Aus der

Neurologischen Klinik und Poliklinik

Klinikum der Ludwig-Maximilians-Universität München

Optimizing Diagnostic and Therapeutic Approaches in Vestibular Disorders: Comparison of Diagnostic Tools and Treatment Efficacy across Various Vestibular Conditions

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät
der Ludwig-Maximilians-Universität München

vorgelegt von
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aus
Dobrich, Bulgarien

Jahr
2025

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

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III. Abbreviations / Abkürzungsverzeichnis

BPPV - Benign Paroxysmal Positional Vertigo

BVP - Bilateral Vestibulopathy

cVEMPs - Cervical Vestibular Evoked Myogenic Potentials

oVEMPs – Ocular Vestibular Evoked Myogenic Potentials

CRT - Caloric Response Testing

EM - Epley Maneuver

MD - Menière's Disease

SM - Semont Maneuver

SM+ - SemontPLUS Maneuver

VEMPs - Vestibular Evoked Myogenic Potentials

VM - Vestibular Migraine

vHIT - Video Head Impulse Test

VOR - Vestibulo-Ocular Reflex

SCC - Semicircular Canal

IV. Publication List / Publikationsliste

1. Mavrodiev, V., Strupp, M., Vinck, A.-S., van de Berg, R., & Lehner, L. (2024). The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière's disease, vestibular migraine, and other vestibular disorders: a confirmatory study in a large cohort of 2,101 patients [Original Research]. *Frontiers in Neurology*, *15*. https://doi.org/10.3389/fneur.2024.1449261

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V. Publication contributions / Beitrag zu den Veröffentlichungen

1. **Contribution to paper I / Beitrag zu Paper I: "**The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière's disease, vestibular migraine, and other vestibular disorders: a confirmatory study in a large cohort of 2,101 patients"

Erstauthor der Arbeit. Erstellung der Datenbank mit retrospektiven Daten aus München, Sammlung der Daten aus den 3 Studienzentren Auswertung und vollständige statistische Analyse inkl. Abbildungen. Erstellung vom Manuskript, Einreichung der Arbeit sowie Kommunikation mit dem Journal und dessen Produktionsteam während des Publikationsprozess.

2. **Contribution to paper II / Beitrag zu Paper II: "**Patterns of Vestibular Impairment in Bilateral Vestibulopathy and Its Relation to Etiology"

Akquisition von retrospektiven Daten und Kommunikation mit den 4 anderen Zentren (Maastricht, NL; Tomsk, RU; Genf, CH und Antwerp, BE). Miterstellung vom Originalmanuskript sowie Beteiligung im Review-Prozess.

3. **Contribution to paper III / Beitrag zu Paper III: "**The Semont-Plus Maneuver or the Epley Maneuver in Posterior Canal Benign Paroxysmal Positional Vertigo: A Randomized Clinical Study"

Erstellung der Datenbank mit Daten aus München, DE; Siena, IT und Antwerp, BE. Vollständige statistische Analyse inkl. Erstellung der Grafiken und Figuren und Erstellung des 1. Manuskripts. Kommunikation mit den Reviewern und Bearbeitung von Änderungsanträgen im Review-Prozess.

VI. Introduction / Einleitung (English)

1. Importance and relevance

Vertigo and dizziness are among the most common reasons for physician consultation in today‘s society. They pose a significant burden in our community, with a point prevalence of over 22% and a yearly incidence of over 3%. Vestibular vertigo accounted for nearly 5% of the prevalence and 1.4% of the incidence (Neuhauser et al., 2008). Patients with vestibular vertigo are spending more nights when it comes to in-patient treatment and have increased odds of seeking the help of a specialist during the diagnostic and therapeutic process in comparison to patients with non-vestibular vertigo (Matthews et al., 2024). These patients often experience extensive diagnostics and multiple consultations with family doctors, neurologists, and ENT specialists. Substantial economic impact, significant personal and social consequences for patients highlight the need for optimized diagnostics and therapeutic approaches, tailored to the specific needs of the patient (Mueller et al., 2012; Mueller et al., 2014; Neuhauser et al., 2008).

2. Scope of the dissertation

This dissertation focuses on optimizing diagnostic and therapeutic strategies for peripheral vestibular disorders, comparing the efficacy of different diagnostic tools and treatment strategies. The overarching topic of this work is enhancing the accuracy of diagnosis and improving treatment outcomes across a spectrum of vestibular conditions with the currently available diagnostic and therapeutic methods. The dissertation is based on three core studies covering peripheral vestibular conditions.

3. The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière’s disease, vestibular migraine, and other vestibular disorders

The first study focused on the diagnostic power of combining two of the more accessible tests today on peripheral-vestibular diagnostics: caloric response testing (CRT) and video head impulse test (vHIT). Menière’s disease (MD) is a severe inner ear disorder characterized by spells of spinning vertigo lasting 20 minutes to 12

hours and fluctuating aural symptoms, such as hearing loss, ear fullness, and tinnitus (Lopez-Escamez et al., 2015). Vestibular migraine (VM) is a condition that includes recurrent spells of vertigo or dizziness, lasting from 5 minutes to 72 hours, a history of episodic or chronic classical migraine with or without aura, as well as a temporal association between the spells of dizziness and migraines-typical headache (Headache Classification Committee of the International Headache, 2013; Lempert et al., 2022). A significant difficulty in clinical decision-making comes from the facts that (1) MD occurs in about 30% of cases during the early stages of the disease without aural hearing loss, and (2) VM can present without headache in also 30% of cases (Gurkov et al., 2019; Neuhauser et al., 2001; Sohn, 2016). Along with occurring aural symptoms in patients with VM, differentiating between MD and VM becomes, in some instances, very challenging (Shi et al., 2022). The retrospective study investigated the diagnostic power of combining the video head impulse test (vHIT), which covers the high-frequency range of the vestibulo-ocular reflex (VOR), and the caloric testing, which depicts the low-frequency range of the VOR (MacDougall et al., 2009; Shepard & Jacobson, 2016). Vestibular abnormalities often lead to an impairment in the high frequencies first, resulting in a “dissociation” between normal caloric excitability and a normal VOR gain in the vHIT. The first study focused on examining and confirming this dissociation between both tests as a diagnostic tool in the diagnosis of MD and, through a large data set, explored its value also in differentiating between MD and other peripheral and central vestibular disorders. We collected retrospective data from 2101 patients from three centers - 2,020 subjects from the Ludwig Maximilian University (LMU) Hospital Munich, Germany; 25 from the Sint-Jan Clinic in Bruges, Belgium; and 56 from the Maastricht University Medical Center, Netherlands. In this group, 627 had MD and 473 VM. Data from a comparison group containing 1001 patients with “other” central or vestibular disorders was collected. In the comparison group, at least one episode of vertigo or dizziness was required for inclusion. All subjects had at least one caloric test and one video head impulse test. We then used 2x2 contingency tables to calculate the sensitivity, specificity, and positive and negative predictive values of the dissociation in terms of correctly diagnosing or ruling out an MD. Our “gold standard” was the Bárány Society criteria 2015 (Lopez-Escamez et al., 2015). Our results in this cohort showed that this dissociation is indeed very valuable not only in differentiating between MD and VM but also between MD and other vestibular

disorders and can provide a specificity of 83.5%, a substantial rule-out test for MD, especially in patients, lacking the typical aural MD symptoms. This can be useful in vertigo and balance centers and neurological and otolaryngologic clinics, where experience shows that patients often receive both tests as part of routine diagnostics. The limitations of this research design need to be addressed when considering the results: misclassification, selection bias, and no control group setting. Although the former two points can never be entirely avoided in the retrospective data collection, they might lead to skewed results despite our efforts to collect a large amount of data to counteract that effect. Furthermore, no control group of healthy subjects was included.

4. Patterns of Vestibular Impairment in Bilateral Vestibulopathy (BVP) and Its Relation to Etiology

The following study discussed patterns of vestibular impairment in patients diagnosed with Bilateral Vestibulopathy (BVP) and their eligibility for vestibular implantation. Data was collected from three vertigo centers. Center 1 was the Department of Otorhinolaryngology and Head and Neck surgery from Maastricht University Medical Center; center 2 was Antwerp University Hospital; and center 3 was the Department of Neurology and the German Center for Vertigo and Balance Disorders, Ludwig Maximilians University Munich. We analyzed the vestibular test results and their relation to the underlying etiology of BVP. The vestibular testing included caloric response testing (CRT), torsion swing test, video head impulse test (vHIT), and vestibular-evoked myogenic potentials (VEMPs). Ten different etiologies were differentiated — idiopathic, genetic disorders, ototoxic substances, infectious disorders, Menière's Disease (MD), (head)trauma, auto-immune disease, neurodegenerative disorders, congenital disorders, and Mixed. "Mixed" etiology refers to multiple identifiable conditions, possibly leading to bilateral vestibulopathy.

i. Video head impulse test (vHIT)

The vHIT is the most extensively applied apparative diagnostic test to quantify peripheral vestibular function. It has been well validated to be as good as the previous "gold standard" in the vestibular diagnostic, i.e., the scleral search coils (Macdougall et al., 2013; MacDougall et al., 2009; Weber et al., 2009). It provides

information by assessing the semicircular canals (SCC) at a frequency of 3-6 Hz and can be performed in all three planes of movement (Halmagyi & Curthoys, 1988). This frequency range is closest to the physiological demands on the vestibular system in daily life activities. This study found that the anterior and posterior canal vHIT did not differ significantly between patients with different BVP etiologies. The horizontal canal vHIT, on the other hand, showed a significantly lower gain in the neurodegenerative group compared to the infectious, MD, idiopathic, and mixed etiologies groups. Trends of anterior canal sparing were observed for MD, infections, ototoxicity, trauma, and idiopathic BVP. This was consistent with previous literature suggesting that anterior canal sparing may originate from a distinct vulnerability of ampullary hair cells to toxic substances and endolymphatic pressure due to a possible superior recovery after damage (Tarnutzer et al., 2016). A reason for that is postulated to be the decreased accumulation of substances and hydrostatic pressure due to gravitational forces and the larger density of aminoglycosides compared to the endolymph.

ii. Vestibular-evoked myogenic potentials (VEMPs)

The vestibular-evoked myogenic potentials (VEMPs) are electrophysiological responses that assess the function of the otolith organs in the vestibular system (Colebatch & Halmagyi, 1992; Rosengren et al., 2010). There are two main types of VEMPs. (1) Cervical VEMPs (cVEMPs), which test the function of the saccule and the inferior vestibular nerve, with responses recorded from the sternocleidomastoid muscle when sound or vibration stimulates the vestibular system and (2) Ocular VEMPs (oVEMPs) which assess the function of the utricle and the superior vestibular nerve, with responses recorded from the extraocular muscles, typically beneath the eyes (Colebatch et al., 1994; Rosengren et al., 2005). Regarding VEMPs, we did not find significant differences in pathologic responses in relation to the BVP etiology groups. This result is possibly due to the variable nature of VEMP testing itself. Furthermore, there is also a fundamental difference in the current diagnostic criteria. The current apparative diagnostic criteria of a BVP are based on an impaired VOR, tested by all three diagnostic tests predominantly on the horizontal semicircular canal (CRT, vHIT and torsion swing test). The otolithic organ (dys)function is currently not a part of the diagnostic criteria for the vestibular disease, which may highly likely contribute to variable VEMP findings in an already

pre-selected group of subjects. Additionally, it is still unknown how much residual otolithic function is enough to get a synchronous motor discharge in VEMP testing (Rosengren et al., 2018).

iii. Caloric testing

The caloric testing is one of the first tests used in modern vestibular medicine and is the reason for the Nobel Prize awarded to Mr. Robert Bárány in 1914 (Bárány, 1906). It assesses the integrity of the horizontal (lateral) semicircular canals and the vestibular nerves (particularly the superior branch) (Aw et al., 2001; Coats & Smith, 1967). This testing involves irrigating the ear canal with warm or cold water (or air). There are two competing theories on how a caloric test triggers spinning sensations and accompanies nystagmus. The original one postulates that the test induces a temperature gradient, affecting the endolymph in the semicircular canal and creating convection currents that stimulate or inhibit the vestibular system. This leads to the induction of nystagmus, which is recorded and analyzed to evaluate each ear's vestibular response independently (Bárány, 1906). An alternative theory, resulting from the persisting caloric response in a zero-gravity environment during the 1983 Spacelab mission, aims to explain a range of abnormalities surrounding the caloric response (Scherer et al., 1986; Scherer & Clarke, 1985; Scherer et al., 1985; Stahle, 1990). In our study, the median results for bithermal maximal peak slow phase velocity of bilateral caloric response did not differ significantly between the 10 described BVP etiologies. The median values for centers 1 and 2 were 0°/s and for center 3 — 6.2°/s.

iv. The torsion swing test

The torsion swing test examines the eye movements with electronystagmography while seated in an automated rotatory chair with a rotation at 0.05 or 0.1 Hz in complete darkness with their eyes open. Our study showed no significantly different torsion swing test results in patients with different BVP etiologies. The results showed, interestingly, that patients with a BVP more frequently had better-preserved function in the torsion swing test than in the vHIT. This is peculiar, given the fact that both tests examine the horizontal SCC. It can be explained through an already existing hypothesis that the optimum of the human vestibular system lies around 0.1 Hz. Therefore, as tested in the torsion swing test, as opposed to higher frequencies

by the vHIT and lower frequencies in caloric testing, these frequencies get affected last (Gresty, 2002). Hence, this indicates that the torsion swing test suits the initial diagnostics better than the caloric testing and vHIT that measure earlier affected frequencies.

v. Cluster analysis

In our study, a cluster analysis with two clusters of BVP severity showed only a slight tendency of MD patients to perform better in vestibular testing compared to patients with an idiopathic and ototoxic BVP etiology. The two clusters were defined as “severe” and “moderate” BVP, with the “severe” cases meeting predominantly all three criteria of the Bárány Society and the “moderate” cases meeting predominantly only 1 criterion (Strupp et al., 2017, 2023). Furthermore, after performing a hierarchical cluster analysis and plotting the data on a dendrogram, we found that vestibular tests like the cVEMPs and oVEMPs correlated closely and tended to have similar results in patients with a similar vestibular impairment. This is quite intuitive as they both measure the otolithic organs that are anatomically in tight proximity to each other. Whereas the caloric response, the horizontal vHIT and the torsion swing test are all tests of the horizontal semicircular canal, in the current study, they ended up being further apart on the dendrogram. Instead, the posterior plus the horizontal vHIT were close to the caloric testing, and the torsion swing test showed similar results to the posterior vHIT.

vi. VEMPs in relation to vestibular implantation criteria

The vestibular implantation criteria differ from the Bárány society’s BVP criteria, taking into account the function of all three semicircular canals and all included vestibular tests of semicircular canal function, i.e., caloric response, vHIT, and rotary chair, to show an impaired function as opposed to only horizontal canal testing in the BVP criteria (van de Berg et al., 2020). Otolithic organ function is currently not included in consensus criteria. We do not know the amount of disability caused by its isolated dysfunction, which can be an exciting topic for future research and can prove a relevant factor when selecting patients for a vestibular implant. Seventy-six percent of the subjects in the study with diagnostic data fulfilled the criteria for vestibular implantation (Rosengren et al., 2018). This is probably an overestimation concerning the daily clinical practice as we did not consider other general surgical

eligibility, such as somatic and psychiatric comorbidities. Regarding VEMPs, we observed higher rates of bilaterally absent oVEMPs than cVEMPs. This can be explained by the pre-selection of subjects by the BVP criteria that require a horizontal semicircular canal dysfunction and the fact that both the horizontal canal and the utricle, tested by the oVEMPs, project onto the superior branch of the vestibular nerve as opposed to the saccule which projects on the inferior one.

5. The Semont-Plus Maneuver or the Epley Maneuver in Posterior Canal Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo, with nearly one-third of patients by the age of 70 having experienced at least one episode of BPPV in their lifetime (Brandt, 2013). Population-based studies estimate the lifetime prevalence of BPPV to be 2.4% (Neuhauser et al., 2008). It poses a significant healthcare burden, with a reported prevalence of 10.7 to over 140 per 100,000 people (Kim et al., 2018). The symptoms are characterized by short spells of vertigo, usually lasting between 20 and 60 seconds, and provoked by sudden movements of the head, inducing a movement of the canaliths that are most commonly inside the posterior semicircular canal (Dix & Hallpike, 1952; von Brevern et al., 2017). Cupulolithiasis was later described as a condition in which the mineral aggregates are deposited on the cupula of the semicircular canals instead of freely moving in the endolymph (Schuknecht, 1969). In this study, we compared the effectiveness of the Epley maneuver (EM) to that of the SemontPLUS maneuver (SM+) by the endpoint “days until full recovery without spells of vertigo” in patients with a posterior canal BPPV.

i. The SemontPLUS Maneuver (SM+)

Using a biophysical computational model of the already widely used Semont Maneuver (SM), the maneuver was found to be not optimal, and the SemontPLUS was developed by increasing the angle of extension of the head in the first step towards the affected side to at least 150° or 60° below the horizontal line of the body, parallelled to the earth (Obrist et al., 2016). The SemontPLUS maneuver (SM+) was

previously found to perform better than the SM in treating posterior canal BPPV (Strupp et al., 2021).

ii. The Epley Maneuver (EM)

The Epley Maneuver (EM) is a method of repositioning canaliths, also called otoconia, from the ampulla of the posterior semicircular canal (SCC) beyond the apex of the canal toward the common crus of the anterior and posterior SCC and into the vestibulum near the utricle where the otoconia. It is performed with the patient lying in the supine position with the head turned 45° towards the affected ear and turning the head in steps toward the “healthy” ear (Epley, 1992).

iii. Comparison between SemontPLUS and Epley maneuvers

In the current study, we found the SM+ superior to the EM in treating posterior canal BPPV in terms of number of days until full recovery with no vertigo attacks anymore from 3.3 days in the EM group compared to 2.0 days in the SM+ group. This is adequately in line with our biophysical understanding of the anatomical structure of the semicircular canals as an overextension of the head should and does allow the canaliths to move further into the canal and with a higher probability over the apex of the canal, which would enable them to exit the canal in the last step of the maneuver.

6. Conclusion

In summary, through its three core studies, this work examines diagnostic and therapeutic strategies for four of the most common peripheral vestibular disorders – Menière’s Disease, Vestibular migraine, Benign paroxysmal positional vertigo, and bilateral vestibulopathy. The 3 manuscripts underline the importance of the multimodal diagnostic approach and evidence-based therapeutic strategies. Hopefully, the work can contribute to optimizing patient care and improving outcomes. In conclusion, I would like to emphasize the importance of personalized medicine. No matter how conclusive scientific studies are, they are always more or less shaped by the researcher's assessment. It is crucial to remember that the human factor is an inherent limitation of scientific research. Every patient is unique,

and their symptoms and needs cannot always be put into categories by scientific studies.

VII. Abstract / Zusammenfassung (Deutsch)

Bedeutung und Zielsetzung:

Schwindel und Benommenheit gehören zu den häufigsten Beschwerden, die zu Arztbesuchen führen, und haben erhebliche persönliche, soziale und wirtschaftliche Auswirkungen. Vestibulärer Schwindel betrifft eine Untergruppe von Patienten, bei denen schwerere Fälle eine spezialisierte Betreuung und langwierige diagnostische Prozesse erfordern. Dies unterstreicht die Notwendigkeit optimierter diagnostischer und therapeutischer Ansätze, um Menschen mit vestibulären Störungen besser zu versorgen. Das Hauptziel dieser Dissertation ist die Verbesserung der diagnostischen Genauigkeit und der Behandlungsergebnisse bei verschiedenen vestibulären Störungen, darunter der Morbus Menière, vestibuläre Migräne, bilaterale Vestibulopathie und benigner paroxysmaler Lagerungsschwindel (BPPV).

Design und Methoden:

Die Dissertation besteht aus drei zentralen Studien, die sich jeweils auf eine spezifische vestibuläre Störung konzentrieren. Die erste Studie untersucht den diagnostischen Wert der Kombination aus Video-Kopfimpulstest (vHIT) und kalorischer Testung zur Differenzierung zwischen Morbus Menière und vestibulärer Migräne und adressiert die Herausforderung überlappender Symptome. Die zweite Studie analysiert die Muster vestibulärer Beeinträchtigungen bei Patienten mit bilateraler Vestibulopathie und deren Zusammenhang mit verschiedenen Ätiologien anhand mehrerer vestibulärer Tests. Die dritte Studie vergleicht die Wirksamkeit der SemontPLUS- und Epley-Manöver bei der Behandlung des posterioren Kanal-BPPV in einer prospektiven, randomisierten klinischen Studie.

Ergebnisse:

Die Kombination aus vHIT und kalorischer Testung zeigte eine Spezifität von 83,5 % beim Ausschluss des Morbus Menière, insbesondere bei Patienten ohne typische aurale Symptome. Die Studie zur bilateralen Vestibulopathie ergab, dass der horizontale Kanal im vHIT bei Patienten mit neurodegenerativer Ätiologie signifikant stärker beeinträchtigt war als bei anderen Ursachen, während die Funktion des anterioren Kanals häufig erhalten blieb. Die Cluster-Analyse offenbarte Muster

vestibulärer Beeinträchtigungen, die zur Verfeinerung zukünftiger diagnostischer Kriterien beitragen könnten. Der Vergleich der Behandlungsmanöver für BPPV zeigte, dass das Semont-Plus-Manöver zu einer schnelleren Erholung führte, wobei Patienten im Durchschnitt nach 2,0 Tagen vollständig beschwerdefrei waren, verglichen mit 3,3 Tagen beim Epley-Manöver.

Schlussfolgerung:

Diese Dissertation zeigt, dass die Kombination diagnostischer Verfahren wie vHIT und kalorische Testung die Differenzialdiagnose vestibulärer Störungen verbessern kann. Gleichzeitig bietet das Semont-Plus-Manöver eine effektivere Behandlung des posterioren Kanal-BPPV. Diese Erkenntnisse unterstreichen die Bedeutung personalisierter und präziser diagnostischer sowie therapeutischer Strategien im Management vestibulärer Störungen, die die Patientenversorgung erheblich verbessern könnten.

VIII. Abstract / Zusammenfassung (English)

Importance and Objective: Vertigo and dizziness are among the most common complaints leading to physician consultations, with significant personal, social, and economic impacts. Vestibular vertigo affects a subset of patients with more severe cases requiring specialist care and prolonged diagnostic processes. This highlights the need for optimized diagnostic and therapeutic approaches to serve individuals with vestibular disorders better. The primary objective of this dissertation is to improve diagnostic accuracy and treatment outcomes for a range of vestibular disorders, including Menière's disease, vestibular migraine, bilateral vestibulopathy, and benign paroxysmal positional vertigo (BPPV).

Design and Methods: The dissertation consists of three core studies, each focusing on a specific vestibular disorder. The first study examines the diagnostic value of combining video head impulse testing (vHIT) and caloric testing to differentiate between Menière's disease and vestibular migraine, addressing the challenges of overlapping symptoms. The second study investigates the patterns of vestibular impairment in patients with bilateral vestibulopathy and their relationship to various etiologies using multiple vestibular tests. The third study compares the effectiveness of the SemontPLUS and Epley maneuvers in treating posterior canal BPPV through a prospective randomized clinical trial.

Results: The combination of vHIT and caloric testing provided a specificity of 83.5% in ruling out Menière's disease, especially in cases without typical aural symptoms. The study on bilateral vestibulopathy found that horizontal canal vHIT was significantly impaired in patients with neurodegenerative etiology compared to other causes, while anterior canal function was often spared. The cluster analysis revealed patterns of vestibular impairment that could help refine future diagnostic criteria. The comparison of treatment maneuvers for BPPV showed that the Semont-Plus maneuver led to faster recovery, with patients experiencing complete relief in an average of 2.0 days compared to 3.3 days with the Epley maneuver.

Conclusion: This dissertation demonstrates that combining diagnostic tools such as vHIT and caloric testing can improve the differential diagnosis of vestibular disorders. At the same time, the Semont-Plus maneuver offers a more effective treatment for posterior canal BPPV. These findings underscore the importance of personalized and precise diagnostic and therapeutic strategies in managing vestibular disorders, which could significantly improve patient outcomes.

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X. Acknowledgements / Danksagung

I would like to express big appreciation to my wife – Kae, who supports me unconditionally and helps me grow as a person every single day. I am proud to be the man, standing next to you! Many thanks to my mom – Zlatina, my dad – Vergiliy and my sister – Darina, who supported my studies all these years in Munich. I am blessed to have such a family! A very special role in my life has played the person who supported me professionally and academically on the highest level possible – Prof. Michael Strupp. After probably the didactically best seminar throughout my studies at the LMU during the Neurology block at the fall of 2019 on the topic of peripheral vestibular disorders, I asked Michael if he has an available spot and a project idea for a doctoral student. Since that moment onwards, I was fortunate to have a collaboration with Michael that has inspired me to be the best clinician and best scientist I can be. Michael ignited the spark of passion for neurology that does not seem to be stopping any time soon.

XI. Paper I

The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière's disease, vestibular migraine, and other vestibular disorders: a confirmatory study in a large cohort of 2,101 patients

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RECEIVED 14 June 2024
ACCEPTED 29 July 2024
PUBLISHED 14 August 2024

CITATION
Mavrodiev V, Strupp M, Vinck A-S, van de Berg R and Lehner L (2024). The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière's disease, vestibular migraine, and other vestibular disorders: a confirmatory study in a large cohort of 2,101 patients.
Front. Neurol. 15:1449261.
doi: 10.3389/fneur.2024.1449261

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 14 August 2024
DOI 10.3389/fneur.2024.1449261

OPEN ACCESS

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The dissociation between pathological caloric testing and a normal video head impulse test helps differentiate between Menière's disease, vestibular migraine, and other vestibular disorders: a confirmatory study in a large cohort of 2,101 patients

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Vestibular migraine (VM) and Menière's disease (MD) are characterized by episodes of vertigo of similar duration. It is well known that differentiation between both diseases is not always possible based only on the patient history, physical examination, and audiological testing. In addition, the quantification of the vestibular function can also be helpful since, among patients with MD, there is often a dissociation between a normal/pseudo-normal video head impulse test (vHIT) and reduced caloric testing. The goal of this confirmatory study was to determine the sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of this dissociation to differentiate between MD and VM as well as between MD and other vestibular diseases. We performed a retrospective analysis of 2,101 patients. The examination group consisted of 1,100 patients; of these, 627 (57%) had MD according to the diagnostic criteria of the Bárány Society and 473 (43%) had VM. The comparison group consisted of 1,001 patients with other peripheral, central, or functional vestibular disorders. Statistical analysis revealed the following findings for the dissociation: MD vs. VM: specificity: 83.5%, sensitivity: 58.9%, PPV: 82.6%, and NPV: 60.5%, and MD vs. all other vestibular disorders (VM plus others): specificity: 83.5%, sensitivity: 58.9%, PPV: 60.3%, and NPV: 82.7%. The dissociation between a normal vHIT and a reduced caloric response is due to the high specificity and PPV suited for the differentiation between MD and VM. This part of the study confirms previous findings in a large cohort of patients. When it comes to differentiating between MD and all observed vestibular disorders, if there is no dissociation, the diagnosis of MD is unlikely.

KEYWORDS

vertigo, Menière's disease, vestibular migraine, video head impulse test, caloric testing, retrospective analysis, dissociation

1 Introduction

Differentiating episodic vestibular disorders can be a challenge for any clinician, but it is crucial to ensure specific treatment. In particular, the differentiation between Menière's disease (MD) (1) and vestibular migraine (VM) (2) is important because they share many similarities in terms of the duration of the symptoms and accompanying signs and symptoms. In typical presentations, the presence of headache, other migraineous symptoms, and history of migraine vs. hearing impairment differentiates well between the two diseases (3). On the other hand, there are also atypical forms of presentation. Especially in the early stages, approximately one-third of MD patients do not experience any auditory symptoms (4). Similarly, VM patients do not experience headaches in approximately 30% of all episodes (5, 6) and can also show an impairment of hearing (7). Finally, there are also overlap syndromes, i.e., patients fulfill the diagnostic criteria for both diseases (8).

This diagnostic clinical dilemma parallels that we do not know the exact pathophysiology and etiology of either VM (9) or MD (10, 11). It is also assumed that there is a link between both diseases (12, 13). This is reflected in many findings, for instance, the demonstration of endolymphatic hydrops in patients with VM (14), the assumption of a parallel activation of vestibular and meningeal nociceptive pathways (9, 13), and the probable role of calcitonin gene-related peptide (CGRP) in both diseases (15, 16).

Several studies demonstrated a normal vHIT and reduced caloric response (17–23) in patients with MD. This "dissociation" might serve as a diagnostic marker for MD (19). One hypothesis to explain the dissociation is that the reduced caloric excitation in MD is a result of an enlargement of the membranous duct in the hydropic labyrinths (22). This concept has been supported by animal models with similar findings to those seen in MD patients (24).

This study aimed to investigate the diagnostic significance of a normal vHIT and pathological caloric testing to (a) differentiate patients with MD from those with VM with a confirmatory approach and (b) differentiate patients with MD from patients with other vestibular disorders in a large cohort of 2,101 patients.

2 Methods

In this retrospective study, a total of 2,101 patients were included between January 2010 and February 2020: 2,020 subjects from the Ludwig Maximilian University (LMU) Hospital Munich, Germany; 25 from the Sint-Jan Clinic in Bruges, Belgium; and 56 from the Maastricht University Medical Center, Netherlands. The study was approved by the institutional ethics review boards (No. 19-301) The study group consisted of 1,100 patients who fulfilled the diagnostic criteria defined by the Bárány Society for certain ($n = 374$) or probable ($n = 253$) MD or certain ($n = 142$) or probable ($n = 331$) VM (1, 2). The comparison group consisted of 1,001 patients with various central, peripheral, and functional vertigo disorders (Table 1; Figure 1). All subjects had a complete diagnostic work-up, including caloric and vHIT testing.

2.1 Video head impulse testing

The vHIT was performed using the device "Otometrics®" with a visual target fixation distance of 1.8 m and a peak velocity horizontal plane >150°/s. The device consists of a headset that uses an accelerometer and a camera mounted on a set of goggles to measure head and eye movement. The patients were instructed to stare at a target positioned at eye level, and several passive quick head rotations were performed by the examiners. Ideally, the head movements are accompanied by eye movements that are equal in velocity and opposite in direction. This is then described as an eye/head gain of 1.0 (25). An impaired vestibulo-ocular reflex (VOR) causes a reduced acceleration of the eyes, resulting in a lower gain than 1 with catch-up overt or covert saccades (26). A vHIT gain ≥0.7 was considered normal (27).

TABLE 1 Demographic and clinical characteristics.

Characteristics	*N* (%)/Median (range)		
	Menière's disease	Vestibular migraine	Other vestibular disorders
N	627	473	1,001
Sex			
Men	325 (51.8%)	166 (35.1%)	444 (44.3%)
Women	302 (48.2%)	307 (64.9%)	557 (55.6%)
Age	58.2 ± 14.5 (11–88)	46.8 ± 14.4 (5–84)	55.0 ± 16.6 (9–95)
Certainty of diagnosis[1]			
"Diagnosis of …"	374 (59.6%)	142 (30.0%)	
"Probable diagnosis of …"	253 (40.3%)	331 (70.0%)	
Right	253 (40.3%)		
Left	260 (41.5%)		
Bilateral MD	114 (18.2%)		
Pathological vHIT (gain on either side <0.7)	101 (16.1%)	25 (5.3%)	240 (24%)
Pathological caloric testing[2]	446 (71%)	99 (20.9%)	333 (33.3%)
Normal vHIT and pathological caloric testing	369 (58.9%)	78 (16.5%)	165 (16.5%)

[1]Barany Society criteria (2015), Vestibular migraine. Diagnostic criteria (2012).
[2]A variability of ≥25% and/or a total caloric excitability of <10°/s in both ears was considered pathological.
vHIT, video head impulse test.

2.2 Caloric testing

Caloric testing was performed using "Atmos Variotherm®" as a caloric water stimulator and "Interacoustics VOG®" for recording eye movements. The caloric testing relies on the application of cold and warm water in the external ear canal. The differences in temperature cause the endolymphatic liquid in the horizontal semicircular canal to move. This results in a calorically induced nystagmus, whose slow phase is then measured by a camera, mounted on a set of goggles. The VOR frequencies evaluated by the caloric stimulation are within the range of 0.003–0.008 Hz, which is lower than those of the vHIT (28). The irrigations were performed with a minimum of 100 mL of water for a duration of 30 s. The

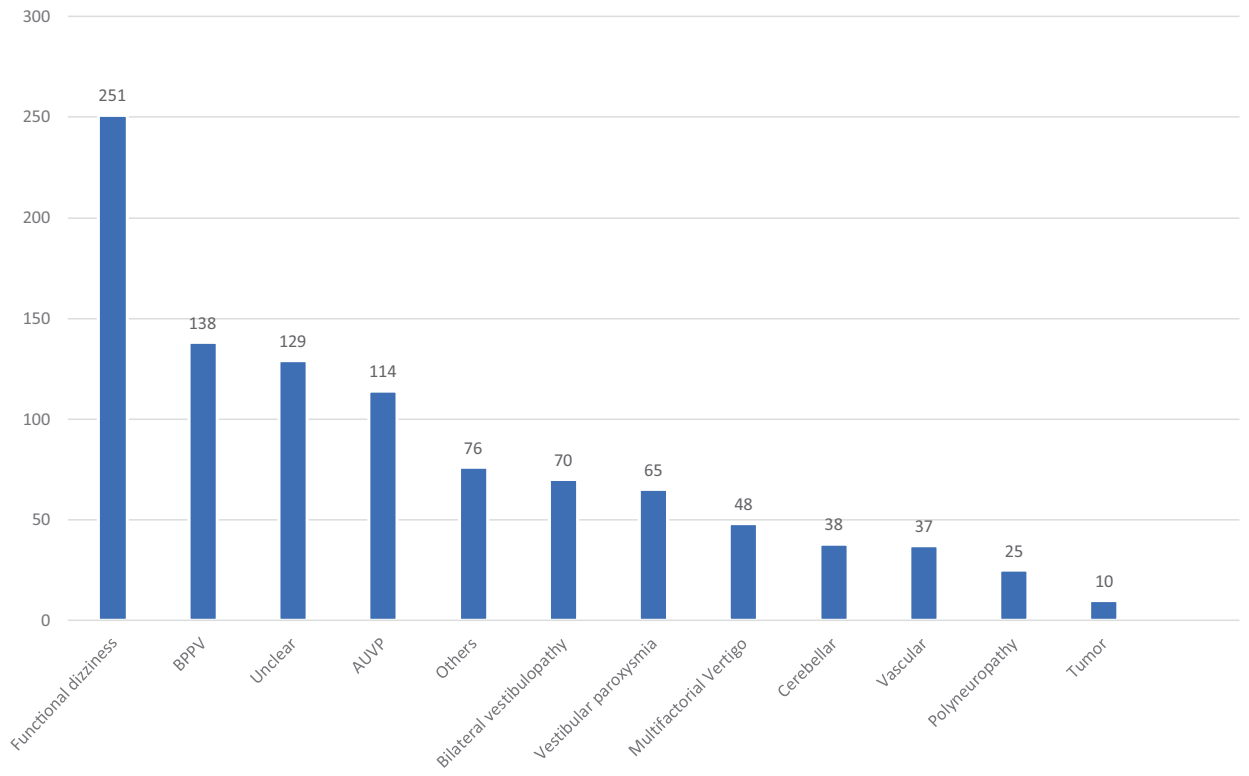

FIGURE 1
Different vertigo entities in the comparison group. BPPV, benign paroxysmal positional vertigo; AUVP, acute unilateral vestibulopathy (including residual vertigo/dizziness in the post-acute phase).

interval between the first irrigation and the following irrigation was 300 s. The cold stimulation was performed at 30°C, and the warm stimulation was performed at 44°C. Unilateral weakness or canal paresis was calculated according to Jongkees' formula; a variability of ≥25% was considered pathological. A bilateral canal paresis was defined as a reduced total slow phase velocity of the warm and cold stimuli of less than 10°/s (27).

2.3 Data analysis

Statistical analysis was performed using SPSS. Categorial data were expressed as numbers (%), and continuous values were expressed as median and range. To assess whether the discrepancy between a normal vHIT and a reduced caloric excitation can serve as a marker for MD, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and compared the individual groups with each other (MD vs. VM, MD vs. comparison group, and MD vs. comparison group + VM). Furthermore, we assessed the diagnostic significance of caloric testing only. Receiver operating characteristic (ROC) curves were used to compare the diagnostic value of a normal vHIT and a reduced caloric excitation with pathological caloric testing alone. Comparisons of sensitivity/specificity between the two methods (normal vHIT + reduced caloric excitation vs. reduced caloric excitation only) were performed using the McNemar test for paired samples. A p-value of <0.05 was considered statistically significant.

3 Results

A total of 627 patients with MD and 473 patients with VM were included (Table 1). In MD, 59.6% of the patients met the diagnostic criteria for "definite MD" and 40.3% for "probable MD." The median age in the MD group was 58 years, and the gender distribution was almost equal, with 51.8% men and 48.2% women. In the VM group, only 30% of the patients were classified as "VM" and 70% as "probable VM." The median age was 46.8 years, and the majority were women (64.9%). The comparison group consisted of 1,001 patients with various other vestibular disorders; at least one episode of vertigo or persisting dizziness was required for inclusion. The details of the comparison group are given in Figure 1.

The McNemar test was used to determine the statistical significance of the result in the 2 × 2 contingency tables depending on the analysis of paired data.

3.1 Diagnostic value of normal vHIT and pathological caloric testing (dissociation) for identifying patients with MD among other vestibular disorders

In the MD group, 369 patients (58.9%) showed a discrepancy between the vHIT and caloric testing, with normal vHIT (gain >0.7), while caloric testing yielded asymmetric results (>25% and/or total caloric excitation <10°/s for one side). Thus, the sensitivity for identifying MD patients via a discrepant vHIT and caloric testing,

what we will call "dissociation" in the following, was 58.9% (Table 2). Compared to the comparison group, the proportion of false-positive findings was 16.5%, defining the specificity at 83.5%. The PPV was 69.1%, and the NPV was calculated at 76.4% ($p < 0.001$, McNemar test).

3.2 Diagnostic value of dissociation for identifying patients with MD vs. patients with VM

In the VM group, the specificity of the discrepancy was 83.5% (395 out of 473 patients). Due to the low false-positive rate, the PPV was 82.6% (Table 2) and the NPV was 60.5% (Figure 2).

3.3 Diagnostic value of dissociation for identifying MD patients vs. all other vestibular disorders (comparison group plus VM)

The following results were obtained by comparing the diagnostic value of a normal vHIT and pathological caloric testing to identify MD patients among other vestibular disorders (comparison group plus VM): The sensitivity and specificity remained the same at 58.9 and 83.5%, respectively. The NPV was 82.7%, and the PPV was 60.3%.

3.4 Diagnostic value of caloric testing alone for identifying MD patients

Among MD patients ($N = 627$), caloric testing was pathological in 71%. Overall, 20.9% of the patients in the VM group and 33.3% of the patients in the comparison group showed a reduced caloric response. The specificity of caloric testing alone was significantly lower when compared to the specificity of a normal vHIT and pathological caloric testing (Tables 2, 3). When comparing MD and VM, the sensitivity of caloric testing was 71% and the specificity was 79% (PPV: 81.8% and NPV: 67.3%). The specificity for identifying MD patients among other vertigo entities (comparison group) via caloric testing was lower at 70.7%.

3.5 Caloric testing vs. caloric testing and vHIT for identifying MD patients

It was also assessed whether a dissociation of vHIT and caloric testing (normal vHIT vs. pathological caloric testing) has a higher diagnostic value than caloric testing alone. Due to their low sensitivity (58.9% vs. 71%), both tests are quite unsuited for screening patients without typical clinical symptoms. We illustrated the receiver operating characteristics curve (ROC curve, Figure 3) to depict the diagnostic power of the two tests. The caloric testing showed the largest area under the curve when diagnosing MD vs. VM (0.75, 95% CI, 0.73–0.78). This is in line with the fact that the dissociation consists of two paired diagnostic tests, thus delivering a lower sensitivity. However, the combination of caloric testing and vHIT ensures a higher specificity when a dissociation is present (83.5% vs. 66.7%, $p < 0.001$). Accordingly, a dissociation of vHIT and caloric testing can serve as a rule-out test and has a higher diagnostic value than caloric testing alone.

4 Discussion

In the confirmatory part of this retrospective analysis in a large patient cohort ($N = 2,101$), the diagnostic value of the—well-known—discrepancy between a pathological caloric excitation and a normal vHIT test in patients with MD was analyzed. Considering the differentiation between MD and VM, the discrepancy was highly specific for MD (83.5%). Together with a low percentage of false-positive results and a high positive predictive value (82.6%), it can be used as an assisting rule-out test for MD—especially in patients lacking the typical MD symptoms in the early stages of the disease.

When the working diagnosis included distinguishing between MD and other vestibular disorders, the discrepancy remained highly specific for MD (83.5%). A higher PPV (69.1%) and a similar NPV (76.4%) made the dissociation the better MD exclusion test.

Recently, with the dissociation getting more attention from researchers, several theories have been introduced as to what the pathophysiological mechanism behind the dissociation might be. MD might affect regular and irregular afferents differently, leading to a loss of type II hair cells in the crista ampullaris starting peripherally (23, 29). The peripheral zones might be more sensitive to low-frequency regular afferent excitation, which is performed in a caloric test, leading to pathological results. The high-frequent irregular afferents, located centrally, are thought to be damaged by the disease in much later stages—they are tested by the vHIT test, which often leads to a normal result of the test. Some reasonable doubt regarding the theory can be expressed due to the observation of type I and II hair-cell loss as well as basal membrane damage in patients with MD (30). A second, more widely distributed theory is the one explaining the pathophysiology of MD with a physical hydropic enlargement of the membranous duct, also known as endolymphatic hydrops (22).

In conclusion, the discrepancy between a normal vHIT test and pathological caloric excitability is a useful parameter showing high specificity for patients suffering from MD. It offers better diagnostic power than vHIT and caloric testing taken separately and requires a little more effort to investigate, especially for patients who receive both tests as a first-line diagnostic tool. The dissociation proves to be a

TABLE 2 Sensitivity and specificity of normal vHIT and pathological caloric testing for identifying MD among other vertigo entities.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p*-value
MD vs. CP	58.9	83.5	69.1	76.4	<0.001[a]
MD vs. VM	58.9	83.5	82.6	60.5	<0.001[a]
MD vs. VM + CP	58.9	83.5	60.3	82.7	<0.001[a]

MD, Menière's disease; CP, comparison group; VM, vestibular migraine; [a]McNemar Test.

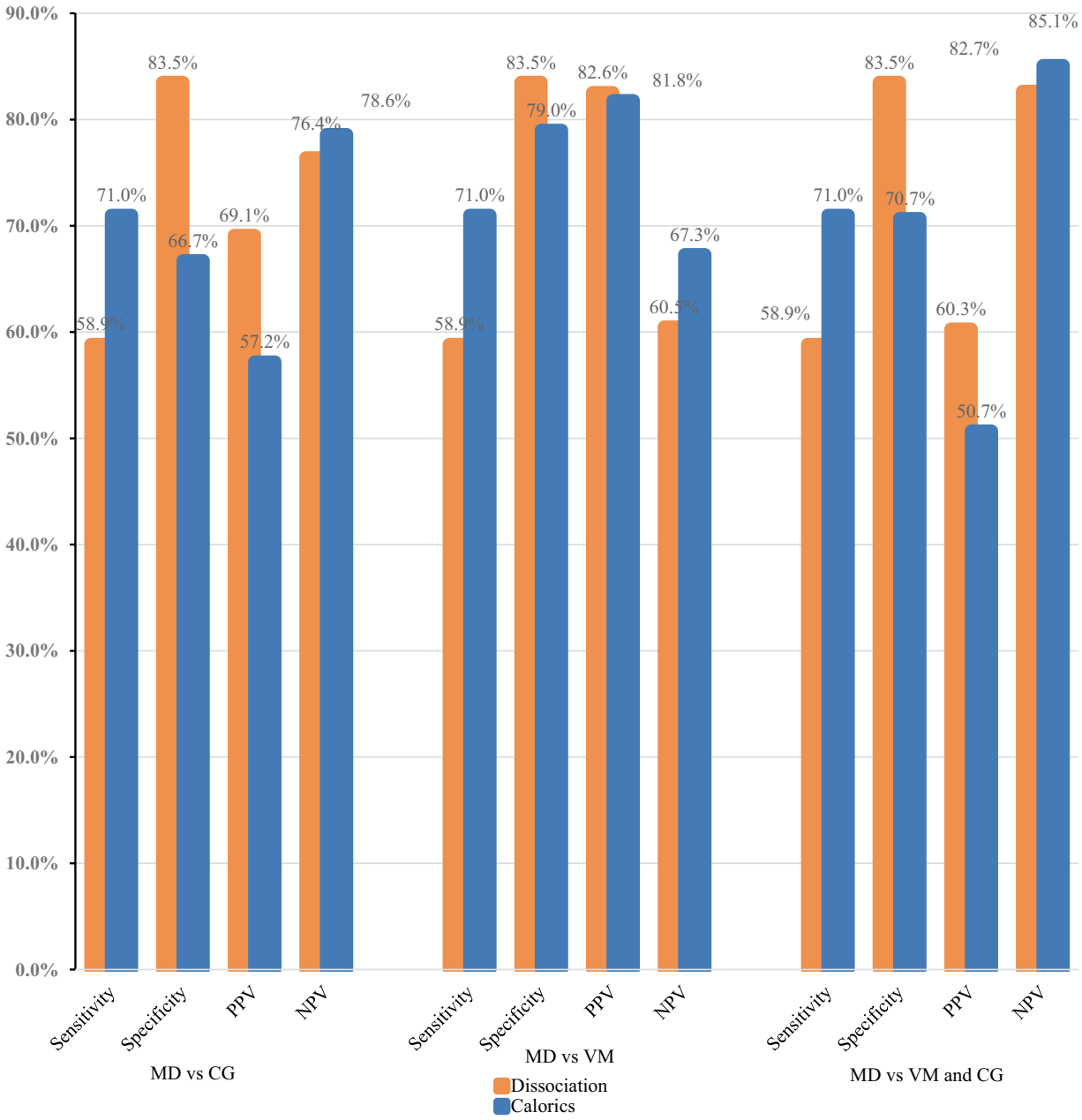

FIGURE 2
Comparison of the diagnostic power of a normal video head impulse test and a pathological caloric excitation (dissociation) to caloric testing alone. PPV, positive predictive value; NPV, negative predictive value; MD, Menière's disease; CG, comparison group; VM, vestibular migraine.

TABLE 3 Sensitivity and specificity of caloric testing only for identifying MD among other vertigo entities.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p*-value
MD vs. CG	71	66.7	57.2	78.6	<0.001[a]
MD vs. VM	71	79	81.8	67.3	<0.001[a]
MD vs. VM + CP	71	70.7	50.7	85.1	<0.001[a]

MD, Menière's disease; CG, comparison group; VM, vestibular migraine; [a]McNemar test.

relevant MD exclusion test in the differential diagnostics of MD against various vestibular disorders, not only vs. VM, on which the research has been focused so far. The quantification of this discrepancy and whether it reflects the current MD stage or moments of evaluation—non-ictal vs. ictal—may be of interest to future research. Setting optimal values for pathological caloric and video head impulse testing should also be considered, namely due to the larger variability from center to center (27).

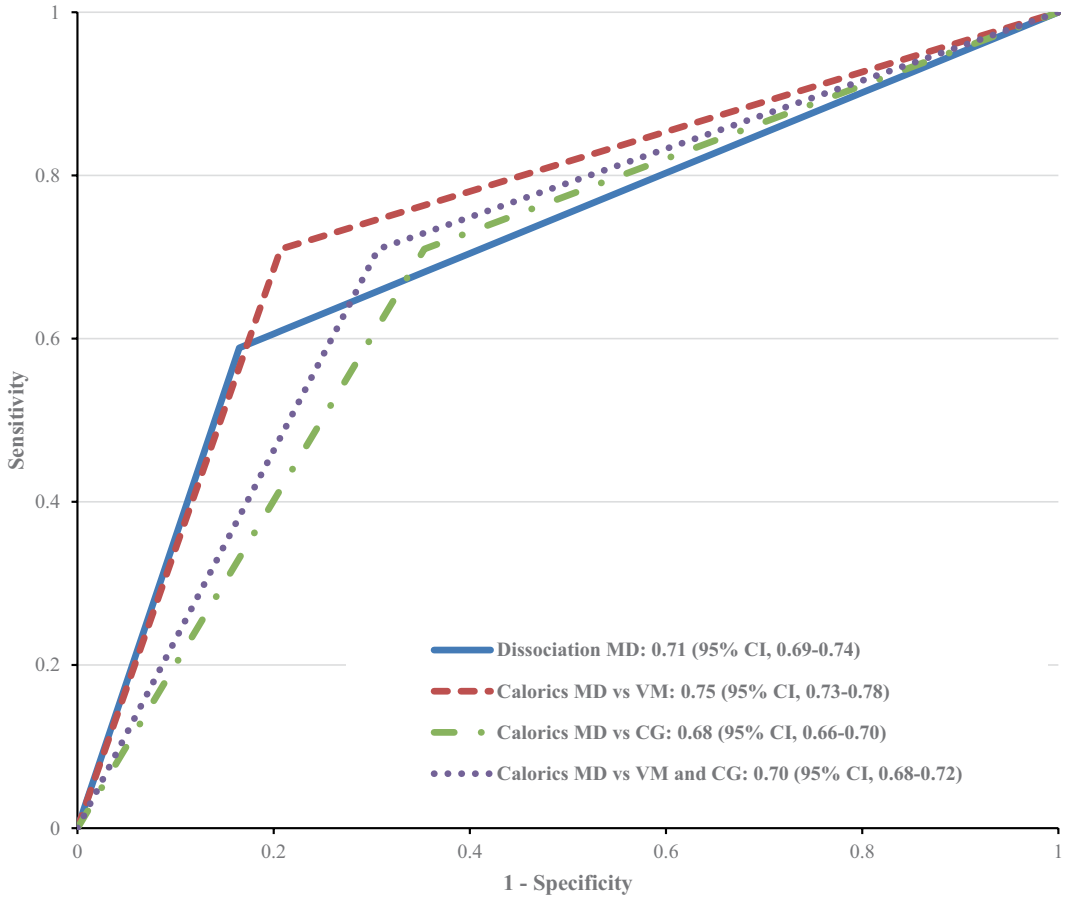

FIGURE 3
Receiver operating characteristic (ROC) curve for the diagnostic power of pathological caloric testing alone vs. pathological caloric testing combined with a normal video head impulse test (dissociation) in the diagnosis of: MD vs. VM, MD vs. other vestibular disorders (comparison group CG), and MD vs. VM and comparison group. The ROC curve and the area under the curve are the same when it comes to using the dissociation as a test to diagnose MD vs. VM; MD vs. other vestibular disorders, and MD vs. VM and others.

5 Limitations

As a retrospective study, our study has certain limitations. Despite our efforts to record a large number of subjects' data as objectively as possible, misclassification and selection biases can never be fully excluded and can lead to skewed results and untrue or incomplete conclusions. A further limitation that needs to be pointed out is the lack of a control group consisting of patients without dizziness to control the study, which could help further investigate the diagnostic power of the described dissociation. The primary goal of the study was to provide more insight and assistance to diagnosis-making in an everyday clinical setting where usually the patients with some form of dizziness are going to be the ones who receive a video-head-impulse test and caloric testing. We aimed to help clinicians more efficiently interpret the two tests in an environment where the tests have already been carried out, as opposed to using the dissociation as a form of screening test and determining its presence in healthy individuals. Considering this, we did not include subjects without vertigo or dizziness as a part of this study. To diminish the aforementioned limitations, a further prospective blinded study design with the inclusion of a control group of healthy individuals is required.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilian University of Munich (Approval number: 19-301). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

VM: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing

– original draft, Writing – review & editing. MS: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. A-SV: Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. RB: Data curation, Supervision, Writing – original draft, Writing – review & editing. LL: Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Hereby, we express our acknowledgments to the whole audiological team from the AZ Sint-Jan Brugge AV, Brugge, Belgium, as well as to Sophie Paredis from the Division of Vestibular Disorders, Maastricht University Medical Center, Maastricht, the Netherlands, for assisting with the retrospective data collection.

Conflict of interest

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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XII. Paper II

Patterns of Vestibular Impairment in Bilateral Vestibulopathy and Its Relation to Etiology

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RECEIVED 17 January 2022
ACCEPTED 17 February 2022
PUBLISHED 21 March 2024

CITATION
van Stiphout L, Pleshkov M, Lucieer F, Dobbels B, Mavrodiev V, Guinand N, Pérez Fornos A, Widdershoven J, Strupp M, Van Rompaey V and van de Berg R (2022) Patterns of Vestibular Impairment in Bilateral Vestibulopathy and Its Relation to Etiology. Front. Neurol. 13:856472. doi: 10.3389/fneur.2022.856472

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 March 2022
doi: 10.3389/fneur.2022.856472

Patterns of Vestibular Impairment in Bilateral Vestibulopathy and Its Relation to Etiology

Lisa van Stiphout[1†], Maksim Pleshkov[1,2*†], Florence Lucieer[1], Bieke Dobbels[3], Vergil Mavrodiev[4], Nils Guinand[5], Angelica Pérez Fornos[5], Josine Widdershoven[1,3], Michael Strupp[4], Vincent Van Rompaey[3] and Raymond van de Berg[1]*

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OPEN ACCESS

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Reviewed by:
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Specialty section:
This article was submitted to Neuro-Otology, a section of the journal Frontiers in Neurology

Received: *17 January 2022*
Accepted: *17 February 2022*
Published: *21 March 2022*

Citation:
van Stiphout L, Pleshkov M, Lucieer F, Dobbels B, Mavrodiev V, Guinand N, Pérez Fornos A, Widdershoven J, Strupp M, Van Rompaey V and van de Berg R (2022) Patterns of Vestibular Impairment in Bilateral Vestibulopathy and Its Relation to Etiology. Front. Neurol. 13:856472. doi: 10.3389/fneur.2022.856472

Objective: This study aimed to investigate (1) the patterns of vestibular impairment in bilateral vestibulopathy (BVP) and subsequently, the implications regarding patient eligibility for vestibular implantation, and (2) whether this pattern and severity of vestibular impairment is etiology dependent.

Methods: A total of one hundred and seventy-three subjects from three tertiary referral centers in Europe were diagnosed with BVP according to the Bárány Society diagnostic criteria. The subjects underwent vestibular testing such as the caloric test, torsion swing test, video Head Impulse Test (vHIT) in horizontal and vertical planes, and cervical and/or ocular vestibular evoked myogenic potentials (c- and oVEMPs). The etiologies were split into idiopathic, genetic, ototoxicity, infectious, Menière's Disease, (head)trauma, auto-immune, neurodegenerative, congenital, and mixed etiology.

Results: The caloric test and horizontal vHIT more often indicated horizontal semicircular canal impairment than the torsion swing test. The vHIT results showed significantly higher gains for both anterior canals compared with the horizontal and posterior canals ($p < 0.001$). The rates of bilaterally absent oVEMP responses were higher compared to the bilaterally absent cVEMP responses ($p = 0.010$). A total of fifty-four percent of the patients diagnosed with BVP without missing data met all three Bárány Society diagnostic test criteria, whereas 76% of the patients were eligible for implantation according to the vestibular implantation criteria. Regarding etiology, only horizontal vHIT results were significantly lower for trauma, neurodegenerative, and genetic disorders, whereas the horizontal vHIT results were significantly higher for Menière's Disease, infectious and idiopathic BVP. The exploration with hierarchical cluster analysis showed no significant association between etiology and patterns of vestibular impairment.

Conclusion: This study showed that caloric testing and vHIT seem to be more sensitive for measuring vestibular impairment, whereas the torsion swing test is more suited for measuring residual vestibular function. In addition, no striking patterns of vestibular impairment in relation to etiology were found. Nevertheless, it was demonstrated

that although the implantation criteria are stricter compared with the Bárány Society diagnostic criteria, still, 76% of patients with BVP were eligible for implantation based on the vestibular test criteria. It is advised to carefully examine every patient for their overall pattern of vestibular impairment in order to make well-informed and personalized therapeutic decisions.

Keywords: bilateral vestibulopathy, etiology, vestibular implantation, preclinical implantation criteria, Bárány Society diagnostic criteria, vestibular impairment, patterns

INTRODUCTION

Bilateral vestibulopathy (BVP) is a chronic disease which is characterized by bilaterally reduced or absent vestibular function due to deficits of the vestibular organs, the vestibular nerves, and/or the brain (1–3). Patients typically suffer from imbalance, worsening in the dark and/or on uneven ground, and movement-induced blurred vision (oscillopsia) (4). BVP also leads to additional symptoms such as an increased risk of falling, cognitive deficits, impairment of navigation and spatial memory, autonomic dysfunction, anxiety, and depression (4–11). Consequently, BVP leads to reduced quality of life and imposes a significant socioeconomic burden on society (12–14). BVP appears to be a heterogeneous disorder with various clinical characteristics and multiple identified etiologies, such as ototoxicity (e.g., gentamicin exposure), genetic disorders (e.g., DFNA9), Menière's Disease, infectious causes (e.g., meningitis), neurodegenerative and inherited syndromes (e.g., CANVAS), autoimmunity (e.g., Cogan's syndrome), or trauma (2, 15–23). Nonetheless, the reported percentages of idiopathic BVP vary between 20-75%, indicating that identifying the etiology can be challenging (2, 13, 15, 18, 24).

To date, the prognosis for the recovery of vestibular function is poor and the effective treatment for BVP is missing (18, 25–27). However, different research groups are in the process of developing a clinically applicable vestibular implant that might be able to address at least the major symptoms of BVP (28–35). Despite reaching important milestones in the development of the vestibular implant, many questions remain, and in order to develop a clinically useful device, it is crucial to gain a better understanding of the underlying disease BVP.

So far, it remains unclear which factors contribute to the severity of the vestibular impairment. The current diagnostic criteria for BVP are primarily based on the function of the horizontal semicircular canals (e.g., caloric test, video Head Impulse Test (vHIT), and torsion swing test) (3). However, recent studies have highlighted the varying pattern of impairment of the other vestibular sensors in patients with BVP (i.e., the otolith organs and the anterior and posterior semicircular canals) (24, 36–42). For example, anterior semicircular canal sparing was found in aminoglycoside-related BVP due to bilateral Menière's Disease and in idiopathic BVP (24, 39, 42). Ocular vestibular evoked myogenic potentials, most likely reflecting utricular function, showed to be the most impaired in aminoglycoside-related BVP and the least impaired in BVP due to bilateral Menière's Disease (38). An evidently rare subtype of idiopathic BVP was proposed in which the saccular function was impaired in the presence of normal functioning horizontal semicircular canals (37), while another study showed that horizontal semicircular canal function was more often affected than saccular function in aminoglycoside-related BVP (41).

All studies mentioned above either included small patient groups, retrospectively analyzed the data, did not always include patients with BVP according to the Bárány Society criteria, or investigated only one or two of the vestibular sensors. To date, no studies investigated the pattern of vestibular impairment of all vestibular sensors with relatively large patient groups, while recently published vestibular implantation criteria developed for research settings take all vestibular sensors into consideration. According to these criteria, for instance, all vestibular tests (i.e., caloric test, horizontal and vertical vHIT, and torsion swing test) need to show a significantly impaired function in order to qualify as a vestibular implant candidate (43).

This study provides a description of vestibular function, in a large cohort of patients with BVP diagnosed according to the Bárány Society criteria. The objective was to 1) investigate the patterns of vestibular impairment in BVP in general, and subsequently, the implications regarding patient eligibility for vestibular implantation, and 2) investigate whether the pattern and severity of vestibular impairment depend on the etiology.

METHODS

Subjects

Study subjects were recruited from three tertiary referral centers in The Netherlands, Belgium, and Germany: The Department of Otorhinolaryngology and Head and Neck surgery from Maastricht University Medical Center (MUMC+, center 1) and Antwerp University Hospital (UZA, center 2), and the Department of Neurology and the German Center for Vertigo and Balance Disorders, Ludwig Maximilians University Munich (LMU, center 3). Enrolled subjects were diagnosed with BVP in accordance with the BVP diagnostic criteria, which included unsteadiness and/or oscillopsia during walking or head movements, and a reduced bithermal caloric response (sum of the bithermal maximal peak slow phase velocity $<6°$/s bilaterally) and/or a bilaterally reduced horizontal vHIT gain of <0.6, and/or a vestibulo-ocular reflex (VOR) gain <0.1 during torsion swing test at 0.1 Hz (3). In center 1 and center 2, all patients diagnosed with BVP at the outpatient clinic of the Department of Otorhinolaryngology were asked to participate in the study. These studies consisted of a full day of clinical testing [e.g., caloric

test, horizontal and vertical vHIT, torsion swing test, ocular vestibular evoked myogenic potentials (oVEMP), and/or cervical vestibular evoked myogenic potentials (cVEMP)]. In center 3, all patients presented with BVP at the outpatient clinic of the Department of Neurology within the study period were included in the study. Subjects below the age of 18 and subjects who were not able to stop vestibulosuppressive medication were excluded from participation in this study.

Vestibular Testing

All centers performed vestibular testing to confirm a BVP diagnosis, although the number of tests performed differed between centers. In center 1, vestibular testing included electronystagmography with caloric and rotatory chair testing, as well as horizontal and vertical vHIT and c- and oVEMPs. In center 2, subjects underwent electronystagmography with caloric and rotatory chair testing, horizontal and vertical vHIT, and cVEMPs. In center 3, videonystagmography with caloric testing was performed, together with a horizontal vHIT. An overview of different tests performed in each center is shown in **Supplementary Table 1** of the supplementary materials (SM).

The Caloric Test

An extensive description of caloric testing was described previously (44). To summarize, in all centers, bithermal caloric testing was performed in both ears whilst patients were in supine position with a forward head inclination of 30°. Each irrigation lasted 30 s with a volume of at least 250 ml of water in centers 1 and 2 and at least 100 ml of water in center 3, for both cold (30°C) and warm (44°C) irrigations with a 5-min stimulus interval between irrigations (Variotherm Plus device, Atmos Medizin Technik GmbH, Lenzkirch, Germany for all three centers). Eye movements were recorded using electronystagmography with self-adhesive electrodes at centers 1 and 2 (Blue sensor, Ambu, Denmark) and with videonystagmography at center 3 (Interacoustics, Munich, Germany). The maximum peak slow phase eye velocity at the culmination phase (°/s) was measured (KingsLab 1.8.1, Maastricht University, Maastricht, The Netherlands at center 1; Nystagliner, Toennies, Germany at center 2; Interacoustics, Munich, Germany at center 3).

Torsion Swing Test

During the torsion swing test, patients were seated in a servo-controlled rotatory chair in complete darkness with their eyes open (Ekida GmbH, Buggingen, Germany at center 1 and ServoMed AB, Varberg, Sweden at center 2). Sinusoidal rotatory stimulation was performed at 0.1 Hz at center 1 and 0.05 Hz at center 2 with a peak velocity of 60°/s. Again, eye movements were recorded with electronystagmography with self-adhesive electrodes (Blue sensor, Ambu, Denmark in both center 1 and 2) and the VOR gain was calculated as the ratio between peak eye velocity and peak head velocity (KingsLab 1.8.1, Maastricht University, Maastricht, The Netherlands at center 1; Nystagliner, Toennies, Germany at center 2).

Video Head Impulse Test

The horizontal vHIT and the vHIT in the Right-Anterior-Left-Posterior (RALP) and Left-Anterior-Right-Posterior (LARP) canal planes were performed using the Video-Head Impulse Test device from Otometrics at center 1 and 2 (Otometrics, Taastrup, Denmark). At center 3, horizontal vHIT was performed using the Eye-SeeCam (Interacoustics, Munich, Germany). The testing method was described previously (45, 46). In brief, the technician stood behind the subject (who was sitting on a static chair) and held their head firmly without touching the goggles. The subject was instructed to maintain visual fixation on an earth-fixed target at a distance of 2 m at centers 1 and 2 and 1.8 m at center 3. Head impulses comprised fast unpredictable, low-amplitude (±20°) head movements in the horizontal plane (all three centers, peak head velocity >150°/s) and in the RALP and LARP planes (center 1 and 2, peak head velocity >100°/s). The Otometrics system defines the VOR gain as the ratio of the area under the eye velocity curve to the area under the head velocity curve from the impulse onset until the head velocity drops to zero again (47). The inter-acoustics system divides the eye and head velocity at a certain point in time (around 60 ms after impulse onset) (46).

Vestibular-Evoked Myogenic Potentials

Both centers 1 and 2 used the Neuro-Audio system with electromyographic software (v2010, Neurosoft, Ivanovo, Russia) and self-adhesive electrodes (Blue sensor, Ambu, Denmark) to record the o- and/or c-VEMPS. cVEMPs were measured over the sternocleidomastoid muscle after stimulating the ipsilateral vestibular organ with air-conducted tone bursts of 500 Hz, provided via inserted earphones at a stimulation rate of 13 Hz. oVEMPs were measured over the inferior oblique muscle after stimulating the contralateral vestibular organ with the same stimulation parameters as for cVEMPs. Details on the procedure have been published previously (44, 48, 49). In brief, for cVEMPS, subjects were in a supine position with their back tilted at an angle of 30° from the horizontal plane and were instructed to turn their head away from the stimulus and to lift their head up slightly. A total of 200 EMG traces with a minimum rectified voltage of 65 μv and a maximum rectified voltage of 205 μv were accepted. A visual feedback system (v2010, Neurosoft, Ivanovo, Russia) provided patient feedback to maintain correct muscle contraction. For oVEMPS, subjects were in a supine position and were instructed to keep their gaze fixed on a focus point 30 degrees behind the head to achieve superomedial gaze. A minimum of 300 EMG traces were accepted.

Vestibular-evoked myogenic potentials (VEMPs) were first recorded starting at maximum stimulus intensities of 130 dB sound pressure level (SPL) (center 1) or 95 dB hearing level (HL) (center 2). Then recordings were attempted again using stimulus amplitudes successively decreasing by 5 dB at each step. Thresholds were determined in consensus between two independent technicians at the level where a biphasic wave response was present. When no typical biphasic wave was found at 130 dB SPL at center 1 or 95 dB HL at center 2, a patient was considered to have an absent c- or oVEMP response.

Data Collection, Processing, and Analysis

The caloric test was performed in all three centers. The torsion swing test was performed in centers 1 and 2, but at different frequencies (0.1 and 0.05 Hz respectively). Since the frequency of sinusoidal rotatory stimulation at center 2 differed from the frequency stated in the BVP diagnostic criteria, the patients from center 2 were not included in this analysis based on their VOR gain measured during the torsion swing test alone. As described above, the horizontal vHIT was performed in all three centers, vertical vHIT and cVEMPs in centers 1 and 2, and oVEMPs only in center 1. Therefore, the amount of data available for analysis differed between tests.

IBM SPSS Statistics version 25 (Armonk, NY: IBM Corp.) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis. Descriptive statistics were used to describe the basic features of the data (e.g., percentages). Non-parametric methods were applied to determine the significant differences between the test results (e.g., Kruskal Wallis H test with *post hoc* Dunn's test and Mann-Whitney *U* test). *P*-values ≤ 0.05 were considered significant and were adjusted and reported with Benjamini-Hochberg correction for multiple testing. Fisher's exact test and the Chi-squared test were used to compare proportions of categorical outcomes.

Before the data was analyzed extensively, it was checked whether the data between the centers could be pooled. Caloric test results differed between the three centers ($\chi 2(2) = 40.8$, $p < 0.001$), therefore, the data could not be pooled. The torsion swing test results from center 1 and center 2 could not be pooled since the frequency of sinusoidal rotatory stimulation at center 1 (0.1 Hz) differed from center 2 (0.05 Hz) and the results were significantly different (Mann-Whitney U = 1,954.5, $p = 0.002$). No significant differences for vHIT results between centers for five out of six semicircular canals were found (Kruskal-Wallis H test, $p > 0.05$). The left horizontal canal showed a significant difference between centers ($\chi 2(2) = 7.2$, $p = 0.029$), however the Levene's test for homogeneity of variance did not show a significant difference ($F = 1.32$, $p = 0.192$). Therefore, the vHIT results of all centers were pooled per canal.

The VEMP results were categorized in absent vs. present responses (i.e., when no typical biphasic wave was found at 130 dB SPL at center 1 or 95 dB HL at center 2, a patient was considered to have an absent c- or oVEMP response). cVEMPs were analyzed for each center separately since 1) the decibel measurement level differed between center 1 (dB SPL) and center 2 (dB HL) and 2) the Chi-squared test showed that there was a significant association between centers and absent vs. present cVEMP responses ($\chi(2) = 8.57$, $p = 0.014$).

To investigate the patterns of vestibular impairment in BVP in general, the vestibular test results were first analyzed using descriptive statistics to describe the basic features of the data. Subsequently, the results were interpreted according to the Bárány diagnostic criteria for BVP, which included a reduced bithermal caloric response (sum of bithermal maximal peak slow phase velocity $<6°$/s bilaterally) and/or a VOR gain <0.1 during the torsion swing test at 0.1 Hz and/or a bilaterally reduced horizontal vHIT gain of <0.6 (3). To investigate patient eligibility for vestibular implantation regarding the results from vestibular reflex testing, vestibular test results were interpreted according to the vestibular implantation criteria, which included a bilaterally reduced or absent angular VOR function documented by at least one of the major criteria and all minor criteria (i.e., in case only one or two major criteria were met, the remaining tests should comply the minor criteria). The major criteria included a reduced bithermal caloric response (sum of bithermal maximal peak slow phase velocity $\leq 6°$/s bilaterally), a reduced horizontal VOR gain ≤ 0.1 during the torsion swing test at 0.1 Hz, and a pathological horizontal VOR gain ≤ 0.6 bilaterally with at least one vertical VOR gain <0.7 bilaterally, measured with vHIT. The minor criteria included a reduced bithermal caloric response (sum of bithermal maximal peak slow phase velocity $<10°$/s bilaterally), a reduced horizontal VOR gain <0.2 during torsion swing test at 0.1 Hz, and pathological VOR gains of at least two semicircular canals <0.7 bilaterally, measured by vHIT (43).

Hierarchical cluster analysis was applied to explore and visualize patterns of vestibular impairment with respect to etiology. Cluster analysis requires complete cases (i.e., no missing data), therefore, only patients with complete data for caloric testing, torsion swing test, horizontal and vertical vHIT, cVEMPs, and oVEMPS were included (i.e., 45 patients from center 1). Before clustering, the data were standardized in Z-scores (i.e., the individual scores minus the mean, divided by the standard deviation), in order to have the variables weigh equally in the cluster analysis. Ward's method with the distance measure squared Euclidian distance was used since Ward's method has the highest agglomerative coefficient compared with the other hierarchical clustering methods. The silhouette method was used to determine the optimum number of clusters (50). Hierarchical cluster analysis resulted in two dendrograms with etiology on the x-axis and vestibular tests results on the y-axis. A heatmap was created. Each column represented one subject and each row represented the output of a specific vestibular test. A "relatively bad (vestibular) score" was illustrated by lower Z scores in the color red. A "relatively good (vestibular) score" was illustrated by higher Z scores in the color blue. After performing the analysis, etiology and patient characteristics, and vestibular test results were compared between clusters.

Ethical Considerations

The study was approved by the local ethical committee of center 1 (protocol number NL52768.068.15 / METC 151027), the local ethical committee of center 2 (protocol number 16/42/426), and the local ethical committee of center 3 (project number 20-174). The study was registered on trialregister.nl [center 1, Trial NL5446 (NTR5573)]and ClinicalTrials.gov [center 2, (NCT03690817)]. All study participants gave their written informed consent prior to inclusion in the study.

RESULTS

Patient Characteristics

A total of 173 patients (50 from center 1, 58 from center 2, and 65 from center 3, 53% males) were included in this study with a mean age of 60 ± 15 years (range 19–91 years). A diagnosis of the underlying etiology of BVP could be identified

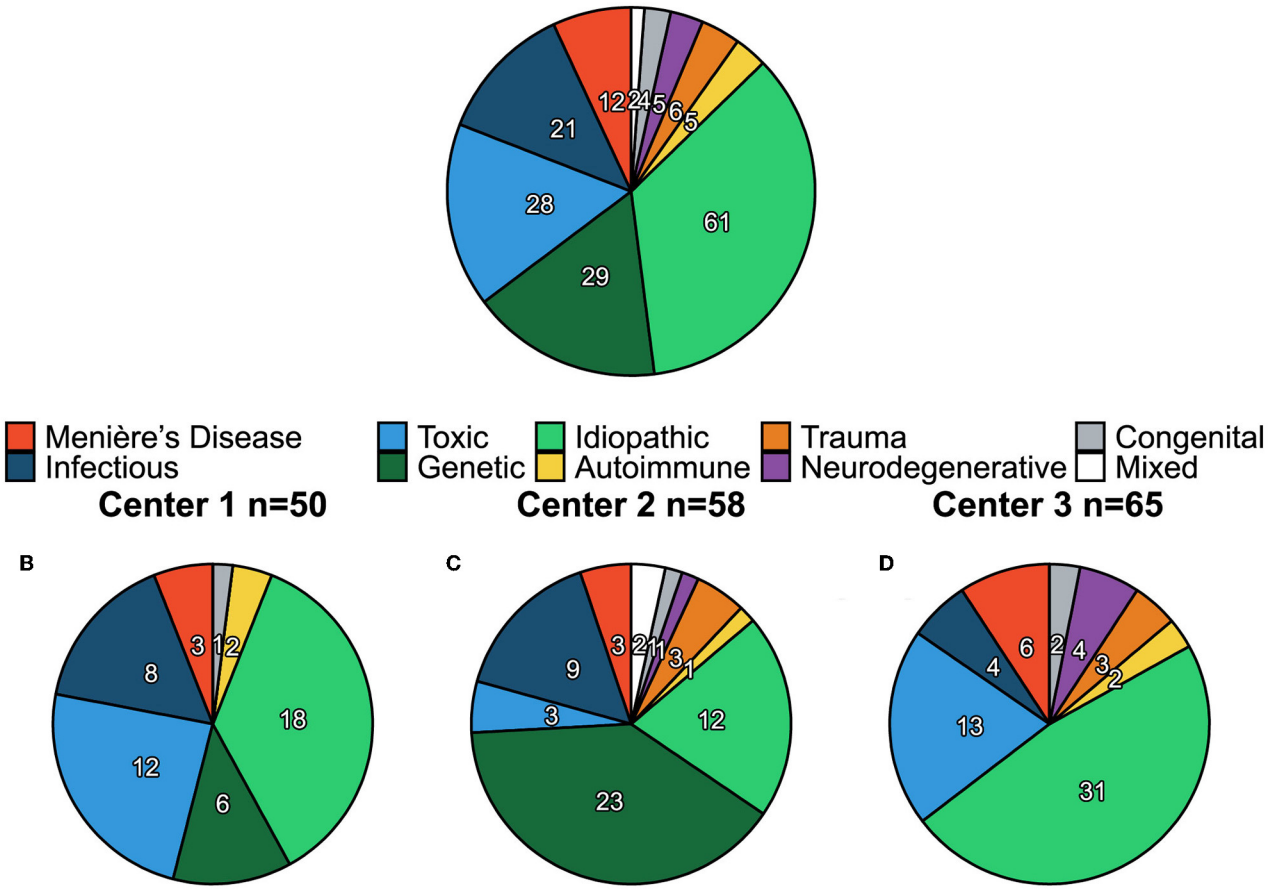

FIGURE 1 | Distribution of etiology of bilateral vestibulopathy (BVP) for all three centers combined **(A)** and per center separately **(B–D)**. Numbers shown in each pie chart represent the count (*n*) of each etiology.

in 112 out of the 173 patients. Genetic disorders ($n = 29$, 17%), ototoxicity ($n = 28$, 16%) and infectious disorders ($n = 21$, 12%) were the most common etiologies. Less frequently, the cause of BVP was due to Menière's Disease ($n = 12$, 7%), (head)trauma ($n = 6$, 4%), auto-immune disease ($n = 5$, 3%), neurodegenerative disorders ($n = 5$, 3%), or congenital disorders ($n = 4$, 2%). Two patients presented with a mixed etiology (vestibular schwannoma on one side and idiopathic etiology on the other side). In approximately one-third of the cases ($n = 61$, 35%), no underlying etiology could be identified. The distribution of etiology (**Figure 1**) was significantly different between centers (Fisher's Exact Test $p < 0.01$). A detailed overview of all etiologies is shown in **Supplementary Table 2**.

Vestibular Function

Vestibular Test Results

Median caloric test results were significantly higher for center 3 (6.2°/s) compared with centers 1 and 2 (both 0°/s) ($\chi 2(2) = 39.6$, $p < 0.001$, **Figure 2**). No significant differences were found between the median caloric test results for centers 1 and 2. The torsion swing test results from center 1 (0.1Hz) were significantly higher compared with center 2 (0.05 Hz) (Mann-Whitney $U = 1{,}954.5$, $p = 0.002$, **Figure 2**).

The vHIT results showed a median VOR gain below 0.5 for all semicircular canals, with the lowest VOR gain measured at the horizontal canals and the highest VOR gain measured at the anterior canals ($\chi 2(5) = 35.5$, $p < 0.001$, **Figure 3**). After analyzing the data separately per center, this trend was detectable in both centers 1 and 2 but only significant in center 2 after correction for multiple comparisons ($\chi 2(5) = 35.7$, $p < 0.001$, **Supplementary Figures 1, 2** and **Supplementary Table 3**).

The percentage of bilaterally absent cVEMP responses was higher in center 2 compared with center 1 (66 and 44% respectively, $\chi(2) = 8.57$, $p = 0.014$). When looking at the cVEMP and oVEMP responses at center 1, the rates of bilaterally absent oVEMP responses were higher compared to bilaterally absent cVEMP responses (74 vs. 44% respectively, $\chi(2) = 9.30$, $p = 0.010$) (**Figure 4**).

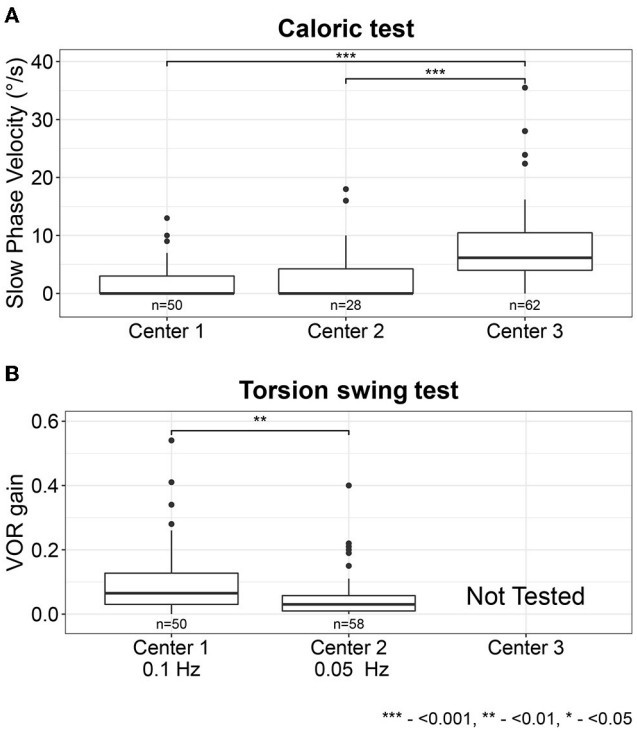

FIGURE 2 | Vestibular test results for the caloric test (sum of the bithermal maximal peak slow phase velocity bilaterally) **(A)** and torsion swing test (VOR gain) **(B)** per center. Each box plot represents the 25 to 75 percentiles, bold black lines the median, dots the outliers, and asterisks (*) illustrate statistically significant differences. Statistical significance levels: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

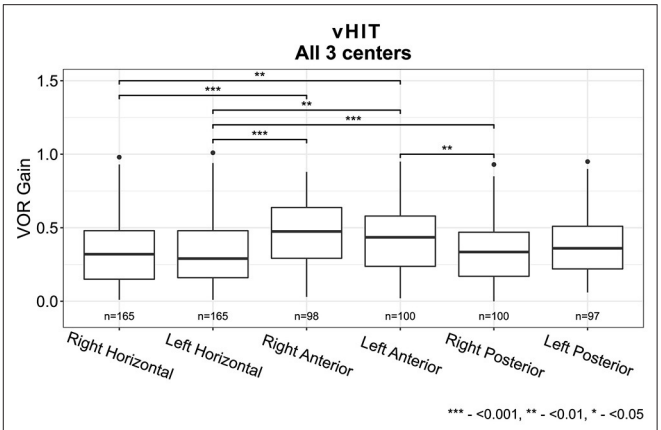

FIGURE 3 | Vestibulo-ocular reflex (VOR) gain for all six semi-circular canals measured with video Head Impulse Test for all three centers combined (Horizontal canals: center 1, 2 and 3, Vertical canals: center 1 and 2). Each box plot represents the 25 to 75 percentiles, bold black lines the median, dots the outliers, and asterisks (*) illustrate statistically significant differences.

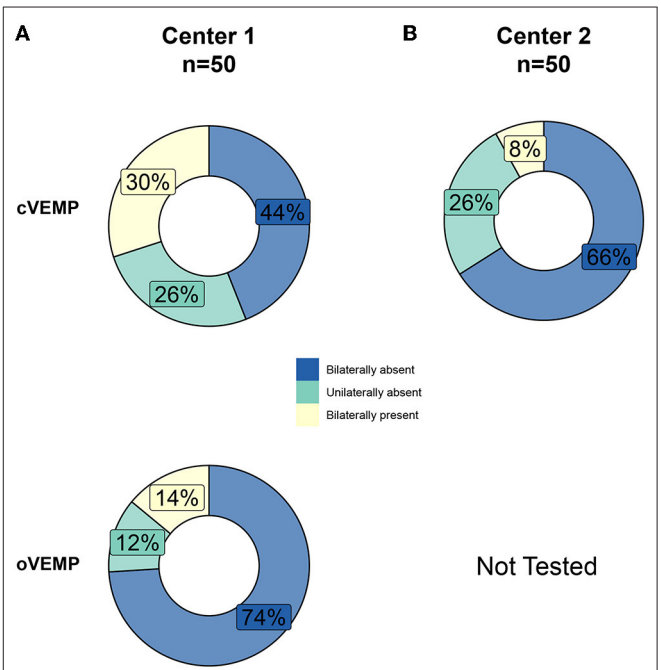

FIGURE 4 | Percentages of bilaterally absent, unilaterally absent, and bilaterally present cervical and ocular vestibular evoked myogenic potentials (cVEMPs, oVEMPs) of patients with BVP at center 1 **(A)** and center 2 **(B)**.

Vestibular Impairment According to the Bárány Diagnostic Criteria for BVP

Regarding the cases without missing data for caloric testing, torsion swing test, and horizontal vHIT, the majority of the patients (54%) met three of the criteria of the Bárány Society described earlier, whereas 21% met two of the Bárány criteria, and 25% only met one criterion. In the group of patients who met two out of three Bárány criteria, an impaired VOR gain measured with vHIT combined with a reduced caloric response was most prevalent (19%). In the group of patients who only met one of the Bárány criteria, a reduced caloric response was most prevalent (17%), followed by an impaired VOR gain measured with vHIT (6%) and torsion swing test (2%) (**Figure 5**).

When considering the total study population, the caloric test and horizontal vHIT more often indicated horizontal semicircular canal impairment than the torsion swing test (**Figure 6**). For example, in center 1 only one patient was diagnosed with BVP according to the Bárány criteria based on the torsion swing test alone, whereas the rest of the population was diagnosed with the caloric test or horizontal vHIT or both.

Patient Eligibility for Vestibular Implantation According to the Implantation Criteria

Regarding the cases without missing data for caloric testing, torsion swing test, and horizontal and vertical vHIT ($n = 45$), the majority of the patients ($n = 34$, 76%) met the implantation criteria. A total of 71% of this group met three of the major criteria, whereas 24% met two major criteria, and 6% only met one major criterion. In the group of patients who met two out of three major implantation criteria, an impaired VOR gain measured with vHIT combined with a reduced caloric response was most prevalent. In the group of patients who only met one of the major implantation criteria, a reduced

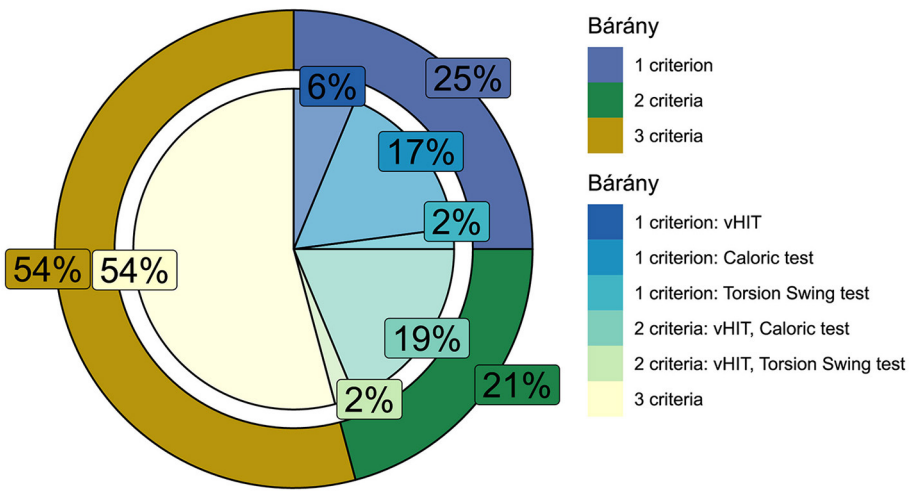

FIGURE 5 | Percentages of patients with BVP meeting one, two or three of the diagnostic criteria of the Bárány Society (shown in the outer circle, i.e., a reduced bithermal caloric response with a sum of the bithermal maximal peak slow phase velocity <6°/s bilaterally and/or a VOR gain <0.1 during torsion swing test at 0.01 Hz and/or a bilaterally reduced horizontal video Head Impulse Test gain of <0.6). The inner-circle shows the percentages of which tests are met by patients meeting one or two of the diagnostic criteria. Only cases without missing data for caloric testing, torsion swing test, and horizontal video Head Impulse Test were included (center 1, $n = 48$).

caloric response and an impaired VOR gain measured with vHIT were equally common. None of the patients only met the major implantation criteria for the torsion swing test (**Figure 7**).

Vestibular Function and Possible Relations to Underlying BVP Etiology

The median vestibular test results for caloric testing and torsion swing test did not differ between different etiologies (Kruskal-Wallis H test with *post hoc* Dunn test and Benjamini Hochberg correction $p > 0.05$, **Supplementary Tables 4, 5**). The vHIT results did not differ between etiologies for the anterior and posterior canals in the total group (Kruskal Wallis H test, $p > 0.05$, **Supplementary Table 4**). However, the horizontal vHIT results were significantly lower in the total group for neurodegenerative disorders compared with the idiopathic group, infectious disorders, Menière's Disease, and the mixed etiology group. The horizontal vHIT results were also significantly lower for genetic disorders compared with the idiopathic group and Menière's Disease. Lastly, horizontal vHIT results were significantly lower for (head)trauma compared with the idiopathic group, Menière's Disease and mixed etiology (Kruskal-Wallis H test with *post hoc* Dunn test and Benjamini Hochberg correction $p < 0.05$, **Figure 8** and **Supplementary Tables 4, 5**). After analyzing the data separately per center, some trends were detectable per center (e.g., lower horizontal vHIT results for genetic disorders in center 1 and lower horizontal vHIT results for (head)trauma in center 2), however, no significant differences were found except for lower horizontal vHIT results for neurodegenerative disorders compared with the idiopathic group and Menière's Disease in center 3 (Kruskal-Wallis H test with *post hoc* Dunn test and Benjamini Hochberg correction, **Supplementary Table 5**, **Supplementary Figure 3**).

Regarding VEMPs, the highest fraction (≥50%) of bilaterally absent cVEMP responses in center 1 was found in patients with ototoxic, infectious, autoimmune, and congenital etiologies, whereas in center 2 almost all etiologies showed high fractions (>60%) of bilaterally absent cVEMP responses (except neurodegenerative disorders). Next to this, all etiologies showed high fractions (≥50%) of bilaterally absent oVEMP responses (center 1) (**Supplementary Figures 4, 5**). No significant differences were found between the different etiologies and the proportion of patients with pathologic VEMP responses (Fisher's exact test $p = 0.52$ and $p = 0.99$ for cVEMPs centers 1 and 2 respectively and Fisher's exact test, $p = 0.36$ for oVEMPs center 1).

To investigate the pattern of vestibular impairment and its relation with etiology, hierarchical cluster analysis was performed, which resulted according to the silhouette method in two clusters (**Figure 9**). The first cluster "severe BVP" ($n = 30$; 47% female; mean age 58 years) showed overall lower median vestibular test results compared with the second cluster "moderate BVP" ($n = 15$; 60% female; mean age 60 years), which is illustrated by lower Z scores in the color red for relatively low vestibular scores and in the color blue for

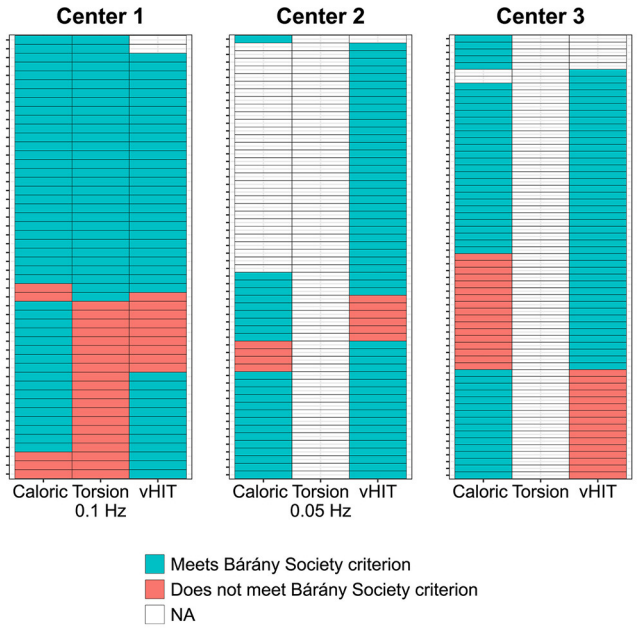

FIGURE 6 | Distribution of patients with BVP meeting the diagnostic criteria of the Bárány Society, presented for each test separately in the color blue (i.e., for the caloric test a reduced response with a sum of bithermal maximal peak slow phase velocity <6°/s bilaterally; for the torsion swing test (0.1 Hz) an impaired VOR gain <0.1; for horizontal video Head Impulse Test (vHIT) a bilaterally reduced VOR gain <0.6). Patients not meeting the diagnostic criteria for each test separately are indicated with the color red. Each column represents one of the diagnostic criteria per center; each row represents one subject per center. NA, no data available.

relatively high vestibular scores compared with the study group in **Figure 9**. This was significant for the caloric test, torsion swing test, horizontal vHIT, vertical vHIT (Mann-Whitney U, $p < 0.001$), and cVEMP (Fisher's Exact Test $p = 0.04$). A detailed overview of all median test results and statistics can be found in **Supplementary Tables 6, 7**. Next to this, the distribution of the amount of Bárány criteria met, was significantly different among clusters: cluster 1 "severe BVP" consisted of patients who predominantly met three criteria, whereas cluster 2 "moderate BVP" mainly included patients who only met one criterion (**Supplementary Figure 6**).

Some etiologies were more prevalent in one of the two clusters. For example, genetic disorders were more prevalent in the first cluster "severe BVP", whereas Menière's Disease was more prevalent in the second cluster "moderate BVP" (**Supplementary Figure 7**). However, no significant association between etiology and clusters was found (Fisher's Exact Test $p = 0.854$, **Supplementary Table 8**).

Next to this, some similarities in vestibular reflex tests were found in the cluster analysis (**Figure 9**, left dendrogram). It was observed that the horizontal and anterior vHITs were arranged close to each other and to caloric testing; the posterior vHIT was located close to the torsion swing test; and oVEMPs and cVEMPs formed a pair.

DISCUSSION

This study provided a description of patterns of vestibular impairment and its relation to BVP etiology in a cohort of 173 patients with BVP from 3 centers, diagnosed according to the Bárány Society criteria. Vestibular function was measured using the caloric test, torsion swing test, horizontal and vertical vHIT, cVEMPs, and/or oVEMPs. Etiologies were split into 10 separate groups (i.e., idiopathic, genetic disorders, ototoxicity, infectious disorders, Menière's Disease, (head)trauma, auto-immune disease, neurodegenerative disorders, congenital disorders, and mixed etiology). The patterns of the vestibular impairment and their relation to BVP etiology are discussed below.

Patterns of Vestibular Impairment

Overall, this study demonstrated that more than half of patients diagnosed with BVP according to the Bárány Society diagnostic criteria met all three criteria regarding vestibular testing. In patients who only met one or two of the criteria, the caloric test and horizontal vHIT criteria were most often met, in contrast to the torsion swing test criterion. The same trend was found when adhering to the vestibular implantation criteria. However, since the implantation criteria also include the vertical semicircular canals, the percentage of patients meeting the horizontal and vertical vHIT implantation criterion was lower compared with the percentage of patients meeting the horizontal vHIT diagnostic (Bárány Society) criterion. Despite the fact that the Bárány Society diagnostic criteria and vestibular implantation criteria seem to be, to some extent, similar to each other, they set different goals and have therefore several substantial differences. As stated above, the vestibular implantation criteria include all three semicircular canals. As a consequence, the vertical canal function should be considered next to the horizontal canal function. Additionally, although the major and especially the minor implantation criteria are less strict in terms of cut-off values for the caloric test, torsion swing test, and horizontal vHIT compared with the Bárány Society diagnostic criteria, a potential implant candidate must meet all the implantation criteria (**Figure 5** vs. **Figure 7**). Therefore, 76% of the patients diagnosed with BVP according to the Bárány Society diagnostic criteria were eligible for implantation according to the vestibular implantation criteria. Furthermore, apart from vestibular reflex testing, the vestibular implantation criteria also include assessment of comorbidities and eligibility to undergo surgery (43). Therefore, only a subgroup of the BVP population will be eligible for implantation.

When investigating vestibular test results per test and per center separately, it was observed that the slow phase eye velocities measured during the caloric test were significantly higher in center 3 compared with centers 1 and 2 (**Figure 2**). This can be explained by different factors, varying from differences in caloric testing methods used (namely electronystagmography at center 1 and 2 and videonystagmography at center 3) which can result in different phase velocities values due to different blink detection and image processing algorithms used (51), to different patient populations included in each center (2). Next to this, torsion swing test results were significantly higher in center

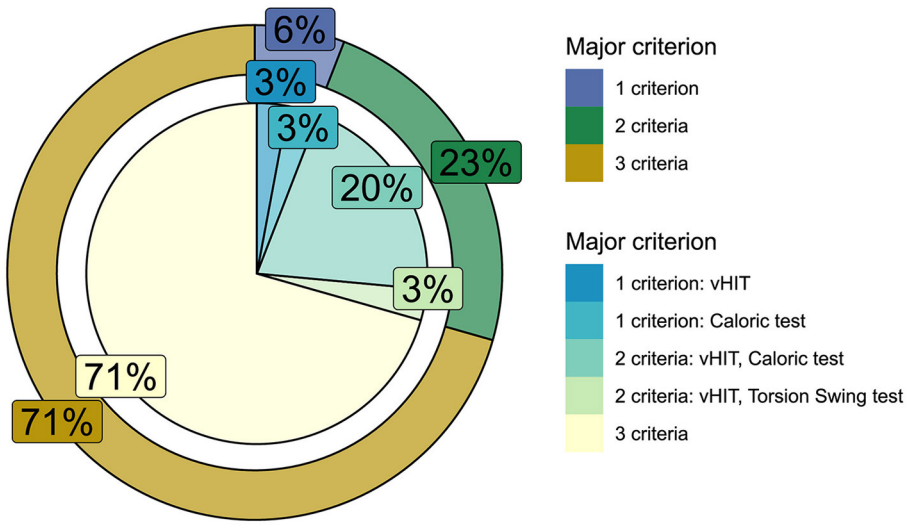

FIGURE 7 | Seventy-six percent of the patients met the criteria for vestibular implantation ($n = 34$). For this group, the outer circle shows the percentages of patients meeting one, two, or three of the major implantation criteria (i.e., for caloric testing bilateral impaired caloric responses with a sum of bithermal maximal peak slow phase velocity $\leq 6°/s$, for torsion swing test a reduced VOR gain ≤ 0.1 and for vHIT a bilaterally reduced horizontal VOR gain ≤ 0.6 combined with at least bilaterally one vertical VOR gain < 0.7). The inner-circle shows the percentages of which tests are met by patients meeting one or two of the major implantation criteria.

1 compared with center 2, which can be explained by the differences in the used frequency (0.1 Hz at center 1 and 0.05 Hz at center 2): the vestibular system is more sensitive for rotations at 0.1 Hz than 0.05 Hz, leading to a higher response (i.e., VOR gain) (2, 52, 53). This sensitivity might also account for the fact that the diagnostic torsion swing test criterion was less often met than the criteria of the caloric test. After all, since the vestibular system has its optimum sensitivity around the frequencies tested by the torsion swing test at 0.1 Hz (in contrast to the frequencies tested by the caloric test), a uniform decrease in semicircular canal function across all frequencies might result in losing responses to caloric testing first. Although frequencies tested with vHIT are also within the optimum frequency range of the vestibular system, vHIT more often indicated horizontal semicircular canal impairment than the torsion swing test. Therefore, it might be hypothesized that the vestibular system shows an impairment for conditions earlier that demand a relatively large vestibular output in response to high accelerations and velocities. This hypothesis needs further investigation. Nevertheless, the results of this study showed that the response to torsion swing testing might be preserved the longest (53). Therefore, the torsion swing test is least sensitive in detecting BVP, but most sensitive in measuring residual vestibular function, whereas caloric testing and vHIT seem to be more sensitive for measuring vestibular impairment (2).

The variability of VEMP responses in this study is in line with results from previous studies, which also demonstrated the wide range of otolith function (as measured with c- and oVEMPs) in patients with BVP (36, 38, 54). This variability could be explained by the large range of VEMP responses present in normal subjects, the heterogeneous nature of BVP, and the nature of VEMP testing itself (e.g., it is still unknown how much residual otolith function needs to be present to produce a synchronous motor discharge) (54). Furthermore, because of the diagnostic inclusion criteria, all of the included patients have horizontal semicircular canal impairment, whereas the function of the other vestibular end organs can have variable degrees of (dys)function. Since the utricle (tested with oVEMPs) projects into the superior branch of the vestibular nerve together with the horizontal semicircular canal, it can be hypothesized that patients included based on horizontal canal impairment also show bilaterally absent oVEMP responses (55). This might explain why rates of bilaterally absent oVEMP responses were higher compared to bilaterally absent cVEMP responses in center 1 (**Figure 4**) since there is possibly an intact inferior vestibular nerve function on which the saccule projects. Currently, it is not known whether isolated bilateral dysfunction of both otolith organs also causes significant disability (54). Therefore, all vestibular end organs should be evaluated before and after vestibular implantation in order to create awareness about potential damage to intact vestibular structures.

Contribution of Etiology to Vestibular Impairment

The distribution of etiologies (**Figure 1**) was significantly different among the three centers, indicating the inhomogeneity

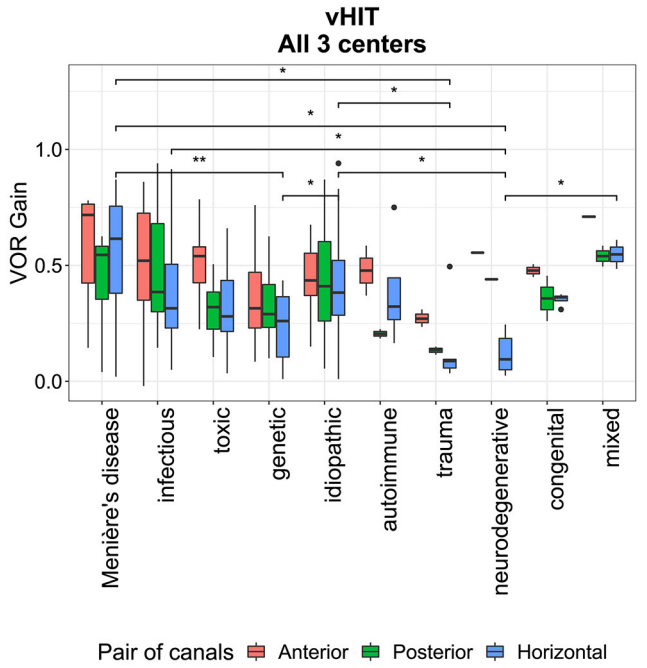

FIGURE 8 | Vestibular Ocular Reflex (VOR) gain per etiology for all three pairs of semi-circular canals (i.e., horizontal, anterior, and posterior canals) measured with video Head Impulse Test, presented for all three centers combined. Each box plot represents the 25–75 percentiles, bold black lines the median, dots the outliers and asterisks (*) illustrate statistically significant differences.

of the data. This can potentially be caused by differences in clinical settings, namely ENT clinics (center 1 and center 2) compared with a neurological clinic (center 3). This fact can explain the trend that among all 3 centers the biggest fraction of neurodegenerative and idiopathic patients was observed in center 3, whereas the biggest fraction of infectious and genetic disorders were observed in centers 1 and 2.

The distribution of the vHIT VOR gains between different etiologies indicated several trends, although not every trend proved to be statistically significant (**Figure 9**). Overall, the vHIT results showed significantly better gains for both anterior canals compared with the horizontal and posterior canals, which corresponds with previous literature (24). The vHIT results did not differ significantly between etiologies for anterior and posterior canals although trends of anterior canal sparing were observed for Menière's Disease, infectious disorders, ototoxicity, trauma, and idiopathic BVP. This is congruent with previous literature (24). Next to this, horizontal vHIT results were significantly lower for neurodegenerative disorders, genetic disorders, and trauma, whereas horizontal vHIT results were significantly higher for Menière's disease and infectious disorders.

Cluster analysis identified two separate clusters of patients with BVP in center 1 (which was the center with the most available vestibular test data) with significant differences in residual vestibular function according to vestibular testing. This was also reflected by the amount of diagnostic and vestibular implantation criteria met between clusters. Cluster 1 "severe BVP" consisted of patients who predominantly met 3 criteria, whereas cluster 2 "moderate BVP" mainly included patients who met only 1 criterion (**Supplementary Figure 6**). Although, no statistically significant differences were found in the etiology distribution between clusters (**Figure 9**), a slightly higher prevalence of Menière's Disease was observed in cluster 2 "moderate BVP" that performed "better" in all vestibular tests, whereas the idiopathic and ototoxicity etiologies prevailed in cluster 1 "severe BVP" and performed "worse" (**Supplementary Figure 4**). This could imply that the contribution of etiology to specific patterns of vestibular impairment might be limited and would eventually result in an overall better or worse vestibular function. Despite some patterns being found for a few BVP etiologies, one should consider every case individually and investigate every part of the vestibular system separately to obtain a full understanding of the vestibular impairment.

Order of Vestibular Test Outcomes According to Cluster Analysis

The cluster analysis showed similarities in the vestibular reflex tests used in center 1 (**Figure 9**, left dendrogram). For example, horizontal and anterior vHITs were arranged close to each other and to caloric testing; posterior vHIT was located close to torsion swing test; and oVEMPs and cVEMPs formed a pair. It is quite intuitive for VEMP results to be correlated to each other since the two otolith organs are located next to each other. However, the opposite was found when testing the semicircular canal function. The caloric test, torsion swing test, and horizontal vHIT are aimed to measure horizontal canal function and it could be hypothesized that they would closely correlate to each other. However, this was not observed in the cluster analysis, which showed the close correlation of the anterior and horizontal vHIT results together with the caloric test, and the close correlation of posterior vHIT results with the torsion swing test. The proximity of the horizontal and anterior vHIT in the cluster analysis can be partly explained in terms of anatomy. The horizontal and anterior canals ampullae are located close to each other and project into the same superior vestibular nerve division, whereas the inferior vestibular nerve division receives input from the posterior canals (56). Next to this, as stated before, vHIT and the caloric test seem to be able to indicate vestibular impairment, whereas the torsion swing test is more sensitive to measure the residual vestibular function (53). This could explain why the torsion swing test is not in close proximity to the horizontal vHIT and caloric test in the cluster analysis. The trends found in this cluster analysis differed from the trends described by a previous study (40). For example, differences in the arrangement of the variables after clustering [e.g., horizontal and posterior canals in close proximity to the utriculus according to the previous study (40)]. Furthermore, in contrast to the study presented here, no differences in vestibular impairment were found. This could be the result of different approaches used, namely: (1) Normalization of data using single test results across patient groups (this study) compared with

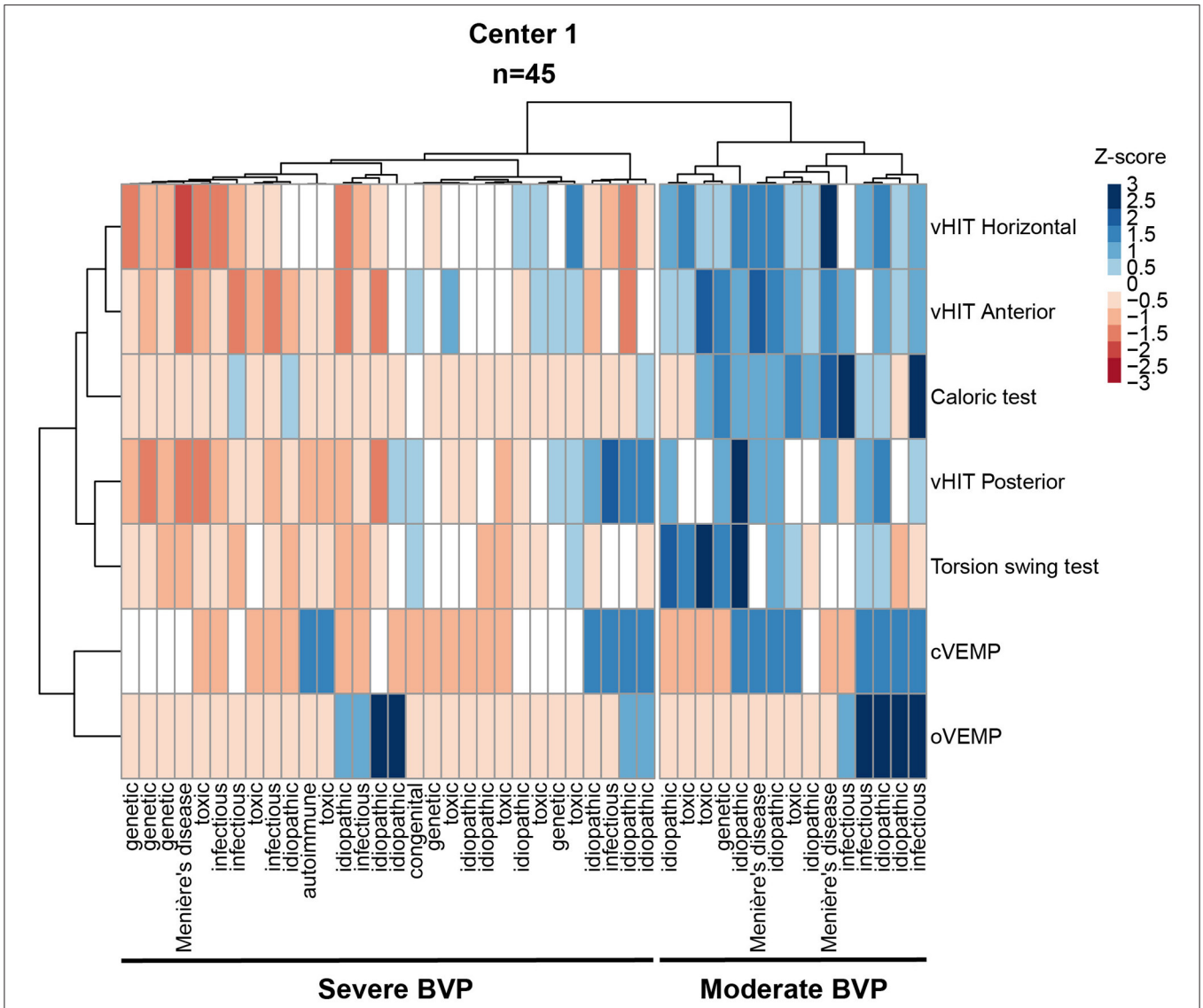

FIGURE 9 | Heatmap as a result of hierarchical cluster analysis with two dendrograms; Each column represents one subject; each row represents the results of a specific vestibular test. A "bad (vestibular) score" (i.e., low scores on tests of vestibular reflexes) is illustrated by lower Z scores in the color red. A "relatively good (vestibular) score" (i.e., relative high scores on tests of vestibular reflexes) is illustrated by higher Z scores in the color blue. Bold underlining indicates the 2 clusters; "Cluster 1, severe BVP" and "Cluster 2, moderate BVP". Only cases without missing data for caloric testing, torsion swing test, and horizontal and vertical vHIT, and o- and c-VEMPs ($n = 45$). vHIT, video Head Impulse Test; oVEMP, ocular Vestibular Evoked Myogenic Potential; cVEMP, cervical Vestibular Evoked Myogenic Potentials.

using all vestibular test results within one single patient (40); (2) scoring of vestibular function using results from separate vestibular reflex tests (this study) compared with considering separate vestibular organs [canals and otoliths, (40)]. To sum up, the different study goals could result in a different distribution of patients among clusters and different interpretations regarding etiology, despite the implementation of the same analysis. Therefore, it is advised to investigate all vestibular end organs separately to appreciate the vestibular impairment as a whole.

Limitations

Most importantly, some etiology groups included small amounts of patients ($n < 5$), which complicated statistical analysis. Next to this, the vestibular implantation criteria include a number of items that are not related to the vestibular reflex testing, which were not considered in this study (e.g., psychological or psychiatric disorders or an ability to undergo surgery). This could imply that the number of patients eligible for implantation in this study is an overestimation. Due to the study setting in centers 1 and 2, it cannot be ruled out that this study potentially

suffered from selection bias due to the inclusion of a relative "healthy" BVP population (i.e., patients with severe symptoms would potentially not want to participate in a full day of clinical testing). However, when comparing centers 1 and 2 with center 3, the results indicate that this might not be the case. A potential risk of referral bias in center 1 could not be excluded, since center 1 is involved in research regarding future vestibular implant therapy (43). This could lead to specific referrals or third opinion consultations in this center. Finally, the torsion swing test phase, being the 4th criterion according to Bárány criteria, was not used in this study, because either it was not measured or the automatic calculation algorithm was not considered reliable.

Future Perspectives

In order to gather a much bigger dataset from different sources that can be pooled and analyzed together, an international standardized approach for vestibular testing will be crucial (57). In particular, (1) different VEMP devices should be compared to each other in order to obtain the relation between stimuli and the threshold values; (2) the same torsion swing frequency and velocity should be used; and (3) raw traces of eye movements in both vHIT [obtained from different devices (46)] and caloric testing (electronystagmography vs. videonystagmography) should be analyzed, since different processing algorithms may lead to a significant difference in results of gain and SPV. In the case of a larger dataset, etiologies can be defined more specifically and at a more pathophysiological and morphological level (e.g., etiologies that lead to fibrosis). Next to this, future research between objective vestibular reflex test results and self-reported symptom severity could provide more insight into the effect of different patterns of vestibular impairment and degree of specific BVP symptoms (e.g., anterior canal sparing and self-reported oscillopsia severity).

CONCLUSION

This study provided a description of vestibular function in a large cohort of patients with BVP diagnosed according to the Bárány Society criteria. Overall, this study showed differences in the degree of vestibular impairment measured with different vestibular tests such as caloric test, vHIT, torsion swing test, and VEMPs. More specifically, some tests (i.e., caloric testing and horizontal vHIT) seem to be more sensitive for detecting vestibular impairment, whereas other tests (e.g., torsion swing test) are more suited for measuring residual vestibular function. In addition, no striking patterns of vestibular impairment in relation to etiology were found. Nevertheless, when comparing the Bárány Society diagnostic and vestibular implantation criteria, it was shown that although the implantation criteria are more strict, still 76% of the patients with BVP were eligible for implantation based on vestibular test criteria. It is advised, especially in the research setting, to carefully examine every patient for their overall pattern of vestibular impairment (i.e., all five vestibular end organs), in order to make well-informed and personalized therapeutic decisions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Maastricht, Antwerp and Munich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP and LS conducted the analysis and wrote the manuscript. FL, BD, and VM ensured data acquisition. RB supervised the writing and edited the manuscript. MS, NG, AP, and JW reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

LS and FL were supported through funding of MED-EL (Innsbruck, Austria). RB, AP, and NG received funding for travel from MED-EL. MP was supported by the Tomsk State University Development Program (≪Priority-2030≫). MS receives support for clinical studies from Decibel, U.S.A., Cure within Reach, U.S.A. and Heel, Germany. MS distributes M-glasses and Positional vertigo App. The funders had no role in study design, data collection, data analysis, interpretation of data, decision to publish, or preparation of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.856472/full#supplementary-material

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Conflict of Interest: MS acts as a consultant for Abbott, AurisMedical, Heel, IntraBio, and Sensorion. MS has received speaker's honoraria from Abbott, Auris Medical, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, J & J, MSD, NeuroUpdate, Otometrics, Pierre-Fabre, TEVA, UCB, and Viatris.

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

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XIII. Attachment A: Paper III

The Semont-Plus Maneuver or the Epley Maneuver in Posterior Canal Benign Paroxysmal Positional Vertigo: A Randomized Clinical Study

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RECEIVED 18 February 2023
ACCEPTED 18 March 2023
PUBLISHED 26 June 2023

CITATION
Strupp M, Mandala M, Vinck A, et al. The Semont-Plus Maneuver or the Epley Maneuver in Posterior Canal Benign Paroxysmal Positional Vertigo: A Randomized Clinical Study. *JAMA Neurol.* 2023;80(8):798–804. doi:10.1001/jamaneurol.2023.1408

JAMA Neurology | Original Investigation

The Semont-Plus Maneuver or the Epley Maneuver in Posterior Canal Benign Paroxysmal Positional Vertigo
A Randomized Clinical Study

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IMPORTANCE Questions remain concerning treatment efficacy for the common condition of benign paroxysmal positional vertigo (BPPV).

OBJECTIVE To compare the effectiveness of the Semont-plus maneuver (SM-plus) and the Epley maneuver (EM) for treatment of posterior canal benign paroxysmal positional vertigo (pcBPPV) canalolithiasis.

DESIGN, SETTING, AND PARTICIPANTS This prospective randomized clinical trial was performed at 3 national referral centers (in Munich, Germany; Siena, Italy; and Bruges, Belgium) over 2 years, with a follow-up to 4 weeks after the initial examination. Recruitment took place from June 1, 2020, until March 10, 2022. Patients were selected randomly during routine outpatient care after being referred to 1 of the 3 centers. Two hundred fifty-three patients were assessed for eligibility. After consideration of the exclusion criteria as well as informed consent, 56 patients were excluded and 2 declined to participate, with 195 participants included in the final analysis. The analysis was prespecified and per-protocol.

INTERVENTIONS After being randomized to the SM-plus or the EM group, patients received 1 initial maneuver from a physician, then subsequently performed self-maneuvers at home 3 times in the morning, 3 times at noon, and 3 times in the evening.

MAIN OUTCOME AND MEASURES Patients had to document whether they could provoke positional vertigo every morning. The primary end point was the number of days until no positional vertigo could be induced on 3 consecutive mornings. The secondary end point was the effect of the single maneuver performed by the physician.

RESULTS Of the 195 participants included in the analysis, the mean (SD) age was 62.6 (13.9) years, and 125 (64.1%) were women. The mean (SD) time until no positional vertigo attacks could be induced in the SM-plus group was 2.0 (1.6) days (median, 1 [range, 1-8] day; 95% CI, 1.64-2.28 days); in the EM group, 3.3 (3.6) days (median, 2 [range, 1-20] days; 95% CI, 2.62-4.06 days) (P = .01; α = .05, 2-tailed Mann-Whitney test). For the secondary end point (effect of a single maneuver), no significant difference was detected (67 of 98 [68.4%] vs 61 of 97 [62.9%]; P = .42; α = .05). No serious adverse event was detected with both maneuvers. Nineteen patients (19.6%) in the EM group and 24 (24.5%) in the SM-plus group experienced relevant nausea.

CONCLUSIONS AND RELEVANCE The SM-plus self-maneuver is superior to the EM self-maneuver in terms of the number of days until recovery in pcBPPV.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05853328

Visual Abstract

Multimedia

Supplemental content

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JAMA Neurol. 2023;80(8):798-804. doi:10.1001/jamaneurol.2023.1408
Published online June 26, 2023.

Benign paroxysmal positional vertigo (BPPV) is characterized by recurrent brief episodes of spinning positional vertigo, provoked by lying down or turning over in the supine position.[1] Benign paroxysmal positional vertigo is caused by otoconia that most often move freely in the affected semicircular canal (canalolithiasis).[2] In about 60% to 90% of cases, the posterior canal is affected,[3,4] termed *posterior canal BPPV* (pcBPPV) *canalolithiasis*.

Changes of head position relative to gravity can move the otoconia out of the affected canal. At present, the therapy of choice for pcBPPV is the Epley repositioning maneuver (EM)[5] and the Semont maneuver (SM).[6] Both treatments are classified as level 1 efficacy based on evidence-based medicine with a high success rate of up to 95%[7,8] if performed correctly.

The EM requires the supine patient's head and trunk to be rotated after being tilted backward into a slightly head-hanging position[5] with a pillow under the patient's shoulder to reduce the discomfort.[9] The success rate can be improved by repeating the maneuver 2 to 3 times in 1 session.[10]

With the SM, the patient's head is first rotated by 45° to the side of the nonaffected labyrinth to bring the affected posterior canal into the plane of the positional maneuver.[6] Then the patient is turned 90° to the side of the affected labyrinth; he or she should maintain this position for 1 minute, lying on their side.[11] Afterward, the patient is quickly turned by 180° to the side of the unaffected labyrinth, where he or she again has to remain lying for 1 minute. Finally, the patient sits up and has to maintain this position for 1 minute.

A direct comparison of the SM and the EM found no differences in their efficacy.[7,12-16] The choice of the maneuver should depend on which maneuver the therapist has the most experience with or whether there are any individual contraindications. Patients with obesity are easier to treat with the EM, while the SM is more suitable for patients with shoulder and neck problems. Although the treatment maneuvers per se are effective for the treatment of BPPV, a meta-analysis[17] showed that elderly patients in particular experience BPPV longer and are more impaired than previously assumed.

The SM and EM can also be successfully applied as self-maneuvers, namely with the modified Epley self-maneuvers with a pillow under the shoulder,[18] which was also used in this study. For self-maneuvers, thorough guidance by demonstration and pictures is necessary. The success rates (50%-90% after 1 week containing 21 treatment sessions) are not as high as when a therapist performs the maneuver, and it takes longer until the patient is symptom-free.[19]

A biophysical model and computer simulations showed that during the rotation of the labyrinth, the crystals move about 25° less than during rotation in the plane of the affected canal.[11] Based on these findings, the SM-plus was developed (**Figure 1**, **Video 1** [demonstration of the SM-plus], and **Video 2** [demonstration and computer simulation of the SM-plus]; the EM is shown in Figure 1 and in **Video 3**). When the patient's body is moved toward the affected side, the angle should be at least 150°, that is, 60° below the earth horizontal; in this way, the otoconia move much further in the direction of the utricle. Subsequently, the patient is moved by at least 240° toward the nonaffected side and the clot of otoconia is then already putatively beyond the vertex of the canal,[11] which increases the efficacy of the maneuver. In a previous prospective randomized tricenter study,[20] it was found that the SM-plus is superior to the regular SM; in the 194 patients analyzed (96 receiving SM and 98 receiving SM-plus), a median of 2 (range, 1-21; mean, 3.6) days was needed for recovery with SM and 1 (range, 1-8; mean, 1.8) day with SM-plus ($P < .001$; $\alpha = .05$, Mann-Whitney test).

In the current study, we applied a similar study design with the same primary end point (mornings until recovery) to compare the efficacy of the SM-plus with the EM in patients with pcBPPV canalolithiasis. Because patients with BPPV typically have symptoms more frequently in the morning, we chose morning symptoms as an end point measurement. This can be explained by an aggregation of the otoconia during rest in the night, which has a higher hydrodynamic impact on the endolymphatic fluid than a single otoconium.[11] Further, since self-maneuvers are less effective than those by a therapist, patients should perform the treatment maneuvers 3 times in the morning, 3 times at noon, and 3 times at night (ie, 9 times per day) in this study.

Key Points

Question Is the Semont-plus maneuver (SM-plus) or the Epley maneuver (EM) a better therapeutic option in patients with posterior canal benign paroxysmal positional vertigo?

Findings In this randomized clinical trial of 195 participants, the mean (SD) days until no positional vertigo attacks could be induced was 2.0 (1.6; median, 1 [range, 1-8]) in the SM-plus group and 3.3 (3.6; median, 2 [range, 1-20]) in the EM group.

Meaning The SM-plus is superior to the EM in terms of the number of days until recovery in posterior canal benign paroxysmal positional vertigo.

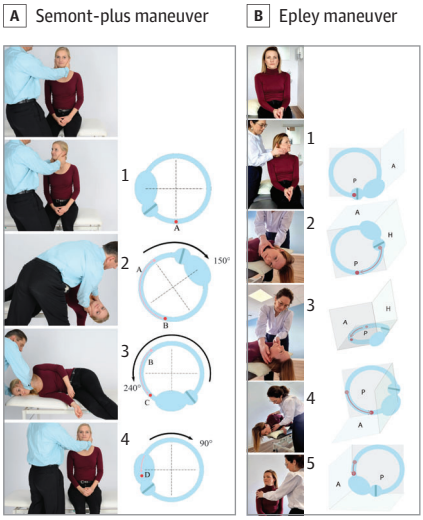
Methods

Study Population and Randomization

Patients were recruited in 3 academic centers in 3 countries: Department of Neurology and German Center for Vertigo and Balance Disorders, Ludwig Maximilian University Hospital, Munich, Germany; Department of ENT (Ear, Nose, and Throat), AZ Sint-Jan Brugge, Brugge, Belgium; and Department of ENT, University of Siena, Siena, Italy. Recruitment took place from June 1, 2020, until March 10, 2022. The analysis was prespecified and per protocol (Supplement 1). Written consent was obtained from all participants. The study was approved by the local ethics committees of each center, with an exception for Siena. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

This study was retrospectively registered because, according to German and European regulators, registration was not required; however, we registered the trial at the

Figure 1. Schematic Drawing of the Movement of the Otoconia of the Semont-plus Maneuver and Epley Maneuver for Benign Paroxysmal Positional Vertigo of the Left Posterior Canal



A, The Semont-plus maneuver includes the upright position with (1) turning of the head by 45° toward the nonaffected side; (2) movement of the body by 150° toward the affected side, which moves the otoconia further in the direction in which they should move (A toward B); (3) and since the clot is beyond the vertex (B toward C), the movement of body by 240° moves the clot into the direction (4) of the vestibulum (position D of the otoconia). B, The Epley maneuver includes upright position and (1) rotation of the head 45° toward the affected ear; (2) movement of the body backward so that the head is in a hanging position below the earth horizontal; (3) rotation of the head 90° toward the nonaffected ear; (4) rotation of the whole body downward so that the patient faces the floor and their affected ear is pointing toward the ceiling; and (5) going into the upright position while keeping a rotation of the head 45° toward the nonaffected ear, and turning the head back to the neutral position at the end. A indicates anterior semicircular canal; H, horizontal semicircular canal; and P, posterior semicircular canal.

request of the editors. (Regulation EU No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.)

Inclusion Criteria

Patients were eligible for inclusion if 18 years or older with a capacity to consent and a diagnosed pcBPPV canalolithiasis according to the diagnostic criteria of the Classification Committee of Vestibular Disorders of the Bárány Society in 2015.[1] The diagnostic criteria include repetitive episodes of vertigo or dizziness provoked by rapid head acceleration or deceleration, duration of attacks of less than 1 minute, and positional vertical-torsional nystagmus provoked in the diagnostic Dix-Hallpike maneuver[14] or diagnostic SM with a crescendo-decrescendo time course.

Exclusion Criteria

Patients without a capacity for consent, younger than 18 years, and/or not willing or not able to perform the assigned maneuver were excluded. A method of simple randomization was used to generate the random allocation sequence (coin flip or a random number generator).

Treatment and Study Flow

The patients presented to routine outpatient care in 1 of the 3 centers. The patient history was taken followed by a standard neurological and neuro-otological examination, a video head impulse test, and caloric testing. After performing the routine diagnostic maneuvers, a pcBPPV canalolithiasis was diagnosed according to the aforementioned criteria.[1] The patient was informed about the study, consented, and was allocated randomly 1:1 to one of the treatment groups (EM or SM-plus) in a consecutive order.

A first treatment maneuver was performed once by a physician according to the assigned treatment group. For the SM-plus, the angle of the 60° overextended head and body was measured by an inclinometer application. The patient simultaneously received verbal instructions on how to perform the maneuver. Fifteen minutes after the first diagnostic maneuver, a second diagnostic maneuver was performed to evaluate the effect of a single maneuver.

For the self-maneuvers, patients received written instructions with figures on how to perform the SM-plus or the EM independently in a home environment. For the self-maneuver at home, the modified Epley self-maneuver[19] was done by the patient with a pillow under the shoulders. The frequency of performance at home was 3 times in the morning, 3 times at noon, and 3 times in the evening (ie, 9 times per day).

The patient received a standardized documentation form. The study participant had to fill out the form, documenting how many mornings it took until the patient experienced no more positional vertigo; in addition, patients could also add additional comments, such as adverse effects of the maneuvers. The morning when the first maneuver induced no positional vertigo was noted and the patient then had to perform the diagnostic maneuvers for another 2 days to make sure that he or she was free of symptoms. If this was the case, they could stop the treatment. If not, the treatment had to be continued as well as the evaluation. The filled-out form was sent back by the patient to the study center in an envelope that the participant had received at inclusion in the study.

End Points

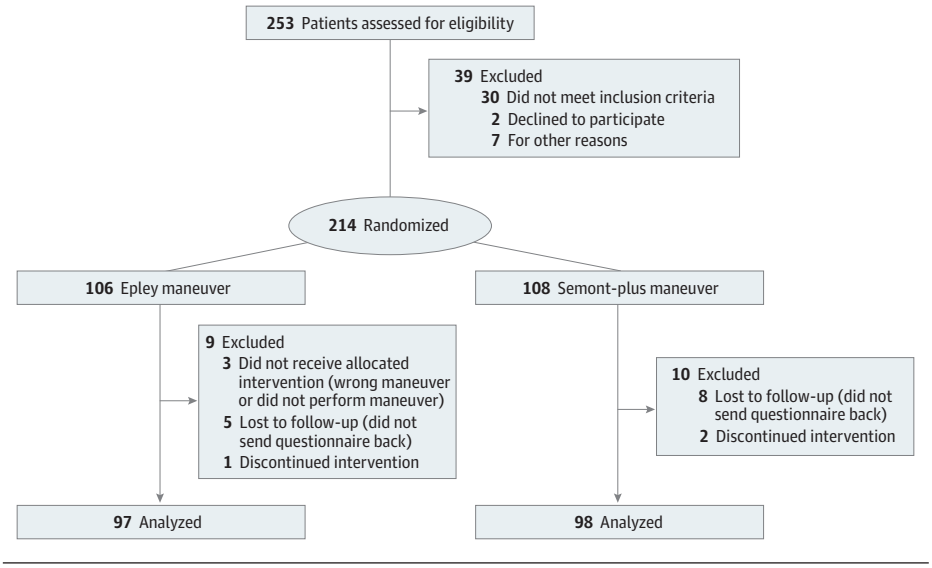
The primary end point is the number of days, specifically the first morning, until the patient was free of positional vertigo for that morning and 2 subsequent mornings. The day of inclusion was defined as day 0.

As a secondary end point, the success rate of a single performance of the maneuver by a physician was tested. In the study population, we investigated how many patients in both treatment groups become free of vertigo and nystagmus after a single performance of the allocated treatment maneuver by a physician.

Statistical Analysis

Since the parameter mornings to recovery was not normally distributed, a 2-tailed Mann-Whitney test was performed to compare the 2 study groups, considering $P < .05$ as statistically significant. For the secondary outcome, χ^2 testing was applied. Dropouts were not replaced or imputed in the end point analyses. Computations and illustrations used R, version 4.1.2

Figure 2. Study Flowchart



(R Project for Statistical Computing), and Adobe Illustrator, version 27.2 (Adobe). Data management and sorting were executed using Excel LTSC MSO, version 16.0.14332 (Microsoft Corp).

Results

In total, 253 patients were assessed for eligibility (**Figure 2**). Thirty were excluded due to not meeting the inclusion criteria, 2 declined to participate, and 7 were excluded for other reasons. Two hundred fourteen patients were randomized in the 2 treatment groups, with 106 allocated to EM and 108 to SM-plus. Of the EM group, 3 patients did not receive the allocated treatment, 1 discontinued the intervention due to anxiety, and 5 were lost to follow-up. Of the SM-plus group, 2 patients were excluded due to discontinued intervention and performing the wrong maneuver and 8 were lost to follow-up. One of these patients went to a physiotherapist who performed the wrong maneuver and 1 more did not apply the 60° overextension of the head due to anxiety; both patients confirmed these experiences during the follow-up. In total, 195 patients were included in the analysis (mean [SD] age, 62.6 [13.9] years; 125 women [64.1%] and 70 men [35.9%]). Of these, 97 patients were allocated to the EM group and 98 to the SM-plus group, with 45 from the center in Germany, 54 from the center in Belgium, and 96 from the center in Italy. The mean (SD) age of the patients allocated to the EM group was 60.9 (13.8) years; for those in the SM-plus group, 64.4 (13.9) years. Thirty men and 67 women were allocated to the EM group; 40 men and 58 women, to SM-plus group. In the SM-plus group, 56 patients were experiencing a first BPPV episode, while the condition was recurrent in 36 and data were missing on 6 occasions; the etiology was idiopathic in 84 of 98 patients. Of the 97 patients who were treated with the EM, 62 had their first BPPV manifestation and in 33 the condition was recurrent. The etiology in the EM group was idiopathic in 84 of 97 patients. Fifty-eight of 97 patients in the EM group and 61 of 98 in the SM-plus group had a right-sided BPPV (**Table**).

The mean (SD) time until no more positional vertigo attacks could be induced by patients in the SM-plus group was 2.0 (1.6) days (median, 1 [range, 1-8] days; 95% CI, 1.64-2.28 days) (**Figure 3**). In the EM group, the mean (SD) time until recovery was 3.3 (3.6) days (median, 2 [range, 1-20] days; 95% CI, 2.62-4.06 days). The 2-tailed Mann-Whitney test revealed a statistically significant difference (P = .01; α = .05). A post hoc descriptive subgroup analysis is given in the Table.

For the secondary end point, effects of a single SM-plus or EM, 67 of 98 patients (68.4%) in the SM-plus group did not experience any vertigo and/or positional nystagmus after performance of a single therapeutic maneuver. In the EM group, this applied to 61 of 97 patients (62.9%). The χ^2 test revealed no difference between groups (P = .42; α = .05). However, of those patients who had no BPPV after the first maneuver, 17 of 67 (25.4%) in the SM-plus group and 15 of 61 (24.6%) in the EM group experienced positional vertigo again the next morning.

Safety

No severe adverse effects were detected in both the SM-plus and the EM group. Nineteen patients assigned to the EM group (19.6%) experienced nausea during the therapeutic self-maneuver, 1 was too anxious during the maneuver, and 1 experienced strong dizziness after the maneuver. A patient in the EM group reported severe transpiration and dizziness during the maneuver. In the SM-plus group, 24 patients experienced severe nausea (24.5%), 1 patient reported vomiting after performing the maneuver, and 1 found the maneuver physically too difficult to execute because of severe anxiety.

Table. Characteristics of the Study Population

Characteristic	Intervention	
	Epley maneuver (n = 97)	Semont-plus maneuver (n = 98)
Age, mean (SD) [range], y	60.9 (13.8) [26-88]	64.4 (13.9) [25-91]
Sex, No. (%)		
Men	30 (31)	40 (41)
Women	67 (69)	58 (59)
Time until recovery, d[a]		
Mean (SD)	3.3 (3.6)	2.0 (1.6)
Median (range)	2 (1-20)	1 (1-8)
95% CI	2.62-4.06	1.64-2.28
No. with first-time/recurrent episode/missing data	62/33/2	56/36/6
No. with affected right side/affected left side/missing data	58/38/1	61/35/2
No. with etiology idiopathic/nonidiopathic/missing data	84/11/2	84/9/5
Time until recovery for patients with a first-time BPPV, d		
Mean (SD)	2.9 (3.6)	1.5 (0.9)
Median (range)	1 (1-20)	1 (1-5)
95% CI	1.96-3.77	1.22-1.67
Time until recovery for patients with a recurrent BPPV, d		
Mean (SD)	4.1 (3.5)	2.7 (2.2)
Median (range)	3 (1-13)	2 (1-8)
95% CI	2.85-5.27	2.02-3.43
Time until recovery for patients with an idiopathic BPPV, d		
Mean (SD)	2.8 (2.9)	2.0 (1.6)
Median (range)	1 (1-14)	1 (1-8)
95% CI	2.20-3.45	1.61-2.29
Time until recovery for patients with a nonidiopathic BPPV, d		
Mean (SD)	6.8 (5.8)[b]	2.0 (1.8)[b]
Median (range)	5 (1-20)	1 (1-8)
95% CI	3.39-10.25	0.80-3.20

Abbreviation: BPPV, benign paroxysmal positional vertigo.

[a] Indicates number of days until no vertigo could be induced after performing a single self-maneuver (P = .01; α = .05, 2-tailed Mann-Whitney test).

[b] Population SD was used due to small sample size.

Discussion

In this prospective randomized clinical trial, we found that in pcBPPV canalolithiasis, the SM-plus is more effective than the EM in terms of days until recovery (median, 1 [range, 1-8] vs 2 [range, 1-20] days). We could confirm and thereby reproduce the findings of the previous study with the SM-plus[20] in terms of the time until patients become free of symptoms (median, 1 day). Additionally, previous direct comparisons of the SM and the EM found no differences in their efficacy.[7,12-16] This agrees with an indirect comparison of the days it takes for the SM to produce recovery in the previous study[20] (mean, 3.6 days) and the EM in the current study (mean, 3.3 days). Both findings show that our data are evidently robust.

In terms of the effect of the first treatment maneuver, which was done by a physician, 68.4% of patients who received the SM-plus and 62.9% of those who received the EM did not experience vertigo or positional nystagmus. However, of those patients who had no BPPV after this first maneuver, 25.4% in the SM-plus group and 24.6% in the EM group experienced positional vertigo again the next morning (ie, they were not cured by a single maneuver). This underlines that in many patients, several maneuvers are needed.

The explanation for the superiority of the SM-plus over the SM[20] was the overextension by 60° of the head and body below earth horizontal during step 2 of the SM-plus. A biophysical model[11] showed that (1) the otoconia move after, for instance, a 90° turn, about 25° less, and (2) by increasing the angle by, for instance, 60°, they move another 60° into the direction of the exit of the canal, positioning them already beyond the apex of the vertex canal when the patient moves by 240° into the opposite direction. If this model is accurate, it demonstrates why the likelihood of expelling the otoconia is increased.

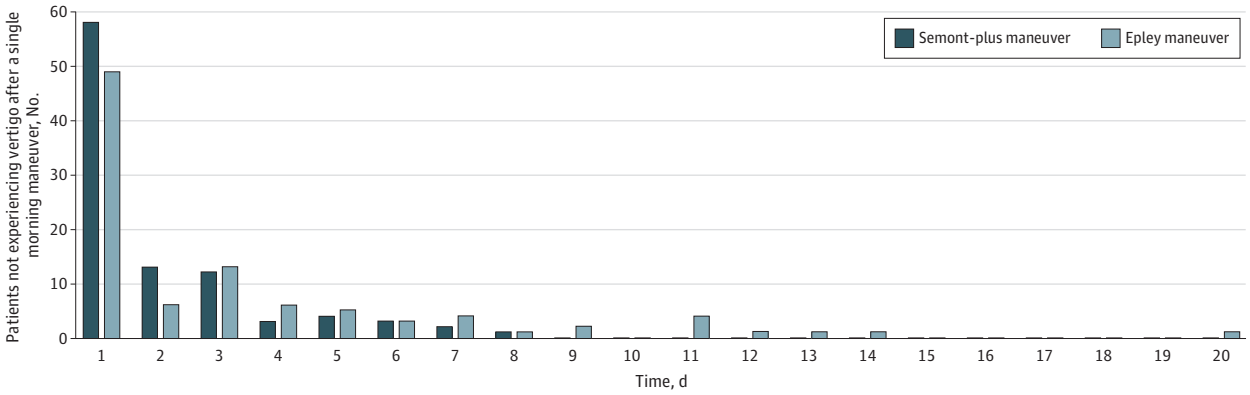
How can the superiority of the SM-plus over the EM be explained? First, in another biophysical study it was demonstrated how important the orientation of the affected canal is during the maneuvers relative to the gravitational vector[21]: angles larger than 67° or smaller than 21° did not lead to a successful repositioning, even after a waiting period of 5 minutes. It is conceivable that for the EM, the orientation relative to the gravitational vector is not always perfect during each step of the movements (Figure 1). This interpretation is supported by 2 recent studies[22,23] in which the angular accuracy of the EM was measured showing a wide range of angular inaccuracy at each stage. Second, recommended duration for each maneuver is different, at 60 seconds for SM-plus and 30 seconds for EM. Since time matters for the movement of the otoconia to reach the lowest point relative to gravity, as was also demonstrated in the biophysical model—namely, if there are only single crystals and not a large agglomerate[11]—this may also explain the difference between the EM and SM-plus.

For the discussion of other aspects of our findings, namely immediate success rate, issues of self-treatment, combination of treatment maneuvers, and total number of maneuvers needed, we refer to the Discussion in the previous study by Strupp et al with a similar design.[20] As for the safety of both maneuvers, no serious adverse effects were detected. The percentage of people who experienced nausea in both study groups was similar and comparable. A systematic review[7] revealed nausea during the EM in 16.7% to 32% of patients, similar to our study. The exaggerated head positions when performing the SM-plus may cause more anxiety and may be more difficult to execute in patients with a limited physical capability as well as cervical issues.

Limitations

The following limitations must be taken into account when considering this trial. First, we had no control over how well patients performed self-maneuvers at home. However, the combination of an initial treatment by the clinician and subsequent

Figure 3. Primary End Point



Histogram of days until no positional vertigo could be induced with the Semont-plus maneuver and Epley maneuver.

self-maneuvers by the patient reflects clinical treatment of BPPV. This issue can be addressed by remote management (eg, with cell phone videos taken by a third person or by the patient themselves). That would also help the physician to evaluate how the maneuvers are performed during an online or an in-person consultation.[24] Second, the primary end point (days until recovery) was left to the patients' self-report. Despite extensive instructions by the examiners, there is no real control over how patients reported this, leaving a margin for falsely documented primary outcome. However, there should be no difference for the SM-plus and EM in our study. Third, we did not compare the efficacy of the SM-plus and EM when performed repeatedly by therapists only.

Conclusions

This prospective randomized study provides evidence that, in patients with pcBPPV canalolithiasis, the SM-plus maneuver is superior to the EM in terms of the time until no positional vertigo could be induced by the patient. Hence, the SM-plus can be recommended in clinical practice.

ARTICLE INFORMATION

Accepted for Publication: March 18, 2023.

Published Online: June 26, 2023. doi:10.1001/jamaneurol.2023.1408

Author Contributions: Dr Strupp and Mr Mavrodiev had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Strupp, Mandala, Bayer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Strupp, Vinck, van Breda, Gerb, Bayer, Mavrodiev, Goldschagg.
Critical revision of the manuscript for important intellectual content: Strupp, Mandala, Vinck, Salerni, Bayer, Mavrodiev.
Statistical analysis: Strupp, Bayer, Mavrodiev.
Obtained funding: Strupp.
Administrative, technical, or material support: Strupp, Mandala, Vinck, van Breda, Salerni, Goldschagg.
Supervision: Strupp, Mandala, Vinck, Bayer.

Conflict of Interest Disclosures: Dr Strupp reported serving as joint chief editor of *the Journal of Neurology*, editor in chief of *Frontiers of Neuro-otology*, and section editor of F1000Research; receiving speaker's honoraria from Abbott Laboratories, Actelion, Auris Medical, Biogen Inc, Eisai Co, Ltd, Grünenthal, GSK PLC, Hennig Arzneimittel GmbH & Co KG, Interacoustics, Johnson & Johnson, Merck & Co Inc, Neuro Update, Otometrics, Laboratoires Pierre Fabre, Teva Pharmaceutical Industries Ltd, UCB, and Viatris Inc; being a shareholder, investor, and chief medical officer of IntraBio; being the distributor of the M-glasses and Positional Vertigo app; receiving support for clinical studies from Decibel Therapeutics, Cures Within Reach, and Heel; and consulting for Abbott Laboratories, Actelion, Auris Medical, Bulbitec AS, Heel, IntraBio, Sensorion, and Vertify. No other disclosures were reported.

Funding/Support: This study was supported by grant 01EO0901 from the Federal Ministry of Research within the framework of the German Center for Vertigo and Balance Disorders.

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank the patient for granting permission to publish the information in Figure 1. We thank Anita Bhandari, MD, Vertigo and Ear Clinic, Jaipur, India, for providing permission to publish Video 2; she was not compensated for this work.

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