test, $p < 0.05$), therefore, each patient of the crossover design was considered individually. Head impulse gain increased with HME by 80% from 0.2 to 0.36 in patient 1 (**Figure 2**, Wilcoxon signed-rank test $Z = -5.05$, $p = 0$) and by 20% from 0.25 to 0.3 in patient 2 ($Z = -4.3$, $p = 0$), and it decreased with EMO (patient 1: $Z = -2.53$, $p = 0.012$; patient 2: $Z = -4.4$, $p = 0$). Compensatory saccade amplitude increased with HME (patient 1: $Z = -5.38$, $p = 0$; patient 2: $Z = -3.18$, $p = 0$), and decreased with EMO (patient 1: $Z = -2.74$, $p = 0.006$; patient 2: $Z = -2.97$, $p = 0.003$).

DISCUSSION

Head movement seems to be an important element of rehabilitation for BVH. It improves dynamic vision, enhancing both VOR function and compensatory saccade strategies.

Clinically, HITD-FT results of >80% are considered physiological. In this light, an increase from 0%, i.e., the inability to see clearly during head motion, to detecting 60 and 75% of Landolt ring orientation, respectively, after HME, appears practically relevant. Similarly, VOR gain improvements with HME (80% in patient 1 and 20% in patient 2) seem meaningful. They exceed minimal detectable change (MDC) suggested by studies in healthy subjects with MDC values ranging from 11% [repeatability coefficient of 0.1 and average VOR gain of 0.94, (18)] to 14% [95% limits of agreement of 0.14 and average VOR gain of 1.06, (19)].

To our knowledge, this is the first time vestibular rehabilitation based solely on head motion is assessed. The fact that head motion exercises improve dynamic vision in our patients underlines the importance of this part of vestibular rehabilitation. This is very much in line with the clinical practice guidelines, the suggestions from former studies using combined head, balance, and gait exercises (8, 9), and with a study comparing eye and head movement exercises within a comprehensive rehabilitation program (7). Interestingly, both head impulse gain and saccade compensation strategies deteriorated after EMO. This supports the notion expressed in the clinical practice guidelines to avoid isolated saccade or smooth pursuit eye-movement exercises during vestibular rehabilitation (4).

Our case study shows an effect of HME on dynamic vision during high-acceleration, passive unpredictable head motion. This result, which is in line with that of another case study reporting an effect of balance and gaze stabilization exercises on passive dynamic visual acuity (8), is promising, as patients are significantly disabled during activities comprising passive high-frequency head motion like walking or driving (1). In these situations, compensatory strategies such as feed-forward eye movement control [for predictable/active head movements (20, 21)], or smooth-pursuit function [for low head velocities (22)] are not readily available, so that patients have to rely mostly on modification of saccade behavior (14, 23–27), or enhanced vestibular function (8).

As underlying mechanism for the dynamic vision improvement we found both an increase in head impulse gain as well as an increase in compensatory saccade amplitude. This combined effect in a program based on head motion is encouraging, especially because some combined vestibular rehabilitation programs found no significant improvement of VOR function (7), an increase solely of VOR function, but not in compensatory saccades [one BVH patient, balance and gaze stabilization exercises (8)] as well as a combined increase in VOR function and compensatory saccades [one BVH patient, balance, gait and gaze stabilization exercises (9)]. The combined effect could be due to central processing via the cerebellum (10).

This study is clearly limited by the small number of participants. This in mind, it suggests that head movement is an important element of rehabilitation for BVH. It improves dynamic vision during passive head motion enhancing both VOR gain and compensatory saccade strategies.

AUTHOR CONTRIBUTIONS

NL, SK, CS, KJ, and CR did study conception. SK performed the rehabilitation. AK and CR collected the data. NL, AK, MH, and CR analyzed and interpreted the data. NL, ES, and CR contributed to the statistical analysis. MH and NL drafted the initial manuscript. NL, MH, and CR revised the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Cognitive Rehabilitation in Bilateral Vestibular Patients: A Computational Perspective

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There is evidence that vestibular sensory processing affects, and is affected by, higher cognitive processes. This is highly relevant from a clinical perspective, where there is evidence for cognitive impairments in patients with peripheral vestibular deficits. The vestibular system performs complex probabilistic computations, and we claim that understanding these is important for investigating interactions between vestibular processing and cognition. Furthermore, this will aid our understanding of patients' self-motion perception and will provide useful information for clinical interventions. We propose that cognitive training is a promising way to alleviate the debilitating symptoms of patients with complete bilateral vestibular loss (BVP), who often fail to show improvement when relying solely on conventional treatment methods. We present a probabilistic model capable of processing vestibular sensory data during both passive and active self-motion. Crucially, in our model, knowledge from multiple sources, including higher-level cognition, can be used to predict head motion. This is the entry point for cognitive interventions. Despite the loss of sensory input, the processing circuitry in BVP patients is still intact, and they can still perceive self-motion when the movement is self-generated. We provide computer simulations illustrating self-motion perception of BVP patients. Cognitive training may lead to more accurate and confident predictions, which result in decreased weighting of sensory input, and thus improved self-motion perception. Using our model, we show the possible impact of cognitive interventions to help vestibular rehabilitation in patients with BVP.

Keywords: cognitive training, bilateral vestibulopathy, bilateral vestibular loss, rehabilitation, vestibular cognition, computational modeling, mental imagery, self-motion perception

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INTRODUCTION

Patients with bilateral vestibulopathy suffer from a severely reduced (incomplete vestibular loss) or totally absent function (complete vestibular loss) of both vestibular end organs, vestibular nerves, or a combination thereof (1). The main symptoms of BVP are unsteadiness of gait, oscillopsia, and postural imbalance (particularly pronounced in darkness) with more pronounced symptoms and worse course of disease in BVP patients with complete vestibular loss. These symptoms are directly related to dysfunctional perception of self-motion (2, 3). There is evidence that vestibular information is

nested and intertwined with higher cognitive processes [see Ref. (4) for a review]. Accordingly, there is growing evidence for cognitive impairments in vestibular patients. Deficits in visuospatial abilities such as mental rotation, spatial navigation, or spatial memory have been shown in patients with BVP (5–7), indicating a changed internal spatial representation (8). Furthermore, atrophy of the hippocampus is strongly correlated with impaired visuospatial abilities in patients with BVP (5, 9). BVP can also lead to cognitive impairments in non-spatial cognitive domains, such as problems with concentration, short-term memory, reading abilities, or executive functions (5, 10–12).

Conventional treatments for patients with BVP include counseling and daily intensive vestibular physical therapy, in combination with neurotological rehabilitation. The goals of vestibular rehabilitation therapy are to improve gaze and postural stability, minimize falls, decrease the sense of disequilibrium, and prevent an increasingly sedentary lifestyle (13). Traditional vestibular rehabilitation therapy includes exercises to promote alternative strategies for gaze stability by potentiation of the cervico-ocular reflex, modification of saccades (decreasing the amplitude of saccades/corrective saccades), increasing smooth pursuit eye movement or central pre-programming of eye movements [for a review, see Ref. (14)]. Self-motion perception can be induced by exposure to large-field visual stimuli (optokinetic stimulation) with the goal of developing compensation by increasing the weight of visual cues. Recent literature suggests using covert saccades during head movements as rehabilitation strategy in patients with BVP, since elimination of oscillopsia was observed in BVP patients who made covert saccades (15, 16). Even though conventional therapies are applied to patients with BVP, recovery is usually incomplete (1).

A largely unexplored approach to rehabilitation is cognitive training (17). The authors suggest that cognitive training methods can lead to reduced symptoms and improved compensation for the lack of sensory signals in patients with complete vestibular loss. While cognitive training has not been applied to BVP patients, its utility for improving balancing ability has been shown in elderly people and people with mild cognitive impairment or dementia (18, 19). The link between cognition and balancing abilities is further shown in cognitively impaired patient groups (20–22). Cognitive training may provide many benefits; it is cost-effective, and can easily be performed on a daily basis in the comfort of patients' own homes. Additionally, patients do not depend on medication and can take action to reduce their symptoms, which enhances their self-efficacy. As described above, vestibular deafferentation has dramatic consequences for higher-order processing of vestibular and spatial information, and cognitive training might be a promising opportunity for treating the adverse consequences of BVP. Conventional treatment attempts to reduce the reliance on abnormal vestibular sensory signals and improve the use of non-vestibular sensory signals. Cognitive training operates at a higher level of processing. In this paper, we explore how cognitive training might aid rehabilitation of BVP patients by considering the computations involved in vestibular processing, the complexity of which is often underestimated.

A COMPUTATIONAL MODEL OF SENSORY INFERENCE

It seems impossible for BVP patients to extract any kind of information about their head movements, because their vestibular signals provide little or no information. However, sensory processing involves much more than extracting information from noisy and ambiguous sensory data; sensory information is combined with prior knowledge about the world (23). Many tasks, from perception (24, 25) to higher-level cognition (26), have been described in a Bayesian framework. Additionally, when timing is essential, as is the case in the vestibular system, purely data-driven processing would lead to time lags. Instead, the brain continuously makes predictions and uses the sensory data to correct those predictions. Decades of vestibular research have provided insight into the type of computations used by the brain (27–30). These can be described as filtering algorithms, which rely on probabilistic models of the dynamics of head movements and the sensory data. The dynamics of head movements (e.g., the head velocity) are represented as a latent process (process model), and the sensory data are represented as depending on this latent process (sensor model). The process model represents the brain's knowledge about the laws of physics, whereas the sensor model represents the brain's knowledge about sensor characteristics.

We present the computational principles using a simplified model of a rotation of the head about the earth-vertical (yaw) axis (**Figure 1A**, angular velocity as pink line). This velocity has to be inferred, using the sensory signals provided by the semicircular canals (SCC). The sensory signals of a healthy person (blue dots) are measurements of the true velocity, with added noise. In contrast, the sensory signals of a BVP patient (orange) cannot track the head velocity. Instead, they merely reflect neuronal noise. The velocity can result from either a passive movement, or an actively initiated movement. In both cases, the head velocity and the resulting sensory signals are identical (31). If the movement was self-initiated, the brain has information about the motor commands (e.g., an efference copy), which is used by the brain in order to attenuate neurons in the vestibular nuclei (32). Recently, Laurens and Angelaki (33) demonstrated that the probabilistic model used to process passive movements also applies when movements are self-initiated. Information about expected head motion must be translated into expected sensory signals, in order to compute prediction errors. The computations involved can be described as a probabilistic graphical model (**Figure 1B**). Head velocity is represented by state variables (Ω) evolving over time according to a process model, which represents knowledge about the physical laws of head movements. If the movement was actively generated, knowledge from the motor commands is used to compute the next state. The sensor model describes how the noisy SCC measurements arise, given the state of the head. This type of probabilistic graphical model can be used for various tasks (34). For example, imagined movement may correspond to running this model in an off-line simulation mode (35–37). In order to infer head velocity, a filtering algorithm performs sequential Bayesian inference, i.e., the brain combines prior knowledge with sensory data to obtain a posterior estimate. This is illustrated in

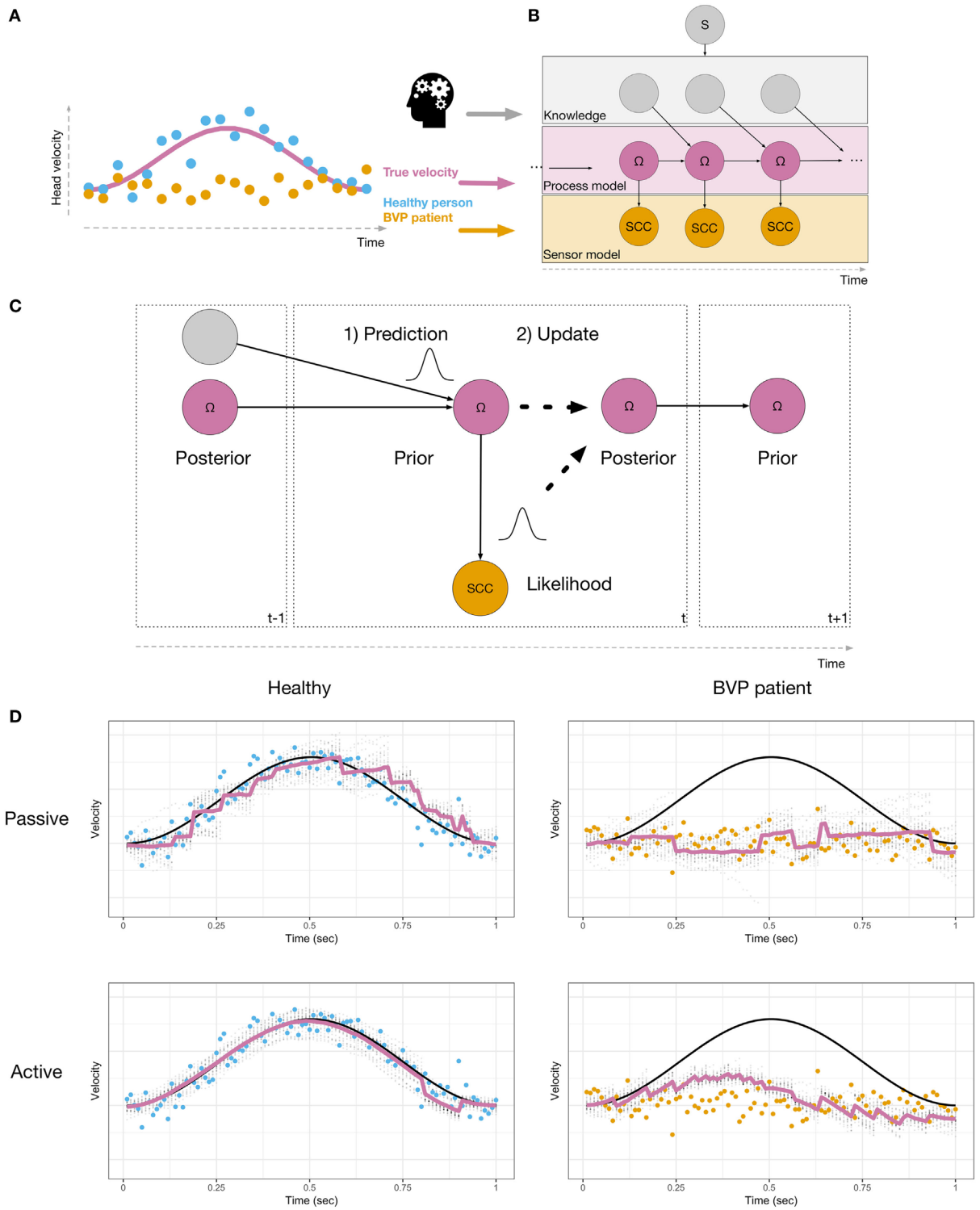

FIGURE 1 | **(A)** Head velocity, shown as a pink line, during a left head turn. Sensory signals are shown in blue for a healthy person, and in orange for a BVP patient. **(B)** Probabilistic model used to perform sensory inference. The velocity Ω (pink nodes) is represented as a sequence of latent states, which need to be inferred, given the sensory observations (orange nodes). Additional knowledge (gray nodes, e.g., derived from motor commands or higher-level knowledge) are used in order to predict Ω. The model includes a binary switch S (gray node), which indicates whether or not knowledge is used (active or passive). **(C)** During inference, the current state is probabilistically predicted (1), based on the posterior from the previous time step and additional knowledge. The prediction is then updated with the likelihood (2), resulting in a posterior state estimate. This is repeated at every time step. **(D)** Simulations of a healthy person (left) and a BVP patient (right) using a particle filtering algorithm and the generative model shown in **(B)**. True velocity is shown in black. Sensory observations are shown as blue (healthy) or orange (BVP patient) dots. Estimated velocity is shown as a pink line, along with the uncertainty in the estimate (gray dots).

Figure 1C. First, during the prediction step (1), a prior is created by predicting the head velocity Ω for the current time t, based on its past estimate. This prediction is probabilistic; the width of the distribution reflects how certain the brain is in its prediction. Second, in the update step (2), the sensory measurement (likelihood) is used to update the prior, resulting in a posterior estimate of Ω. If the head movement was the result of an intended action, then, knowledge about the head movement (e.g., efference copy) may be used in order to make more precise prior predictions for the state Ω. A few recent studies demonstrate that the brain must be able to use not only knowledge derived from motor commands, but also from other sources; vestibular signals can be predicted when these do not result from active self-motion (38). The brain is able to construct models of head dynamics based on various sources of knowledge. This information may be derived from other sensory modalities, such as vision or proprioception, from memory of recent movements (38) or prior knowledge obtained by verbal instruction (39). A recent study demonstrated that higher-level prior knowledge plays an important role in self-motion-related perception and decision-making (40). Thus, prior knowledge in different forms can affect vestibular perception. Mertz et al. (41) showed that imagined self-motion either facilitates or impedes the ability to detect linear accelerations, depending on the compatibility of the directions of imagined and actual motion. Nigmatullina et al. (42) found effects of imagined self-motion at the earliest stages of vestibular processing; the onset of the vestibulo-ocular reflex (VOR) was shortened when participants imagined moving in the same direction as the subsequent actual motion. Participants' perception of self-motion was affected in a similar manner. Finally, there is evidence that the gain of the VOR depends on the distance of an imagined target (43). All of these findings point to the fact that vestibular processing must contain a great deal of flexibility and cognitive penetrability (44, 45), in the sense that information that is not directly sensorimotor in nature may affect sensory inference.

The fact that vestibular sensory processing involves a high degree of flexibility creates new possibilities for rehabilitation.

We illustrate this idea using a particle filtering algorithm (46, 47) to simulate a healthy person and a BVP patient inferring their head velocity Ω during a 1-s leftward head turn. A particle filter recursively performs a sequence of computations. First, the state is predicted, according to a model of the process being estimated. This predicted state serves as the dynamic prior. Second, an observation is used to update the prior, resulting in a posterior estimate. The amount of updating that occurs depends on how well the sensory data were predicted, given the predicted state. **Figure 1D** shows the results of our simulations. The top row shows passive motion and the bottom row shows an active, self-initiated movement. The healthy person is able to accurately infer the velocity in both conditions. During passive motion, when the trajectory cannot be predicted, the algorithm requires the sensory data in order to update its 1-step ahead predictions during online sensory inference. This means that the estimated velocity lags the actual velocity. During the self-initiated movement, additional knowledge results in predictions that follow the actual velocity more closely, and the lag is reduced when compared to passive motion. The situation is dramatically different for the BVP patient. During passive movement, the dynamic prior does not follow the actual velocity. In order for inference to be accurate, the brain must update the prior using the sensory signals. In BVP patients, the sensory signals do not provide information about the actual velocity. Thus, the resulting velocity estimate remains at zero—the BVP patient is unable to detect self-motion by means of vestibular information. The patient is only able to construct a better prior estimate of the velocity when the trajectory of motion is predictable. Thus, when self-motion is self-initiated, the patient perceives a velocity in the correct direction, but with decreased amplitude, compared to the true velocity. The resulting posterior estimate is drawn toward the data. This also qualitatively captures the fact that BVP patients show VOR with reduced gain (48, 49).

IMPLICATIONS FOR BVP PATIENTS

The perception of self-motion relies on estimates obtained from multiple sensory modalities. The goal of most conventional rehabilitation methods is to enable BVP patients to increase the weighting of visual and somatosensory cues. In the context of the computational model of the vestibular system, this can be interpreted as enabling patients to rely less on sensory signals provided by the vestibular sensors and more strongly on their dynamic prior while performing Bayesian inference. However, this requires the use of some kind of knowledge to predict the velocity. The simulations illustrate the fact that BVP patients are unable to infer their head velocity during passive movements, due to the chronic loss of sensory input. If a probabilistic model with additional knowledge can be used because the movement is predictable, inference about head velocity can be substantially improved. In addition to this, the mismatch between expected and actual sensory signals needs to be given less weight. While the reweighting of sensory signals may require long-term learning and adaptation, the use of prior knowledge is more flexible. Thus, we claim that cognitive training, if it can be shown to be effective in BVP patients, should operate by enabling patients to improve vestibular sensory inference through the use of prior knowledge during sensory inference.

POSSIBLE EFFECTS OF COGNITIVE TRAINING ON SENSORY INFERENCE

In the context of the probabilistic model used for sensory inference, we can envisage distinct ways in which cognitive training may improve vestibular sensory inference. This is illustrated in **Figure 2A** (blue boxes). In the absence of sensory signals, any residual ability to detect head motion depends on patients' ability to predict their head velocity. This prediction is equivalent to constructing a dynamic prior prediction of head velocity, and this requires the following steps: (1) knowledge about head movements from efference copies and cognitive sources is converted into an expected head velocity. (2) The head velocity is predicted. (3) The prediction of head velocity is made, but is uncertain. In order to improve inference, the confidence predictions are made should be

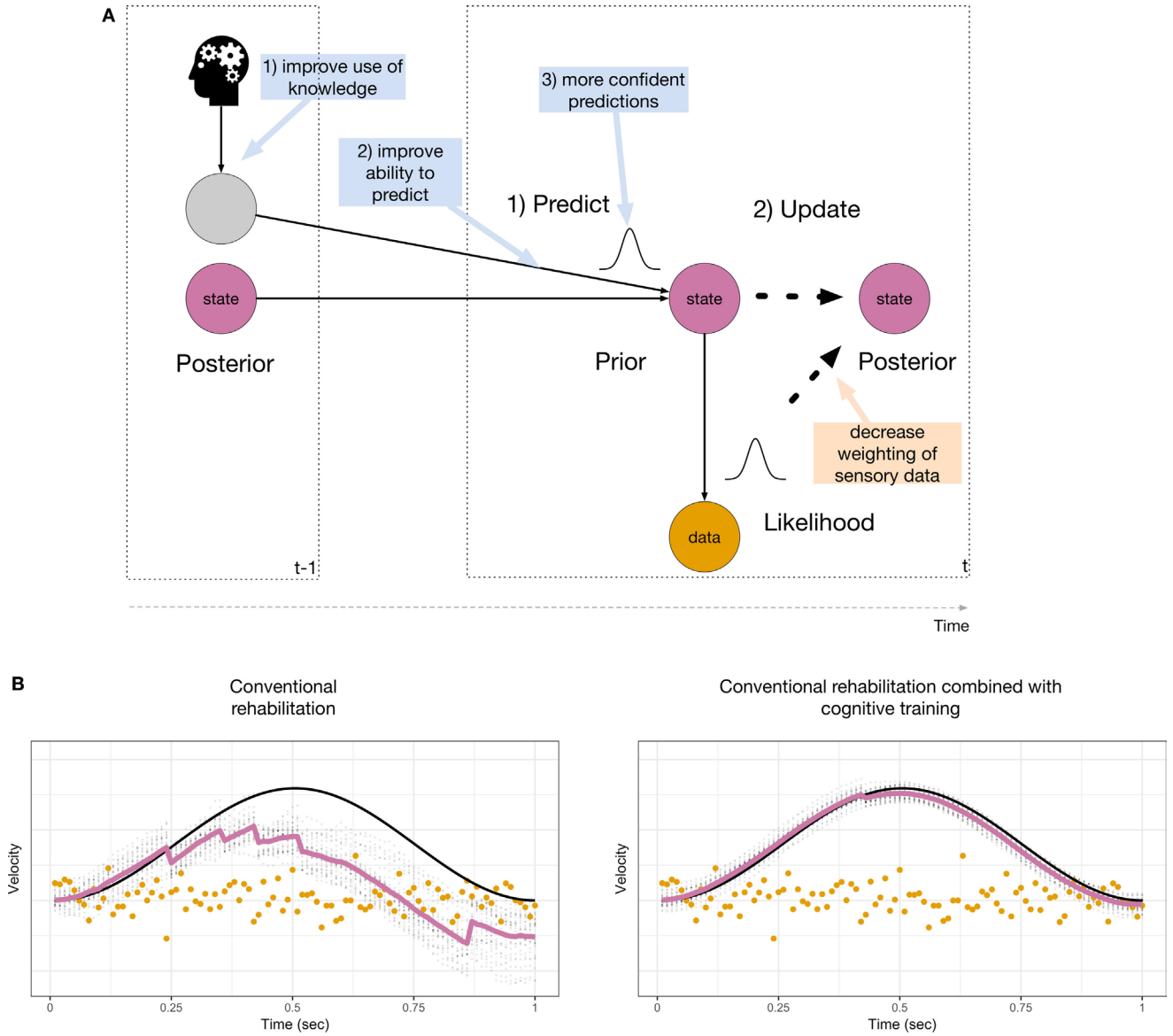

FIGURE 2 | **(A)** Suggested interventions through both conventional rehabilitation (orange box) and cognitive training (blue boxes). Most conventional rehabilitation strategies are targeted at reducing the influence of the sensory data, whereas cognitive training targets the inclusion of prior knowledge for sensory inference. **(B)** Improvements that may be achieved by conventional rehabilitation (left) and additional cognitive training (right). Inference is improved when abnormal sensory data are ignored (compare with **Figure 1D**, bottom right).

increased. In Bayesian inference, this leads to a decreased weighting of the sensory data. This only leads to improved inference if an accurate process model is used. The process model used for sensory inference during active movement can be used off-line in the service of mental simulations, i.e., to imagine self-motion (34, 35). Indeed, there is evidence for the involvement of the vestibular system in spatial perspective taking tasks (50, 51). Although this has not previously been investigated, it is likely that the brain must simulate motion of the self in order to perform cognitive tasks. This ability may be reduced in BVP patients (6). We suggest that mental body rotation training may enable patients to improve their use of knowledge about the dynamics of head movements and to rehearse simulating head motion without the requirement of performing sensory inference. Cognitive training of head and body movements *via* mental imagery will help patients not only to improve their ability to predict movement and the ensuing sensory consequences, but also to increase their confidence in these predictions.

Figure 2B illustrates the results of simulating improvements due to conventional rehabilitation (left) and additional cognitive training (right). Conventional rehabilitation may enable BVP patients to improve their inference during a predictable movement when abnormal sensory data are down-weighted (compared with **Figure 1D**, bottom right). This is achieved by increasing the

width of the sensor noise distribution. The estimated amplitude of the movement is still attenuated. Cognitive training may enable patients to improve their use of knowledge derived from their motor system, other sensory modalities (vision, proprioception) or memory and mental imagery to make better and more confident prior predictions of head movements. This is achieved by decreasing the width of the dynamic prior and yields greater improvements for sensory inference. In our model, the improvements due to cognitive training shown in **Figure 2B** (right) are akin to running the model in a simulation model.

During the course of rehabilitation, patients can learn to construct improved models of their head movements and use these for sensory inference. In addition, they can learn to rely more on their internal estimates and thereby increasingly ignore the abnormal sensory data from their vestibular end organs. More generally, mental imagery training, and other cognitive training methods, for example, targeting executive functions, may help reduce the cognitive load that BVP patients experience (10–12). In order to achieve the re-weighting of the prior predictions while simultaneously inhibiting sensory information, training of inhibition could help patients with BVP. Furthermore, a training of selective attention could lead to better allocation of attentional resources. It may also be beneficial to use cognitive training in combination with galvanic vestibular stimulation (52). Increasing the sensor noise could help patients to down-weight the abnormal sensory data. As a result, patients would be more responsive to cognitive training. Cognitive processes, such as imagined self-motion, have been shown to affect self-motion processing, a case in point being the study by Nigmatullina et al. (42). Even though our computational model was not conceived to make quantitative predictions, it is in line with their results. We are proposing that, in order to be effective, cognitive training methods should be designed with this computational framework in mind.

CONCLUSION

The discussion about the consequences of BVP is largely dominated by focusing on the absence of vestibular sensory information and the use of other sensory sources, such as vision and proprioception. This has guided the conceptualization of treatments and rehabilitation. In patients with BVP, conventional treatments are often insufficient and there are other suitable entry points for interventions. Sensory processing involves prior knowledge about the world and this is necessary for correct inference of physical motion stimuli. Erroneous self-motion perception in BVP patients can be reduced by assigning more weight to prior knowledge and disregarding uninformative sensory data. Cognitive training is a promising tool to rebalance the mechanisms underlying sensory inference in order to react to the chronic loss of sensory data.

AUTHOR CONTRIBUTIONS

AE, CS, DV, MC, and FM wrote the manuscript. AE and FM planned and performed the simulations.

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