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Recent Advances in Diagnosis and Treatment of Vestibular Disorders

Edited by
Nicolas Perez-Fernandez and Angel Ramos-Macias

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About the Editors

Nicolas Perez-Fernandez

Nicolas Perez-Fernandez MD, PhD, is a Professor of Otorhinolaryngology at the University of Navarra, Spain. He has been director of the Oto-Neurology division since 1997 and chaired the department from 2003 to 2013. In 2018, he moved to the Clínica Universidad de Navarra in Madrid. His work has covered several aspects of vestibular medicine, from basic anatomy, otopathology and vestibular physiology to the clinical bedside and laboratory testing. Much of this work has been done based on the accumulation of data from patients in databases with the help of collaborators and residents, allowing for continuous education after graduation and doctoral training. The result of treatment has been another important focus of his research: with intratympanic gentamycin in Menière's disease as well as with different repositioning maneuvers in positional vertigo. Now, he is mainly focused on vestibular reflex assessment and MRI of the inner ear in Ménière's disease, which has the major advantage of in vivo evaluation of endolymphatic hydrops, opening a new way of understanding recurrent and fluctuating hearing loss and vertigo.

Angel Ramos-Macias

Prof Dr. Angel Ramos-Macias is a Professor of Medicine and the Director of the Department of Medical and Surgical Sciences at the University of Las Palmas, and Head of the Otorhinolaryngology Department of the Adults and Maternal-Child University Hospital of the Canary Islands. He is the Director of the Research Group "Medical bioengineering of neural stimulation " and Director of the European Consortium "BionicVest" (Vestibular Implant Research), Director of the National Reference Program in Cochlear Implants of the SCS (Government of the Canary Islands), and Director of 24 doctoral theses, more than 250 publications, and 7 complete books. He is the owner of 12 Intellectual Property Patents. He is the Director of 43 Research Projects and more than 50 scientific collaboration contracts. He is the Associate Editor of various Impact Magazines in JCR and Editor-in-Chief of the prestigious journal *Audiology and Neurootology*.

He received the Academic Award of the Royal Academy of Spanish Medicine (2019), and the Research and Science Award from the Government of the Canary Islands (2013). Also, he is also an honorary member of various foreign universities.

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Editorial

Recent Advances in the Diagnosis and Treatment of Vestibular Disorders

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Vestibular medicine "embraces a wide approach to the potential causes of vestibular symptoms, acknowledging that vertigo, dizziness, and unsteadiness are non-specific symptoms that may arise from a broad spectrum of disorders, spanning from the inner ear to the brainstem, cerebellum and supratentorial cerebral networks, to many disorders beyond these structures" [1]. In recent years, we have seen major changes in the definition and availability of new guidelines for different disorders, a new hierarchy for vestibular examination that begins with vestibular reflex activity evaluation and scales up to vestibular cognition, and the clear assessment of treatment results based on medication, surgery, and vestibular rehabilitation. This framework allows for the correct consideration of new findings from genetics, imaging, and sociodemographic studies. Most of these issues are the topics of the manuscripts in this special collection.

Vestibular implants mark one of the most recent advances in the treatment of patients with bilateral vestibulopathy; in a special subgroup of them, those with profound hearing loss, the treatment challenges are extreme. Electrical stimulation of the saccular afferents is one of the solutions provided to them, and Curthoys et al. have provided data of improved performance. They also proposed an interesting theory to connect this type of stimulation to nonvestibular brain areas that could potentially be of benefit for other gait disorders, such as that which occurs in Parkinson's disease [2].

The importance of correct and complete anamnesis in patients with vestibular disorders has been stressed many times. Van de Berg and Kingma [3] have provided a simple to follow and systematic approach for nonacute symptoms that are of major concern on a daily basis to clinicians, pointing to a step-by-step consideration. They call attention to the possibility of different disorders that could occur metachronically or synchronically, as respectively shown in the next two papers. First, Oka et al. give an interesting functional explanation of the findings in patients with persistent postural-perceptual dizziness that exemplifies the need for thorough clinical evaluation and functional examination: considering previous disorders would enable a better understanding of current problems [4]. Second, the coincidence of two very distinct disorders—a very common one, benign paroxysmal positional vertigo (BPPV), and a very unusual one, bilateral vestibulopathy—has been systematically evaluated for the first time by Pérez-Fernández et al., who rely on, and strongly recommend, complete vestibular examination regardless of a differential diagnosis, and raise the question as to what the limit of vestibular function is for a nystagmic response to appear [5]. Two other papers deal with debatable clinical problems, giving light to a better understanding of them. In the first, Gill-Lussier et al. carried out a scoping review of proprioceptive cervicogenic dizziness [6], showing how heterogeneous this concept is regarding etiology, differential diagnosis, measurement, and treatment, also providing a good characterization for further studies. In the second, Idriss et al. have shown the intriguing place of the narrow internal auditory canal in pediatric vestibular paroxysmia [7]; both are unusual conditions in the studied population, and the authors direct some remarks to the methodology of imaging to obtain an adequate result.

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The vestibular evaluation of patients is always initiated with a bedside examination of vestibular reflexes and nystagmus. In this regard, Gufoni and Casani [8] have made an interesting observation and conducted clinical research to show that pupillary hippus is substantially associated with vestibular migraines, particularly during the interictal phase. Their methodology is so easy to follow as to become something to include in common daily bedside and instrumental examinations, deserving interest when other disorders, such as Ménière's disease or positional vertigo, are coincident with migraines. The development of the video head impulse test (vHIT) since its characterization [9] is still ongoing. One of the first derivatives was the suppression head impulse (SHIMP) test: van Dooren et al. compare the head impulse (HIMP) and SHIMP tests using the video system to track eye movement velocity in patients with bilateral vestibulopathy [10] and show how both tests are well correlated, though the gain in the vestibulo-ocular reflex is lower in the SHIMP test (as has been shown in other disorders or even normal subjects), but without clinical relevance for the final diagnosis. One of the most important vestibular tests of nystagmus is that induced by caloric stimulation, with air or water, of the inner ear through the external auditory canal. The caloric test has been associated with residual symptoms that prevent its frequent and repetitive use; these can be reduced by simply reducing the number of stimulations. According to Alhabib and Saliba, the use of only warm stimulation could solve this problem without losing value, and they recommend proceeding in both ears in cases without spontaneous nystagmus, providing the correct methodology when it is present or the final results are extremely low [11]. One of the missions of the vestibulo-ocular reflex is to maintain visual acuity during active or passive movement of the subject; Rodriguez-Montesdeoca et al. have shown that the unilateral electrical stimulation of the sacculus (not directly involved in that mission) in patients with bilateral vestibulopathy partially restores dynamic visual acuity function [12], and they try to answer this new finding in the correction of oscillopsia. They have opened, as shown in [2], a new avenue of research on the otolithic system.

The treatment of vestibulopathy was one of the main purposes of this Special Issue, and five papers were devoted specifically to it; although, as previously shown, some solutions for others have previously been presented. First, Esteban-Sanchez and Martin-Sanz [13] have covered the topic of acute unilateral vestibulopathy in a rigorous and detailed study during a follow-up, trying to correlate measures of functional damage, postural deficiency, and disability to the clinical state of compensation, with clinical implications when vestibular rehabilitation is the treatment of choice. Induced bilateral vestibulopathy is the unwanted effect of some systemic medications, such as gentamicin; in their study, Ferreira-Cendón et al. have shown how this effect could be reduced in patients with infectious endocarditis when an otoneurologist is included in the treating team to provide careful and continued measures of vestibular function to help in the continuation, or not, of gentamicin [14]. This probably could be expanded to other treatments with potentially ototoxic medications. The treatment of BPPV has been an intense topic in the literature since the description by Epley in 1979 of the first particle repositioning maneuver, or PRM [15]. Lee et al. present a new therapeutic maneuver for horizontal canal cupulolithiasis, which explains some common and difficult cases of BPPV; being aware of the problems that extreme inertia movements or mastoid oscillation have, as used in commonly performed PRM, they present a method that avoids them and should be considered, given their results [16]. Intractable Ménière's disease has been approached with the use of intratympanic medication (dexamethasone, gentamicin) or surgery; Bae et al. present their report on the combined use of both medications to obtain subablative damage with gentamicin and reduce the ototoxic damage inherent to the treatment [17]. This is performed surgically through easy access to the middle ear; it was proposed some time ago, but their results look promising if the treatment is considered first-line or as a rescue when intratympanic gentamicin fails to provide good control of the disease.

The well-known complex relationship between vestibular deficiency, disability, and handicap indicates how important it is to adequately cover all of them to obtain a better understanding of the disease and the limitations of patients. Wood et al. have examined that cases of trau-

matic brain injury (TBI) in military personnel [18]. They have found some differences with nonmilitary patients with TBI (data obtained through peer-reviewed articles) that indicate the need for specific evaluation and treatment in the former based on the specific demographic characteristics of the population under study and the major relevance of vestibular dysfunction. This is an interesting approach to expand in further sociodemographic studies.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Why Should Constant Stimulation of Saccular Afferents Modify the Posture and Gait of Patients with Bilateral Vestibular Dysfunction? The Saccular Substitution Hypothesis

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Abstract: An ongoing EU Horizon 2020 Project called BionicVEST is investigating the effect of constant electrical stimulation (ES) of the inferior vestibular nerve in patients with bilateral vestibular dysfunction (BVD). The evidence is that constant ES results in improved postural stability and gait performance, and so the question of central importance concerns how constant ES of mainly saccular afferents in these BVD patients could cause this improved performance. We suggest that the constant ES substitutes for the absent saccular neural input to the vestibular nuclei and the cerebellum in these BVD patients and indirectly via these structures to other structures, which have been of great recent interest in motor control. One target area, the anterior midline cerebellum (the uvula), has recently been targeted as a location for deep-brain stimulation in human patients to improve postural stability and gait. There are projections from midline cerebellum to basal ganglia, including the striatum, which are structures involved in the initiation of gait. It may be that the effect of this activation of peripheral saccular afferent neurons is analogous to the effect of deep-brain stimulation (DBS) by electrodes in basal ganglia acting to help alleviate the symptoms of patients with Parkinson's disease.

Keywords: bilateral vestibular dysfunction; saccular; posture; gait; vestibular implant; otolith

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1. Introduction

Patients with bilateral vestibular dysfunction (BVD) [1] show postural instability and gait difficulties. One treatment for BVD that is under investigation in a multicentre EU project (called BionicVEST) is to implant a long-term stimulating electrode on one inferior vestibular nerve and deliver a constant train of high-frequency electrical pulses by that electrode (1200 biphasic pulses per second continuously) and measure the behavioural and perceptual effects of that electrical stimulation (ES). The electrode location is such that the ES is probably mainly stimulating saccular afferents. Patients are selected according to strict criteria to meet the Barany guidelines for BVD [2]. As of 3 January 2022 a total of 10 patients has been implanted.

Preliminary results continue to be obtained, some of which have been published [1]. It is clear that this constant electrical stimulation acts to improve the patient's postural stability and gait performance as measured by Computerized Dynamic Posturography (CDP) and the Dynamic Gait Index (DGI). There are also changes in a number of tests of peripheral vestibular function, which are described in detail in [1]. The patients report that this constant stimulation is beneficial, and they do not want it switched off. With this stimulus, they find they have less need for assistance in walking and stabilising themselves.

Here, the aim is to state a simple hypothesis about why this constant, high-frequency electrical stimulation could have these effects and to review the evidence relevant to that

hypothesis. The hypothesis is called the "saccular substitution hypothesis," and it is that the neural activity generated by the ES is substituting for the reduced or absent constant saccular afferent activity from the saccular macula. We reviewed recent evidence relevant to that hypothesis about the role of direct and indirect vestibular input for postural stability and gait performance.

The saccular stimulation activates the descending spinal pathways as well. It may be that the effect of this saccular stimulation is analogous to the effect of deep-brain stimulation (DBS) by electrodes in the basal ganglia acting to help alleviate the symptoms of patients with Parkinson's disease. Possibly, the constant stimulation of the saccular afferents in the vestibular nerve is just a step further back: so, rather than directly stimulating the basal ganglia electrically, now, it is a matter of stimulating saccular afferents electrically, which project via the cerebellum to the basal ganglia and also to the spinal cord and so result in changes in performance.

BionicVEST is a pilot programme to investigate the effect of constant electrical stimulation (ES) of inferior vestibular nerve in patients with BVD [1] according to the consensus criteria of the Barany Society [2]. The aim is to determine if this constant ES results in changes in performance on:

- Tests of peripheral vestibular function,
- Tests of postural stability and gait performance, and
- Patient subjective experience. Do they find constant ES to be an improvement?

2. The Steps in the Research Process

1. Selection. Patients are selected according to carefully defined selection criteria defining bilateral vestibular dysfunction (BVD). It should be stressed that there is some residual peripheral vestibular function in these patients, but their level of function falls below the international accepted standard for bilateral vestibular dysfunction (Barany Society consensus statement [2]);
2. Preoperative testing of peripheral vestibular function, postural stability and gait (e.g., using the DGI and CDP, etc.);
3. The electrode and implantation. A modified cochlear implant electrode is implanted on a branch of the vestibular nerve in one ear. The exact location of the electrode depends on particular anatomical considerations at surgery. The aim is to implant the electrode very close to the inferior vestibular nerve containing afferents from the saccular macula and posterior semicircular canal. From the CT verified electrode locations, it appears that the electrode locations so far have been in the inferior vestibular nerve and so largely otolithic, mainly saccular afferents. It is likely there is some stimulation of the afferents from the posterior canal; however, it is necessary to emphasise that this is uncertain. We will refer to the data as being due to saccular stimulation, whereas in fact, it more likely should be referred to as vestibular stimulation (probably mainly saccular);
4. Post-operative testing. Initially, it is necessary to verify that the stimulating electrode is functional and make adjustments of the stimulus parameters of the ES (relying on patient subjective reports of oscillopsia or subjective sensations);
5. The stimulus. Then, the ES is switched on a constant train of pulses at high-frequency (900 or 1200 pulses/s), and it is kept on continuously. It is important to stress that with this implant, there is, unlike other vestibular implants [3], no modulation of the pulse rate or pulse amplitude in response to the movement of the patient. The ES is composed of a constant pulse train delivered by three electrodes of a modified cochlear implant electrode. Each pulse is biphasic (25 microseconds per phase) and delivered at a frequency of 900 or 1200 pulses per second. Three electrodes are activated, so the stimulus is simply a constant train of pulses, which will activate vestibular afferents at a very high rate, presumably duplicating the constant barrage of action potentials that healthy patients receive;

6. Stimulation phase. The patient is then re-tested on repeated occasions in the postoperative phase (in some patients, this phase has lasted 1.5 years so far). On each testing occasion, this is done first to ensure the electrode is working. Fibrosis or changes in impedance may make the electrode non-functional, in which case vestibular and clinical tests would be rendered meaningless. Then, on each occasion, they are tested on the battery of tests of peripheral vestibular function, postural stability, gait performance, and acceptability. Their results on these tests are then compared to their preoperative measures and their performance in comparison to the electrode OFF condition and measures of patient satisfaction (usually relying on patient subjective reports or oscillopsia).

3. Preliminary Test Results

See Ramos Macias et al. [1] for detailed results. On a priori grounds, we did not expect some vestibular tests to show changes: for example, we did not expect ES of saccular afferents to affect semicircular canal function (as measured by VOR gain using the video Head Impulse Test (vHIT)). However, it was possible that measures of otolith function could change as a result of the ES stimulation. We were particularly concerned to identify if there were improvements in tests of postural stability and gait performance.

4. The Saccular Substitution Hypothesis

With this saccular ES, patients show improved postural stability and gait performance (e.g., measured by the DGI or CDP), and so the question of central importance consists of how constant electrical stimulation of saccular afferents in these BVD patients could cause this improved performance. We consider that this maintained stimulation is generating a barrage of action potentials in the saccular nerve, which is substituting for the reduced or absent saccular afferent action potentials in these BVD patients. The saccular macula is unique in that saccular receptors are continuously stimulated by the force of gravity. There are a large number of primary saccular afferents (around 4000 in humans, [4,5]) and these saccular afferents have high resting discharge rates (probably around 50–100 spikes/s in humans [6]), so each second, a huge barrage of action potentials is continuously reaching the vestibular nuclei and the midline cerebellum and, we suggest, indirectly projecting on to other structures, e.g., the basal ganglia. Bilateral vestibular loss will reduce or remove this sustained neural input, and it appears that the high-frequency electrical stimulation by the implanted vestibular electrode is substituting for this lost natural neural activation.

Hence, their loss is depriving their target nuclei of a huge amount of neural input, which is presumably a major contributing factor to the poor performance of BVD patients on posture and gait tasks pre-operatively.

The questions then become:

1. Where do saccular afferents project to? and
2. How could their sustained activation influence posture and gait performance?

To address these questions, we present a brief overview of evidence about direct and indirect saccular projections and refer to the effect of damage to these target areas on patient performance. There is new evidence about how deep-brain stimulation acts upon some of these target areas to improve patient gait and postural stability. In the following sections, we consider the effects of ES of the vestibular nuclei, basal ganglia, the cerebellum, and the pedunculopontine nucleus (PPN) of the mesencephalic locomotor region in patients with deficits of motor control for improving postural stability and gait performance.

5. Saccular Projections

As is clear from the anatomical evidence of the direct and indirect central projections of saccular afferents, their neural activity has very widespread effects in motor control systems. Saccular afferents project to brainstem vestibular nuclei, to spinal cord, and to cerebellum and indirectly through the cerebellum to the basal ganglia and to other structures, which have been of great recent interest in motor control, especially the pedunculopontine nucleus

(PPN) of the mesencephalic locomotor region (MLR). Therefore, the activation of saccular afferents is indirectly activating many motor control systems.

Saccular afferents travel in the inferior vestibular nerve, along with afferents from the posterior semicircular canal. Saccular afferent fibres branch and send a thinner collateral branch to the cerebellum, with the thicker afferent branch projecting to the vestibular nuclei. Saccular fibres terminate in the lateral and inferior vestibular nuclei. Anatomical evidence shows that saccular afferents project both to vestibular nuclei and the cerebellum, specifically to the anterior midline structures, including the uvula [7–9] and deep cerebellar nuclei [10] (see Figure 1).

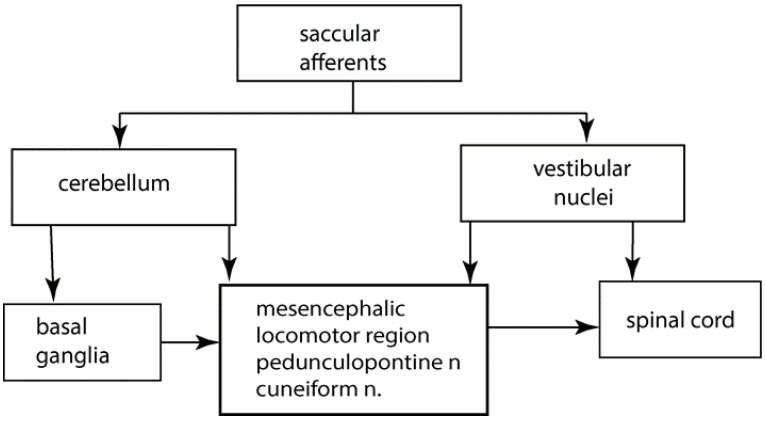

Figure 1. A greatly simplified schematic overview of some of the major structures involved in the control of gait and postural stability.

6. The Role of the Cerebellum in Posture and Gait

There is extensive evidence of the crucial role of the cerebellum in the control of balance and locomotion (see, e.g., [11]). Cerebellar circuits connect with many brain and spinal cord nuclei. Cerebellar activity is required for motor behaviours ranging from coordination to posture and balance and gait. This is clear from the deficits in these behaviours in human patients with localized cerebellar damage [11]. Projections from the deep cerebellar nuclei influence basal ganglia activity by afferents that project to the thalamic nuclei, which project to the basal ganglia primarily the striatum [11]. Dijkstra reported the cerebellum is involved in postural control as shown by image analysis [12]. Mori et al. [13] demonstrated in cats that stimulation of the midline cerebellar locomotor region (the fastigial nucleus) can independently induce locomotion. Neuroimaging suggests a similar region exists in humans. Studies with mental imagery of gait or foot pedals showed that active stepping during fMRI causes focal increases in the fastigial nucleus of the cerebellum and cerebellar vermis [12]. The cuneiform nucleus also appears to be of interest.

All the studies suggested the cerebellum is implicated in all aspects of the pathophysiology of Parkinson's disease. One of the most characteristic signs of cerebellar damage is walking ataxia. Anterior cerebellar damage (to the so-called vestibulo cerebellum) leads to increased postural sway [11,14,15]. Cerebellar damage is also associated with hypermetric postural responses to surface displacements and impaired ability to learn responses to predictable perturbations or step initiation [16]. Some of these deficits that are described for patients with cerebellar loss appear to be similar to those described for patients with bilateral vestibular loss.

It is not known exactly how the cerebellum normally contributes to walking although recent work suggests that it plays a role in the generation of appropriate patterns of limb movements, dynamic regulation of balance, and adaptation of posture and locomotion through practice [17,18]. Patients with cerebellar loss show excessive or diminished responses to perturbations, with poor control of equilibrium during motion and abnormal

oscillation of the trunk. Gait ataxia is often described with distinctive features, including variable foot placement, irregular foot trajectories, wide base of support, a veering path of movement, and abnormal inter-joint coordination [11]. These are similar to the gait disturbances of patients with BVD [1].

7. Cerebellar Locomotor Region

The cerebellar locomotor region is in the midline of the cerebellum [19], and as noted above, it is this region where saccular afferents terminate. Neurons from the central cerebellum project back to the vestibular nuclei [4,7–10,20–22]. Physiological studies from animals suggest that cerebellar control of posture, equilibrium, and locomotion are tightly controlled and localised in the medial zone. There are cerebellar projections to vestibular and reticular nuclei and also to the thalamus. Thus, the medial cerebellar zone can integrate spinal and vestibular inputs and influence motor pathways for walking.

8. Cerebellum to Basal Ganglia

Manto elaborated on the short latency connections between the cerebellum and the basal ganglia [23–25]. These connections may explain the cerebellar involvement in disorders commonly associated with basal ganglia dysfunction, for example, Parkinson's disease. Recently, cerebellar neurons are being stimulated in human patients by brain stimulation techniques, including transcranial magnetic stimulation and transcranial direct current stimulation, to alleviate disturbances of motor control [13,26–29]. In an animal model, Miterko reported that neuromodulation of the cerebellum rescues movement in a mouse model of ataxia [26].

9. The Pedunculopontine Nucleus (PPN)

The mesencephalic locomotor region (MLR) consists of the pedunculopontine tegmental nucleus (PPN), the cuneiform nucleus, and the sub-cuneiform nucleus. It receives input from cerebellar nuclei and basal ganglia [30–32]. Imaging of the PPN during imagined walking shows that it is involved in control of postural stability [33–35], and electrical stimulation of PPN is a target for treating locomotion deficits [36].

10. Vestibular Nuclei to Basal Ganglia

The most convincing evidence that there may be disynaptic projections from the vestibular nuclei to the basal ganglia was published by Lai et al. [37]. Using neuronal tracers, they reported that projections from the medial vestibular nucleus to the parafascicular nucleus (PFN) of the thalamus synapse on neurons that project to the dorsolateral putamen of the striatum. This anatomical evidence suggested the possibility of a disynaptic pathway between the vestibular nuclei and the striatum albeit from the medial vestibular nucleus rather than the inferior and lateral vestibular nuclei, where saccular afferents are known to terminate. The PFN is also strongly connected to the PPN [38]. Although there have been a small number of electrophysiological studies investigating whether electrical stimulation of the peripheral vestibular system can evoke field potentials and single-unit activity in the striatum (see [38,39] for reviews), none of these can exclude the possibility that any responses arise via the cerebellum, and none of them are involved selective saccular stimulation. Nonetheless, there are many regions of the striatum that have not been explored, such the striatal tail, which is known to receive substantial visual and auditory sensory input and may also receive vestibular input (see [40] for a review). Whether saccular information is transmitted to this multisensory integration centre remains to be determined but seems very likely.

11. Gait

Normal gait is a complex process that involves concomitant balance and locomotion processes. A hierarchy of supraspinal regions send signals to the central pattern generators (CPGs) of the spinal cord [35,41]. Supraspinal regions modify stereotyped locomotion

in certain situations, such as initiating gait, turning, stopping, and avoiding obstacles. The locomotor network involves CPGs, mesencephalic locomotor region, the cerebellar locomotor areas, subthalamic locomotor region, and various cortical areas, including frontal and parietal supplementary motor and motor areas [35].

12. Contribution of the Otoliths to Spatial Awareness

Part of any qualitative improvement in BVD patients following ES may be attributable to its effects on higher centres of the brain concerned with the cognitive processing of vestibular information, especially spatial awareness and memory ("spatial cognition"). The effects of inferior vestibular nerve ES on spatial cognition have not been investigated quantitatively in humans; therefore, the only evidence available is from rodents.

There has been increasing evidence that the otoliths, independently of the semi-circular canals, may be important for spatial cognition. It is difficult to surgically manipulate the saccule in animal models without affecting the other vestibular sensors. Therefore, the only evidence available is restricted to mutant mice, which do not generate otoconia (e.g., *tilted Het* and *Otop* mice; see [39] for a review). Inevitably, this means that the mice are devoid of both utricular and saccular function rather than just saccular function. However, due to its role in the perception of gravity, the saccule might be expected to be particularly important in providing a gravitational reference frame for other sensory information. A recent study in rats reported that selective electrical stimulation of the saccule resulted in widespread activation of the bilateral hippocampus, a structure that is important for spatial memory [42]. Quantitative gait analysis has not been performed on these otolith-deficient mouse models as yet; however, they do exhibit substantial deficits on the rotarod, in exploration and in performance in Y maze, radial arm maze, elevated plus maze, and place recognition tasks (see [39] for a review). These results suggest that loss of otolithic function, including saccular function, results in deficits in spatial cognition. Studies of the first 10 days of development indicate that *Het* mice develop abnormally, exhibiting abnormal responses in the righting reflex, cliff drop aversion, and negative geotaxis tests [43]. There is also evidence that thalamic head direction cells and hippocampal place cells function abnormally in otolith-deficient mice (see [39] for a review). Taken together, these studies suggest that the saccule is important for spatial awareness and orientation and that saccular ES may have a beneficial effect in BVD patients.

13. Conclusions

This review has shown the widespread direct and indirect projection of saccular afferent neural activity to brain structures controlling postural stability and gait performance. In patients with BVD, this neural activity will be reduced or absent, and we suggest that the constant ES is activating primary saccular afferents and hence is substituting for the absent saccular afferent neural activity, therefore acting to improve postural stability and gait.

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History Taking in Non-Acute Vestibular Symptoms: A 4-Step Approach

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Abstract: History taking is crucial in the diagnostic process for vestibular disorders. To facilitate the process, systems such as TiTrATE, SO STONED, and DISCOHAT have been used to describe the different paradigms; together, they address the most important aspects of history taking, viz. time course, triggers, and accompanying symptoms. However, multiple (vestibular) disorders may co-occur in the same patient. This complicates history taking, since the time course, triggers, and accompanying symptoms can vary, depending on the disorder. History taking can, therefore, be improved by addressing the important aspects of each co-occurring vestibular disorder separately. The aim of this document is to describe a 4-step approach for improving history taking in patients with non-acute vestibular symptoms, by guiding the clinician and the patient through the history taking process. It involves a systematic approach that explicitly identifies all co-occurring vestibular disorders in the same patient, and which addresses each of these vestibular disorders separately. The four steps are: (1) describing any attack(s) of vertigo and/or dizziness; (2) describing any chronic vestibular symptoms; (3) screening for functional, psychological, and psychiatric co-morbidity; (4) establishing a comprehensive diagnosis, including all possible co-occurring (vestibular) disorders. In addition, pearls and pitfalls will be discussed separately for each step.

Keywords: medical history taking; dizziness; vertigo; vestibular diseases; Menière's disease; benign paroxysmal positional vertigo; migraine disorders; vestibular neuronitis

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1. Introduction

History taking is a crucial aspect in the diagnostic process for vestibular disorders [1], given that symptomatology plays a key role in the diagnostic criteria [2–13]. If history taking is done properly, in combination with physical examination, a diagnosis can be made in many cases, even without additional laboratory tests or imaging. However, in many healthcare settings, history taking tends to be poor, and clinicians might be over-reliant on additional testing, resulting in misdiagnoses [14] and ineffective treatments. It is, therefore, imperative to improve the quality of history taking. To this end, various approaches have been proposed, e.g., asking key questions [15,16], focusing on time course and triggers (TiTrATE paradigm, [17]), on key dimensions (SO STONED paradigm, [18]), and on key symptoms (DISCOHAT paradigm, [19]).

The traditional, widespread approach in history taking is to focus on the quality of the symptoms, e.g., vertigo, presyncope, disequilibrium, or non-specific dizziness. Unfortunately, this approach has proved unreliable, for a variety of reasons: terms like 'vertigo' and 'dizziness' have different meanings to different people and in different languages; patients often have problems defining their symptoms; symptom descriptions might change over time; and the quality of the symptoms has little discriminative value [1,14,20,21]. This was why the TiTrATE (timing, triggers and targeted examination) paradigm was proposed, to emphasize the importance of the time course and triggers of symptoms in history taking. Focusing on the time course enables symptoms to be categorized into three major syndromes: acute vestibular syndrome, episodic vestibular syndrome, and chronic

vestibular syndrome (Table 1) [17]. These syndromes can be subdivided into triggered or untriggered syndromes. For example, benign paroxysmal positional vertigo (BPPV) is an episodic vestibular syndrome triggered by head motion, while, Menière's disease is an episodic vestibular syndrome without any trigger. TiTrATE also gives a quick overview of less urgent and more urgent differential diagnoses in one of the three syndromes (e.g., episodic vestibular syndrome, triggered: this might include BPPV (less urgent) or central positioning nystagmus due to a posterior fossa tumor (more urgent)) [17].

Table 1. Vestibular syndromes categorized by time course and triggers. Modified and updated from [22].

Time Course	Trigger	Diagnosis: Less Urgent	Diagnosis: More Urgent
Acute vestibular syndrome	Spontaneous	Acute unilateral vestibulopathy/ vestibular neuritis Labyrinthitis	Stroke or hemorrhage Brainstem encephalitis Multiple sclerosis * Other internal/neuro
	Postexposure	Labyrinthine concussion	Skull base fracture Postoperative * Vertebral dissection Drugs (e.g., alcohol, anticonvulsants) Carbon monoxide intoxication Wernicke's
Episodic vestibular syndrome	Spontaneous	Menière's Disease Vestibular Migraine Vestibular Paroxysmia Vasovagal Panic *	Cardiac arrhythmia TIA (posterior circulation) Hypoglycemia *
	Trigger	Benign Paroxysmal Positional Vertigo Orthostatic hypotension Third mobile window syndromes * Superior canal dehiscence syndrome	Central positional nystagmus Vertebral artery compression/ occlusion syndrome
Chronic vestibular syndrome	Triggered or spontaneous	e.g., Vestibular hypofunction, Cerebellar dizziness, Functional dizziness	

*: can be less urgent or more urgent, depending on the case.

However, many vestibular disorders can present with a variety of accompanying otological and/or neurological symptoms, which can help in differentiating between disorders. For example, the presence of migrainous features during a vertigo attack might point to vestibular migraine [6], while the presence of fluctuating aural symptoms might point to Menière's disease [7] and the presence of dysarthria or diplopia to a stroke [23]. Good history taking, therefore, goes beyond mere time course and triggers. The SO STONED paradigm was developed as a complementary tool, with a view to systematically acquiring eight key dimensions during history taking (since when, how often, symptom quality, triggers, otological symptoms, neurological symptoms, evolution, duration) [18]. In relation to the TiTrATE paradigm, the dimensions 'how often' and 'triggers' should be emphasized, since these are exactly the same as the 'time course and triggers' mentioned above; they too enable symptoms to be categorized into acute, episodic, or chronic vestibular syndromes. In addition, the DISCOHAT paradigm is specifically able to capture the wide spectrum of symptoms related to vestibulopathy (darkness worsens symptoms, imbalance, supermarket effect, cognitive complaints, oscillopsia, head movements worsen symptoms, autonomic complaints, tiredness) [19].

Combining the emphasis on time course and triggers (TiTrATE) with a systematic evaluation of all relevant dimensions (SO STONED) and specific symptoms (DISCOHAT) enhances the quality of history taking. Nevertheless, there remains an additional major challenge in almost half of all patients with vestibular disorders: the existence of co-occurring disorders; either primary or secondary [24,25]. The fact is that acute, episodic,

and chronic vestibular disorders can co-occur, as can two or more disorders within the same syndrome type. Furthermore, functional, psychological, and psychiatric co-morbidity can, depending on the setting, be found in almost half of all patients as a primary diagnosis; or as a secondary diagnosis, which is often triggered by an acute or episodic vestibular event [8,25,26]. These factors complicate the use of the TiTrATE, SO STONED, and DISCO-HAT paradigms, since co-occurring vestibular disorders might result in multiple different answers being given to the same question during history taking. A simple question about triggers might elicit answers (from the same patient) that would point to different disorders: e.g., 'suddenly' and 'when I move my head very fast' and 'when I visit busy places'. As mentioned above, patients often struggle to describe (and to differentiate between) the different types of dizziness, and spinning and non-spinning vertigo [14], and tend to regard all their symptoms as stemming from 'the same problem'. The clinician has to categorize all these symptoms into one or more vestibular syndrome and disorder.

The aim of this article is to propose a systematic approach to history taking in patients presenting with non-acute vestibular symptoms, consisting of four steps. It sets out to identify all vestibular disorders occurring at the same time in the same patient (e.g., BPPV and co-occurring persistent postural perceptual dizziness), by guiding the clinician and the patient through the process of history taking. This is important, since detecting all the disorders present in a single patient might have therapeutic implications, because it requires a multi-modal response (e.g., BPPV is treated differently from persistent postural perceptual dizziness) [27].

2. Overview of the 4-Step Approach

Figure 1 illustrates the 4-step approach to history taking.

- The first step is to investigate whether there are, or have been, any attacks of vertigo and/or dizziness. If so, the attacks are described.
- The second step involves exploring any chronic vestibular symptoms.
- The third step screens for functional, psychological, and/or psychiatric co-morbidity.
- During the fourth step, the diagnosis is established by explicitly taking into account the possibility of multiple co-occurring vestibular disorders.

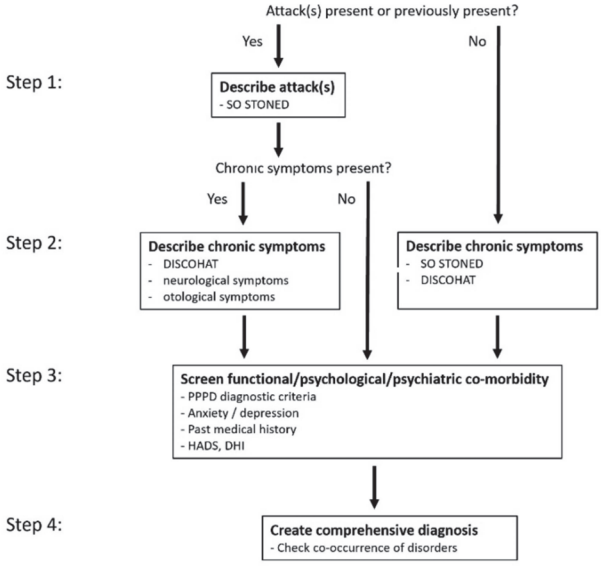

Figure 1. The 4-step approach to history taking in patients with non-acute vestibular symptoms.

Each step investigates different aspects of vestibular disorders, while focusing on 'one aspect at a time'. It explicitly screens for acute and episodic vestibular syndromes (step 1); chronic vestibular syndromes (step 2); and functional, psychological, and psychiatric co-morbidities (step 3). The aim is to identify all vestibular disorders occurring at the same time in the same patient, in order to create a comprehensive diagnosis (step 4). The 'O' and 'T' of 'SO STONED' are underlined, to emphasize the importance of paying specific attention to the aspects 'how Often' (=time course) and 'Triggers' of symptoms. SO STONED = acronym of 'Since when, how Often, Symptom quality, Triggers, Otological symptoms, Neurological symptoms, Evolution, Duration'; DISCOHAT = acronym of 'Darkness worsens symptoms, Imbalance, Supermarket effect, Cognitive complaints, Oscillopsia, Head movements worsen symptoms, Autonomic complaints, Tiredness'; PPPD = Persistent Postural Perceptual Dizziness; HADS = Hospital Anxiety and Depression Scale; DHI = Dizziness Handicap Inventory.

Key Points of the 4-Step Approach

The clinician and the patient are guided through the four steps, in order to systematically assess the (vestibular) symptoms.

Each step investigates different aspects of vestibular disorders: (1) attacks of vertigo and/or dizziness (=acute and/or episodic vestibular syndromes); (2) chronic vestibular symptoms (=chronic vestibular syndromes); (3) functional/psychological/psychiatric co-morbidity; (4) co-occurrence of various vestibular disorders. This systematic approach increases the chance of detecting the presence of multiple disorders, each with their own symptom profile (especially when practiced by less experienced clinicians, such as residents).

History taking focuses on 'one aspect at a time': either attacks, or chronic symptoms, or functional/psychological/psychiatric symptoms. This 'forces' the patient to discuss the relevant dimensions of that aspect alone, leading to a more accurate symptom description of that specific aspect. For example, when explicitly discussing vestibular migraine attacks, a patient is less likely to mention the unrelated tinnitus that is present only when lying in bed.

In the 4-step-approach, attacks of vertigo and/or dizziness are described first, even if they have already ceased. This is because describing the attacks might make it easier to understand the etiology. For example, a patient may initially report only the symptoms of vestibular hypofunction, but they may in fact be sequelae of recurrent attacks of vertigo that occurred previously, leading to bilateral vestibulopathy [28,29].

Steps two and three acknowledge that, for instance, the symptoms of uni- and bilateral vestibular hypofunction can be disabling [30–32] and that many patients with vestibular symptoms might suffer from functional/psychological/psychiatric co-morbidity [26].

3. Background, Pearls, and Pitfalls of the 4-Step Approach

3.1. Step 1: Describe Any Attack(s) of Vertigo and/or Dizziness

3.1.1. Background

First, investigate whether one or more vertigo and/or dizziness attacks are present or have occurred in the past. If so, describe them using the SO STONED paradigm, with the emphasis on how often symptoms appear (=time course) and what triggers them. As described above, the SO STONED dimensions are: since when, how often, symptom quality, triggers, otological symptoms, neurological symptoms, evolution, duration. Please remember: the quality of symptoms (vertigo, dizziness, disequilibrium, etc.) is too unspecific to serve as a basis for a reliable diagnosis [1,14]; e.g., the absence of vertigo does not rule out a peripheral vestibular disorder [33].

The main otological symptoms are hearing loss, tinnitus, aural pressure, sound or pressure induced vertigo, hyperacusis, and symptoms of bone-conduction hyperacusis (e.g., autophony; hearing one's eye movements) [13]. For neurological symptoms, special attention should be paid to migraine features and the 'deadly Ds' (dysarthria, diplopia, dysphagia, dysphonia, dysmetria, dysesthesia). In the acute setting (beyond the scope of

this article), be aware of sudden, severe, or sustained pain, especially in the posterior neck region [6,23].

3.1.2. Pearls and Pitfalls

Make sure the patient knows that the first questions will refer to the attack(s), and not to symptoms experienced during other circumstances. The patient must understand that the aim is to describe the attack(s) only.

It may be helpful to introduce each question with the words 'During an attack . . . .'. Some patients tend to forget that the questions during this first step refer only to the attack(s).

Where there are multiple attacks with (almost) the same features, try to discuss an 'average attack'. This can save time and avoids a comprehensive description of each and every attack. It also gives the patient the opportunity to mention that some symptoms are not always present (e.g., migraine features do not have to be present with each attack) [6] and that attacks might be of different durations, e.g., minimum 5 min to maximum 5 h.

Use a broad range of questions to investigate the triggers, since not all patients will know what is meant by triggers. If the patient cannot determine a trigger, other questions might help, e.g., avoidance of certain situations. Please note: there is a difference between a trigger and something that worsens an existing symptom. For example, acute unilateral vestibulopathy/vestibular neuritis is untriggered, but head movements can worsen the existing symptoms.

A trigger is defined as a factor that directly initiates the attacks. Patients with, say, vestibular migraine or Menière's disease might mention 'periods of stress' or 'change of weather conditions' as triggers. This is not fully correct. Although some of these factors are associated with attacks, they do not seem to directly initiate the attacks and should not be regarded as triggers [34].

Depending on time course and triggers, different types of attacks can be present in the same patient (e.g., BPPV after an acute unilateral vestibulopathy/vestibular neuritis). In these cases, the SO STONED paradigm is applied separately to each type of attack.

The absence of reported accompanying symptoms, such as hearing loss, tinnitus, or aural pressure, does not rule out Menière's disease; during an attack, patients might feel too sick to pay attention to symptoms other than vertigo, nausea, and vomiting.

The presence of accompanying otological and neurological symptoms during an attack does not necessarily mean that these symptoms were initiated or modulated by the attack. Please clarify the relationship between these symptoms (which may be pre-existing) and the attack(s). For example, a BPPV patient might suffer from chronic tinnitus that is not related to BPPV attacks, while a patient with Menière's disease can have chronic tinnitus that might change in relation to an attack of Menière's disease.

A history of migraine can reliably be ascertained by systematically covering all the migraine criteria [6]; not simply by asking 'Do you have migraine?' After all, patients who report having migraine might not actually have migraine, and patients who deny a history of migraine might actually have it.

The duration of symptoms should be the duration of the 'most severe symptoms'. Some patients tend to describe the full time period until they feel (almost) recovered. However, this does not always equate to the duration of each attack. For example, a one-week episode of vertigo might refer to: one week of multiple short attacks, such as BPPV; a vertigo attack lasting several hours with residual symptoms of disequilibrium for one week, such as Menière's disease or vestibular migraine; a vertigo attack lasting one week, such as acute unilateral vestibulopathy/vestibular neuritis.

Presenting different possible symptom scenarios could help patients who have difficulty describing their symptoms. For example, patients with BPPV might overestimate the duration of their vertigo, due to anxiety. In such cases, it can help to present the following two scenarios: 'After rolling over in bed, does the severe spinning dizziness last for literally a couple of minutes?', and 'After rolling over in bed, does the severe spinning dizziness last for less than a minute and then you still feel dizzy for a couple of minutes?'.

3.2. Step 2: Describe Any Chronic Vestibular Symptoms

3.2.1. Background

The second step covers patients with and without attacks of vertigo and/or dizziness.

For patients with attacks, these chronic symptoms are not related to the attacks themselves, but occur in between attacks. Therefore, tell the patient that this part of history taking focuses on all the symptoms that occur in between attacks. The DISCOHAT acronym can be used to evaluate chronic vestibular symptoms, especially those related to uni- or bilateral vestibulopathy. As described above, these symptoms are: darkness worsens symptoms, imbalance, supermarket effect (=visually induced dizziness: sensitivity to moving visual stimuli or complex patterns, which is part of PPPD (see below) [8]), cognitive complaints, oscillopsia, head movements worsen symptoms, autonomic complaints, and tiredness [19]. Additionally, screen for otological and neurological symptoms unrelated to the attacks.

For patients without any attacks of vertigo and/or dizziness, the SO STONED paradigm and the DISCOHAT acronyms can be used in tandem to describe the chronic symptoms. In this group of patients, the time course and triggers are important (e.g., unsteadiness when walking or standing, such as cerebellar ataxia or bilateral vestibulopathy) [9], as are the otological and neurological symptoms (including the 'deadly Ds').

3.2.2. Pearls and Pitfalls

History taking can be challenging, in that certain symptoms are difficult to identify with just one or two questions (e.g., visual auras, visually induced dizziness, oscillopsia). Where in doubt as to whether the patient has understood the concept correctly, consider asking the patient to describe the symptom in a specific situation. For visual auras, for example, the patient might describe eye floaters rather than a visual aura.

3.3. Step 3: Screen for Functional, Psychological, and Psychiatric Co-Morbidity

3.3.1. Background

In this third step, history taking is crucial, since no additional testing is available, which is pathognomonic of these disorders [8]. During this third step, pay special attention to functional dizziness, for instance persistent postural perceptual dizziness (PPPD) and to signs of anxiety and depression, or a medical history of functional, psychological, and psychiatric disorders.

PPPD is an example of a functional disorder, which means it arises from a change in the mode of action of the brain; this is different from a psychiatric disorder. Symptoms include persistent dizziness, unsteadiness, and non-spinning vertigo exacerbated by body movements or perceived movements, such as visually complex moving stimuli (=visually induced dizziness) [8].

Diagnostic keys of functional, psychological, and psychiatric co-morbidity include the following: symptoms congruent with the diagnostic criteria of PPPD [8]; chronic vestibular symptoms lasting for months or longer; fear of falls without falling; decrease of symptoms during mental distraction or alcohol intake; dizziness combined with disabling symptoms of hypersensitivity (e.g., disabling tinnitus and/or hyperacusis); disproportionate anxiety; situational triggers and avoidance behavior; symptoms of depression; chronic unsteadiness and dizziness after riding in a vehicle; a medical history of functional, psychological, and psychiatric disorders (e.g., anxiety disorder, depression, or somatic symptom disorders such as fibromyalgia) [35]. History taking in combination with physical examination and/or laboratory testing may reveal a dissociation between objective test results and the severity of subjective symptoms. Although abnormalities in vestibular testing do not correlate well with reported symptoms [36,37], it is possible to build a general 'frame of reference' to understand which symptoms (and their associated severity) might match which vestibular testing outcomes. For example, an objectively measured unilateral vestibular hypofunction occurring six months after an acute unilateral vestibulopathy/vestibular neuritis might generate some DISCOHAT symptoms, but it would not prevent a patient

returning to work, unless the job is physically highly demanding (e.g., professional sport) or there is a statutory ban (e.g., an airline pilot). This discrepancy between objective findings and subjective symptoms is often explained by a functional, psychological, and/or psychiatric co-morbidity.

3.3.2. Pearls and Pitfalls

Additionally, question patients about their anxiety and balance during physical examination and laboratory testing. They may report fear of falling, imbalance, or general anxiety when undergoing tests, something that will not be reflected in objective test results.

Questionnaires such as the hospital anxiety and depression scale and the dizziness handicap inventory can provide useful insights into the possibility of anxiety and depression as co-morbidities, on the one hand, and the impact of dizziness on daily life, on the other [38,39]. It can be useful to run the questionnaire process prior to consultation, to give the clinician advance knowledge of these aspects and to facilitate history taking.

3.4. Step 4: Create a Comprehensive Diagnosis

3.4.1. Background

In this final step, the diagnosis is established, explicitly taking into account the possibility of multiple co-occurring vestibular disorders. It includes evaluating all three previous steps, i.e., the presence of vertigo and/or dizziness attacks, chronic vestibular symptoms, and functional/psychological/psychiatric symptoms. Each step of this process evaluates whether an additional disorder should be added to the diagnosis. Figure 2 illustrates how a comprehensive diagnosis is arrived at by categorizing symptoms arising from all three previous steps into acute, episodic, and/or chronic vestibular disorders, and/or functional/psychological/psychiatric co-morbidity.

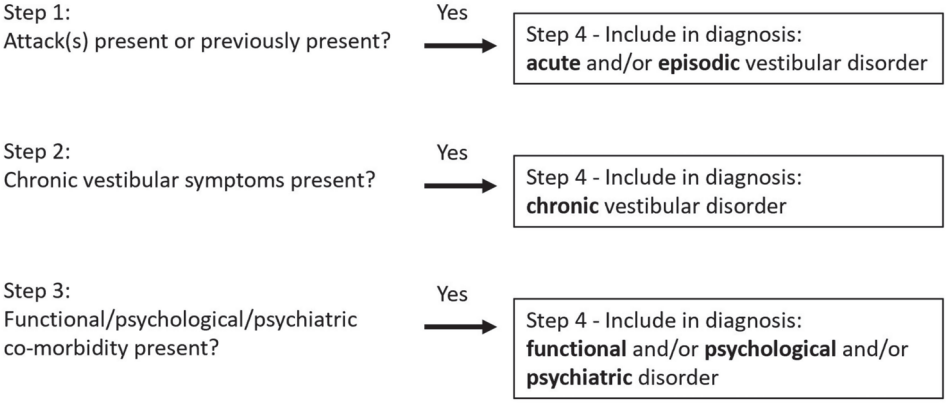

Figure 2. Using the 4-step approach to make a comprehensive diagnosis. Steps 1 to 3 investigate whether specific disorders might be added to the diagnosis. Finally, all co-occurring disorders are included in the diagnosis (step 4). Note: since the 4-step approach is aimed at patients presenting with non-acute vestibular symptoms, the 'acute vestibular disorder' mainly refers to a previous acute event (e.g., an acute unilateral vestibulopathy/vestibular neuritis that occurred five months previously).

Significantly, this final step may result in three categories of disorders, all of which can occur at the same time in the same patient: (1) acute and/or episodic vestibular disorder(s); (2) chronic vestibular disorder(s); (3) functional/psychological/psychiatric co-morbidity. Since these disorders occur together, each category has its own list of differential diagnoses, with varying levels of urgency. For example, the differential diagnoses of episodic vestibular disorders include Menière's disease, vestibular migraine, TIA, and arrhythmia, while the differential diagnoses of chronic vestibular disorders include vestibular hypofunction

and cerebellar dizziness. PPPD is a chronic functional vestibular disorder which overlaps between chronic vestibular syndrome(s) and functional co-morbidity.

Here is a practical example of the 4-step approach:

Step 1:

For two years, symptoms of vertigo and dizziness, including multiple spontaneous attacks of vertigo.

The average attack features:

- Sudden sensation of vertigo
- Triggers: none
- Hearing loss on the left, aural pressure, and tinnitus (high-pitched sound)
- No headache, no photo- or phonophobia, no visual auras, no migraines
- No other neurological symptoms (including the 'deadly Ds')
- Duration: minimum 5 min, maximum 2 h
- Frequency: 2–5 times each month, frequency increased the last couple of months

Step 2:

Chronic symptoms between attacks:

- Darkness does not worsen symptoms; imbalance; supermarket effect (=visually induced dizziness); no problems with concentration or memory; no oscillopsia; fast head movements worsen symptoms; no autonomic complaints, not very tired
- Persistent hearing loss and tinnitus on the left ear, no neurological symptoms

Step 3:

- Significant distress resulting from chronic 'fuzziness' and the supermarket effect (=visually induced dizziness); no avoidance behavior or symptoms of anxiety or depression; no previous history of functional/psychological/psychiatric co-morbidity

Step 4:

- Possible diagnosis based on history taking only: Menière's disease on the left ear + vestibular hypofunction + PPPD

The four steps are explicitly represented in the example above:

1. Description of the attacks: symptoms might indicate Menière's disease on the left ear.
2. Description of chronic symptoms: imbalance and stronger symptoms in relation to fast head movements might indicate vestibular hypofunction; visually induced dizziness might indicate PPPD.
3. Screening for functional, psychological, and psychiatric co-morbidity: apart from significant distress resulting from chronic 'fuzziness' and visually induced dizziness, which indicate PPPD, no indications of other functional/psychological/psychiatric co-morbidity.
4. Creating a comprehensive diagnosis: Menière's disease, vestibular hypofunction, and PPPD all feature in the final diagnosis.

3.4.2. Pearls and Pitfalls

Though the 4-step approach is useful in guiding the clinician towards a comprehensive diagnosis, this can only be a provisional diagnosis. Each disorder has its own variably urgent differential diagnoses. Physical examination and additional testing (laboratory tests, imaging, etc.) might be necessary to arrive at the final diagnosis.

The Bárány Society's Committee for the Classification of Vestibular Disorders has defined consensus-based diagnostic criteria for most of the vestibular disorders [2–13]. These can be used to classify the reported symptomatology and to arrive at the proper diagnosis.

3.5. Other Relevant Questions

The 4-step approach focuses on vestibular disorders. However, other general aspects of history taking retain their importance. These aspects include use of medication

and intoxicants (e.g., gentamicin, alcohol); other medical conditions and surgical procedures (e.g., auto-immune disorders, neurological disorders, ear surgery); family history (e.g., migraine, Menière's disease [40]). Menière's disease is often over-diagnosed [41]. A positive family history of Menière's disease might not directly implicate Menière's disease in the current patient; therefore, consider other (episodic) vestibular disorders, such as vestibular migraine.

4. First Experiences and Final Remarks

The 4-step approach to making a comprehensive diagnosis by guiding the clinician and patient through the process of history taking might at first seem like an unreasonably time-consuming process. The fact is, however, that history taking is a crucial aspect of the diagnostic process [1]. Investing time here might save time in the end, since it helps to establish the right (differential) diagnosis from the beginning of the process. History taking is a skill that can be trained and refined, much like surgery. These four steps require extensive training, but they will reduce the time needed to reach a diagnosis and increase efficiency. On completion of the requisite training, history taking with a 'challenging' patient in a tertiary referral clinic takes around 10–15 min. In secondary care centers, the time needed can be less for the majority of patients. The 4-step approach is, because of the time factor, less suited to patients presenting with acute vestibular symptoms.

The 4-step approach has been in use at a tertiary referral center in the Netherlands (Maastricht UMC+) for more than five years and has become part of the diagnostic process in other teaching hospitals. The initial experience is that more co-occurring disorders are being detected and the training of clinicians (e.g., residents) is improving under the 4-step systematic guidance. Structured discussion of (difficult) cases is on the increase, with the four steps featuring as smart phrases in hospital digital information systems.

A prospective randomized-controlled study might further validate the 4-step approach. This could, for example, comprise three comparable groups of residents (same specialty, same years of experience, etc.). Each group might then use a different paradigm for history taking in patients with vestibular symptoms: (1) the 4-step approach; (2) only SO STONED, with an emphasis on time course and triggers; (3) focusing on the quality of the symptoms. The diagnoses made by the residents could then be verified by experts in vestibular medicine. The main outcome measures might involve the correctness of the diagnoses made and the number of co-occurrent disorders detected.

Finally, the 4-step approach can be used globally to improve history taking in many vestibular patients, and it might also make people more aware of the importance of history taking and of the co-occurrence of vestibular disorders.

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Preceding Balance Disorders Affect Vestibular Function in Persistent Postural-Perceptual Dizziness

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Abstract: Persistent postural-perceptual dizziness (PPPD) is induced by preceding conditions that cause balance disorders. To investigate the association between vestibular function and preceding balance disorders in PPPD patients, a retrospective chart review was performed. Vestibular function in 55 PPPD patients was measured using the caloric test, cervical vestibular evoked myogenic potential testing to air-conducted sound (ACS cVEMP), ocular vestibular evoked myogenic potential testing to bone-conducted vibration (BCV oVEMP), and video head impulse testing (vHIT). Patients were classified according to the type of preceding balance disorder. The age-stratified Cochran–Mantel–Haenszel (CMH) test and the exact test for the common odds ratio were conducted to evaluate the association between preceding n $\geq$ 4 balance disorders and present peripheral vestibular dysfunction. PPPD patients with preceding vestibular neuritis presented a significant positive association with abnormal caloric responses (p = 0.013), while those with preceding benign paroxysmal positional vertigo (BPPV) had significantly lower rates of abnormal BCV oVEMP (p = 0.003). Furthermore, patients with preceding vestibular neuritis showed lateral semicircular canal dysfunction, while those with preceding BPPV presented normal utricular functions. These results present the influence of preceding balance disorders on the vestibular function in PPPD.

Keywords: dizziness; vestibular diseases; caloric tests; vestibular evoked myogenic potentials; persistent postural-perceptual dizziness; video head impulse test

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1. Introduction

Persistent Postural-Perceptual Dizziness (PPPD) is a newly proposed clinical condition which presents a long-lasting sense of dizziness, defined by the Bárány Society in 2017 and included in the International Classification of Diseases by the World Health Organization in 2018 [1]. In PPPD, patients experience non-vertiginous dizziness for more than three months after a preceding balance disorder. The long-lasting sense of dizziness, which cannot be fully explained by preceding or comorbid balance disorders, is exacerbated by upright posture, active or passive movement, and exposure to moving or complex visual stimuli [1–3].

PPPD is the most common cause of chronic dizziness, which accounts for 12–19% of all dizziness patients [4,5]. In addition, PPPD-like chronic dizziness is reported to occur in approximately 25% of patients despite adequate compensation for or recovery from preceding acute vestibular disorders [6]. The most common balance disorders preceding PPPD are peripheral and central vestibular diseases such as BPPV or vestibular neuritis (25–30%), followed by attacks of vestibular migraine, psychological distress (panic attacks or anxiety), concussion or whiplash injuries, autonomic disorders, and a variety of other disorders [1,7,8].

Dizziness in PPPD persists even after the preceding balance disorder has resolved. Although there are no specific laboratory tests for PPPD, the balance function in PPPD

patients may be influenced by a variety of different preceding disorders, leading to complex vestibular test results. Thus, in this study, we have investigated the effect of preceding balance disorders on vestibular function in PPPD patients to deepen the current knowledge of PPPD.

2. Materials and Methods

2.1. Ethical Statement

This study was approved by the research ethics committee of the Graduate School of Medicine and Faculty of Medicine, University of Tokyo (2487). The study was conducted according to the Declaration of Helsinki.

2.2. Subject

A retrospective chart review on patients who were diagnosed with PPPD at the Department of Otolaryngology and Head and Neck Surgery, the University of Tokyo Hospital from 2017 to 2021 was conducted. PPPD was diagnosed using the criteria from the Committee for Classification of Vestibular Disorders of the Bárány Society [1]. Patient age, sex, and any preceding or comorbid balance disorders were recorded. Vestibular function tests included caloric testing, cervical vestibular evoked myogenic potential testing to air-conducted sound (ACS cVEMP), ocular vestibular evoked myogenic potential testing to bone-conducted vibration (BCV oVEMP), and video head impulse testing (vHIT). All tests were performed on the same day for each patient.

2.3. Caloric Test

Caloric testing was performed to clinically assess the function of the lateral semicircular canal (LSCC) and superior vestibular nerve [9]. Patients were asked to take a supine position in a dark room while closing their eyes. All eye movements were recorded using electronystagmography. A 20 s injection of 2 mL ice water (4 °C) into the external auditory canal was performed to induce nystagmus. "Canal paresis (CP) percentage >20%" or "maximum slow phase eye velocity <10°/s for both ears" was considered abnormal.

2.4. ACS cVEMP Testing

ACS cVEMP testing was performed to clinically assess the function of the saccule and inferior vestibular nerve [10,11]. The recording method of ACS cVEMP has been previously described [12]. In brief, surface electromyographic (EMG) electrodes were placed at the center of each sternocleidomastoid muscle (SCM) and the reference electrode was placed on the lateral end of the upper sternum in a symmetric position. During the recording, patients were asked to sit with good posture and rotate the neck to stretch the SCM. A Neuropack MEB-2306 (Nihon Kohden Co. Ltd., Tokyo, Japan) was used to record cVEMP. Acoustic stimuli consisted of air-conducted 500 Hz short tone-bursts (135 dB SPL, rise/ fall time 1 ms, plateau time 2 ms) and were presented through headphones at a stimulation rate of 5 Hz. The signals were amplified and bandpass filtered (20–2000 Hz). The analysis time was 100 ms (20 ms before and 80 ms after the stimulus). Recordings were performed twice for each ear to confirm reproducibility. The amplitude and latency of the first positive–negative peak (p13–n23) was calculated as the average of the two responses. The p13–n23 amplitude recorded by the ipsilateral side stimulation was used for analysis. Corrected amplitude (CA) was calculated as the p13–n23 amplitude divided by the measure of SCM contraction. The asymmetry ratio (AR) for cVEMPs (cVEMP AR) was calculated as $AR = 100 \times (CAu - CAa)/(CAu + CAa)$, where CAu represents the CA on the unaffected side and CAa represents the CA on the affected side. An irreproducible p13–n23 was considered to be an absent response. A value for cVEMP AR greater than the normal upper limit, which was set at 41.6, was considered to be a decreased response [13]. Absent cVEMP responses on both sides measured by SCM contraction were considered to be bilateral abnormal cVEMPs.

2.5. BCV oVEMP Testing

BCV oVEMP testing was performed to evaluate the function of the utricle and the superior vestibular nerve [14,15]. Recording methods for BCV oVEMPs have been previously described [12]. In brief, surface electrodes were placed on the skin 1 cm below (active) and 3 cm below (reference) the center of each lower eyelid. During the recording, patients were asked to sit and look upward about 30°. A Neuropack MEB-2306 was used to record oVEMPs. Bone-conducted stimuli consisted of 500 Hz tone-bursts (rise/fall time 1 ms, plateau time = 2 ms) and were delivered by a Type 4810 Mini-Shaker (Bruel and Kjaer, Naerum, Denmark) placed on the forehead on the midline (Fz), at a stimulation rate of 3 Hz. The driving voltage was adjusted to 8.0 V (peak to peak) to produce a peak force level of 128 dB re 1 mN. The signal was amplified and bandpass-filtered (0.5–500 Hz). The analysis time was 50 ms. Recordings were performed twice to confirm reproducibility. The amplitude and latency of the first negative–positive peak (n1–p1) was calculated as the average of the two responses. The n1–p1 amplitude recorded by the ipsilateral side stimulation was used for analysis. The asymmetry ratio for oVEMP (oVEMP AR) was used to evaluate the abnormality of the n1–p1 amplitude [16]. An irreproducible n1–p1 was considered to be an absent response. A value for oVEMP AR greater than the normal upper limit, which was set at 27.3, was considered to be a decreased response [17]. Absent oVEMP responses on both sides were considered to be bilateral abnormal oVEMPs.

2.6. vHIT

The vHIT was performed to assess the vestibulo-ocular reflex (VOR) in the three semicircular canal planes using an ICS Impulse (Otometrics, Taastrup, Denmark). Subjects were seated 1 m from a black fixation dot on a wall that served as the visual target. While the subject gazed at the fixation dot, the examiner briefly and unpredictably rotated the subject's head. The head rotations were made in the lateral, the left anterior-right posterior, and the right anterior-left posterior planes. VOR gains were analyzed based on the manufacturer's algorithms, using 175 samples out of a total of 250 samples obtained on each trial. Data from the onset of head motion and subsequent zero crossing of head velocity were used to measure the area under the curve (AUC) of head velocity. The value of VOR gain was calculated as (AUC of eye velocity)/(AUC of head velocity). A mean VOR gain of <0.7 for the vertical semicircular canal (VSCC) or <0.8 for the LSCC was considered to be abnormal function with vHIT [18].

2.7. Statistical Analysis

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute). Patient background factors were summarized by mean ± SD for continuous variables and by number and percentage constituent of patients for categorical variables. PPPD patients were classified according to the type of preceding balance disorder. A contingency table relating vestibular function tests and preceding balance disorder was created. Cochran–Mantel–Haenszel (CMH) tests stratified by age (≤40, 41–50, 51–60, 61–70, >70years) were performed to evaluate the association between preceding balance disorder with n ≥4 and the existence of peripheral vestibular dysfunction detected by caloric, ACS cVEMP, BCV oVEMP tests, and vHIT (bilaterally abnormal or unilaterally abnormal/normal) [19]. To complement the CMH test, which might possibly underestimate *p*-values due to the small number of patients, Zelen's common odds ratio test, which provides *p*-values from exact probability calculations while stratifying patients by age [20], was performed in addition. A p-value < 0.05 was considered as statistically significant. The presence of an association between the preceding balance disorder and peripheral vestibular dysfunction was defined as statistically significant results with both the CMH and Zelen's test.

3. Results

A total of 55 patients were diagnosed with PPPD. Of the 55 patients, 38 underwent all four vestibular function tests. Nine refused to take vHIT testing due to worsening of

dizziness with head motion. Three did not undergo vHIT because of neck pain after head injury or whiplash based on concerns that the test may worsen their symptoms. Five did not undergo vHIT for VSCCs, because of the exacerbation of dizziness by passive head rotation during vHIT for LSCCs. One patient received only the caloric and BCV oVEMP test because of a prior cervical spine surgery for congenital scoliosis.

Characteristics of the 55 PPPD patients are shown in Table 1. Average patient age was 51.5 ± 14.8, ranging from 18 to 84 years old. Eleven were males and forty-four were females. Benign paroxysmal positional vertigo (BPPV), Ménière's disease, head injury or whiplash, and vestibular neuritis was observed in eight, seven, six and four patients, respectively. In half of the cases with BPPV (four cases), the responsible semicircular canal could not be identified because the diagnosis was made at another hospital and the specific nystagmus had disappeared by the time the patient came to our institution. The other four cases consisted of two lateral and two posterior semicircular canal BPPV patients. Psychological stress, Ramsay Hunt syndrome, sudden sensorineural hearing loss, vertebrobasilar insufficiency, and delayed endolymphatic hydrops were present in two patient each. Cerebral hemorrhage, migraine, fever due to pyelonephritis and mal de debarquement were reported in one patient each. These preceding diseases were diagnosed at the clinic or hospital of origin. The remaining 16 patients developed PPPD after vertigo of unknown cause, among whom 11 had spontaneous and 5 had positional vertigo, respectively. These cases were not examined by an otolaryngologist when the preceding balance disorder had occurred before PPPD, or otherwise a detailed examination did not lead to a final diagnosis. The average duration of disease was 22.4 ± 36.2 months. Five patients had psychiatric disorders, all with depression, and an additional panic disorder and delusional disorder in one patient each. Five patients were taking sedatives or antidepressants, four of which contained benzodiazepines.

Table 1. Characteristics of 55 persistent postural-perceptual dizziness patients.

Preceding Diseases	n (%)	Age (Years), Mean ± SD	Sex, Female n (%)	Disease Duration (Months), mean ± SD	Psychiatric Comorbidities, n (%)	Use of Sedative Drugs, n (%)
All patients	55	51.5 ± 14.8	44 (80%)	22.4 ± 36.2	5 (10%)	5 (10%)
BPPV	8 (15%)	56.3 ± 18.4	6 (75%)	13 ± 19.2	1 (13%)	1 (13%)
Ménière's disease	7 (13%)	48.1 ± 11.3	5 (71%)	5.4 ± 3.6	1 (14%)	1 (14%)
Head injury/whiplash	6 (11%)	47.7 ± 21.6	6 (100%)	74.2 ± 83.6	1 (17%)	1 (17%)
Vestibular neuritis	4 (7%)	63.0 ± 10.4	4 (100%)	27.8 ± 31.9	1 (25%)	1 (25%)
Psychological stress	2 (4%)	25.0 ± 9.9	2 (100%)	8.0 ± 2.8		1 (50%)
Ramsay Hunt syndrome	2 (4%)	56.5 ± 16.3	2 (100%)	31.5 ± 40.3		
Sudden sensorineural hearing loss	2 (4%)	60.5 ± 6.4	1 (50%)	39.0 ± 12.7	1 (50%)	
Vertebrobasilar insufficiency	2 (4%)	68.0 ± 12.7	1 (50%)	5.5 ± 0.7		
Delayed endolymphatic hydrops	2 (4%)	53.0 ± 9.9	2 (100%)	3.0		
Cerebral hemorrhage	1 (2%)	60.0	0	48.0		
Migraine	1 (2%)	54.0	1 (100%)	15.0		
Fever due to pyelonephritis	1 (2%)	61.0	0	9.0		
Mal de debarquement	1 (2%)	72.0	1 (100%)	72.0		
Vertigo of unknown causes	16 (29%)	46.1 ± 9.2	13 (81%)	13.4 ± 12.4		
Spontaneous vertigo	11 (20%)	44.8 ± 9.3	9 (82%)	16.5 ± 14.0		
Positional vertigo	5 (9%)	48.8 ± 9.6	4 (80%)	6.8 ± 2.6		

PPPD = persistent postural-perceptual dizziness, BPPV = benign paroxysmal positional vertigo, SD = standard deviation. Disease duration indicates the duration of PPPD.

Abnormal caloric responses were observed in 20 patients (36%), with 19 patients presenting unilateral canal paralysis. Abnormal ACS cVEMPs were observed in 34 patients (62%). Among the 34 patients with abnormal ACS cVEMPs, 14, 14, and 6 patients presented bilateral absent responses, unilateral absent responses, and unilateral decreased responses, respectively. Abnormal BCV oVEMPs were observed in 22 patients (40%). Among the

22 patients with abnormal BCV oVEMPs, 3, 10, and 9 patients presented bilateral absent responses, unilateral absent responses, and unilateral decreased responses, respectively. Abnormal vHITs for the LSCC were observed in 8 of 43 patients tested (19%). Among the 8 patients, 2 and 6 patients presented bilateral and unilateral abnormal functions, respectively. Abnormal vHITs for the anterior semicircular canal (ASCC) were observed in 14 of 38 patients tested (37%). Among the 14 patients, 6 and 8 patients presented bilateral and unilateral abnormal results, respectively. Abnormal vHITs for the posterior semicircular canal (PSCC) were observed in 16 of 38 patients tested (42%). Among the 16 patients, 6 and 10 patients presented bilateral and unilateral abnormal outcomes, respectively (Table 2).

Table 2. Results of vestibular function tests in persistent postural-perceptual dizziness patients.

	Total	BPPV	Ménière's Disease	Head Injury /Whiplash	Vestibular Neuritis	Vertigo of Unknown Causes	
						Spontaneous Vertigo	Positional Vertigo
	n = 55	n = 8	n = 7	n = 6	n = 4	n = 11	n = 5
Caloric test							
Bilaterally abnormal	1 (2%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unilaterally abnormal	19 (35%)	4 (50%)	2 (29%)	1 (17%)	4 (100%)	1 (9%)	0 (0%)
Normal	35 (64%)	4 (50%)	4 (57%)	5 (83%)	0 (0%)	10 (91%)	5 (100%)
ACS cVEMPs							
Bilaterally abnormal	14 (26%)	1 (14%)	1 (14%)	0 (0%)	1 (25%)	5 (45%)	1 (20%)
Unilaterally abnormal	20 (37%)	2 (29%)	2 (29%)	3 (50%)	1 (25%)	3 (27%)	1 (20%)
Normal	20 (37%)	4 (57%)	4 (57%)	3 (50%)	2 (50%)	3 (27%)	3 (60%)
Unexamined	1	1					
BCV oVEMPs							
Bilaterally abnormal	3 (5%)	0 (0%)	1 (14%)	1 (17%)	0 (0%)	0 (0%)	1 (20%)
Unilaterally abnormal	19 (35%)	0 (0%)	2 (29%)	2 (33%)	3 (75%)	1 (9%)	2 (40%)
Normal	33 (60%)	8 (100%)	4 (57%)	3 (50%)	1 (25%)	10 (91%)	2 (40%)
vHIT (LSCC)							
Bilaterally abnormal	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
Unilaterally abnormal	6 (14%)	0 (0%)	1 (20%)	0 (0%)	2 (50%)	1 (13%)	0 (0%)
Normal	35 (81%)	7 (100%)	4 (80%)	4 (100%)	2 (50%)	6 (75%)	5 (100%)
Unexamined	12	1	2	2		3	
vHIT (ASCC)							
Bilaterally abnormal	6 (16%)	1 (17%)	1 (20%)	0 (0%)	1 (25%)	1 (14%)	1 (25%)
Unilaterally abnormal	8 (21%)	3 (50%)	1 (20%)	1 (33%)	1 (25%)	0 (0%)	1 (25%)
Normal	24 (63%)	2 (33%)	3 (60%)	2 (67%)	2 (50%)	6 (86%)	2 (50%)
Unexamined	17	2	2	3		4	1
vHIT (PSCC)							
Bilaterally abnormal	6 (16%)	1 (17%)	1 (20%)	0 (0%)	1 (25%)	1 (14%)	1 (25%)
Unilaterally abnormal	10 (26%)	3 (50%)	1 (20%)	1 (33%)	1 (25%)	0 (0%)	1 (25%)
Normal	22 (58%)	2 (33%)	3 (60%)	2 (67%)	2 (50%)	6 (86%)	2 (50%)
Unexamined	17	2	2	3		4	1

Variable distributions are reported as n (%).

Abbreviations: PPPD = persistent postural-perceptual dizziness, BPPV = benign paroxysmal positional vertigo, ACS cVEMP = cervical vestibular evoked myogenic potential testing to air-conducted sound, BCV oVEMP = ocular vestibular evoked myogenic potential testing to bone-conducted vibration, vHIT = video head impulse test, LSCC = lateral semicircular canal, ASCC = anterior semicircular canal, PSCC = posterior semicircular canal.

First, we investigated whether each of the preceding diseases with $n \geq 4$ (BPPV [$n = 8$], Ménière's disease [$n = 7$], head injury/whiplash [$n = 6$], vestibular neuritis [$n = 4$], spontaneous vertigo [$n = 11$], positional vertigo [$n = 5$]) had an association with abnormalities in caloric testing (Table 3). PPPD patients with preceding vestibular neuritis presented a significantly positive association with abnormal caloric responses in both the CMH test ($p = 0.013$, CMH risk ratio 3.12, 95% confidence interval [CI] 1.49–6.55) and the exact test for

the common odds ratio ($p = 0.048$, 95% CI, 1.47–∞), while other preceding diseases failed to show a significant result (Table 3).

Table 3. Cochran–Mantel–Haenszel test and exact test for the common odds ratio (Zelen) to examine the association between abnormalities in vestibular function tests and preceding disease in persistent postural-perceptual dizziness patients.

Variable	Risk Ratio (CMH)	95% CI (CMH)	*p*-Value (CMH)	95% CI (Zelen)	*p*-Value (Zelen)
Caloric test					
BPPV	1.14	0.46–2.84	0.778	0.20–7.73	1.000
Ménière's disease	1.55	0.57–4.26	0.400	0.24–18.46	0.679
Head injury/whiplash	0.31	0.05–2.04	0.144	0.00–2.39	0.313
Vestibular neuritis	3.12	1.49–6.55	0.013 *	1.47–∞	0.048 *
Spontaneous vertigo	0.28	0.04–1.85	0.113	0.00–1.84	0.232
Positional vertigo	0	-	0.151	0.00–2.19	0.379
ACS cVEMP					
BPPV	0.55	0.23–1.32	0.090	0.02–1.87	0.214
Ménière's disease	0.65	0.27–1.58	0.272	0.05–2.83	0.487
Head injury/whiplash	0.86	0.36–2.02	0.730	0.05–8.91	1.000
Vestibular neuritis	0.57	0.19–1.72	0.179	0.00–4.56	0.467
Spontaneous vertigo	1.37	0.86–2.17	0.267	0.42–17.56	0.455
Positional vertigo	0.66	0.22–2.00	0.409	0.03–4.51	0.716
BCV oVEMP					
BPPV	0	-	0.003 *	0.00–0.34	0.004 *
Ménière's disease	1.20	0.43–3.35	0.716	0.17–9.31	1.000
Head injury/whiplash	1.58	0.57–4.39	0.430	0.17–39.89	0.783
Vestibular neuritis	1.67	0.61–4.56	0.343	0.19–188.69	0.691
Spontaneous vertigo	0.17	0.02–1.48	0.037 *	0.00–1.14	0.073
Positional vertigo	2.20	0.85–5.71	0.166	0.36–45.47	0.365
vHIT (LSCC)					
BPPV	0	-	0.156	0.00–2.60	0.416
Ménière's disease	0.97	0.13–7.56	0.980	0.01–13.90	1.000
Vestibular neuritis	1.63	0.26–10.14	0.595	0.09–38.03	1.000
Spontaneous vertigo	1.13	0.24–5.47	0.871	0.09–10.32	1.000
Positional vertigo	0	-	0.281	0.00–4.30	0.740
vHIT (ASCC)					
BPPV	3.31	1.12–9.78	0.041 *	0.68–78.76	0.126
Ménière's disease	0.85	0.26–2.80	0.793	0.04–9.32	1.000
Vestibular neuritis	0.93	0.37–2.33	0.904	0.04–20.11	1.000
Spontaneous vertigo	0.22	0.03–1.46	0.047 *	0.00–1.38	0.106
Positional vertigo	1.28	0.45–3.61	0.691	0.08–26.86	1.000
vHIT (PSCC)					
BPPV	1.63	0.78–3.42	0.274	0.31–35.56	0.512
Ménière's disease	1.10	0.34–3.54	0.880	0.08–12.37	1.000
Vestibular neuritis	1.11	0.18–6.86	0.904	0.05–25.21	1.000
Spontaneous vertigo	0.29	0.04–2.25	0.171	0.00–2.50	0.359
Positional vertigo	1.52	0.39–5.99	0.552	0.12–27.91	0.920

Abbreviations: PPPD = persistent postural-perceptual dizziness, BPPV = benign paroxysmal positional vertigo, ACS cVEMP = cervical vestibular evoked, myogenic potential testing to air-conducted sound, BCV oVEMP = ocular vestibular evoked myogenic potential testing to bone-conducted vibration, vHIT = video head impulse test, LSCC = lateral semicircular canal, ASCC = anterior semicircular canal, PSCC = posterior semicircular canal, CMH = Cochran–Mantel–Haenszel test. * <0.05.

Next, we investigated whether each of the preceding diseases with $n \geq 4$ had an association with abnormalities in ACS cVEMPs. No association was found between preceding diseases and abnormalities in ACS cVEMPs (Table 3).

Then, we investigated whether each of the preceding diseases with $n \geq 4$ had an association with abnormalities in BCV oVEMPs (Table 3). PPPD patients with preceding BPPV had significantly lower rates of abnormal BCV oVEMPs in both the CMH test

(p = 0.003, CMH risk ratio 0) and the exact test for the common odds ratio (p = 0.004, 95% CI 0–0.34). However, those with preceding spontaneous vertigo of unknown cause had significantly lower rates of abnormal BCV oVEMPs with the CMH test (p = 0.037, CMH risk ratio 0.17, 95% CI 0.02–1.48), but not with the exact test for the common odds ratio. Other preceding diseases did not present any significant correlation with abnormalities in BCV oVEMPs.

Finally, we investigated whether each of the preceding diseases with $n \geq 4$ had an association with abnormalities in vHITs (Table 3). Head injury or whiplash was excluded from the analysis because only three cases received vHITs. PPPD patients with preceding BPPV and spontaneous vertigo of unknown cause had significantly higher rates of abnormal vHIT results with the CMH test (p = 0.041, CMH risk ratio 3.31, 95% CI 1.12–9.78/p = 0.047, CMH risk ratio 0.22, 95% CI 0.03–1.46, respectively), but not with exact test for the common odds ratio. Other preceding diseases did not present any significant correlation with abnormal vHIT results (Table 3).

4. Discussion

In this study, we have revealed the association of vestibular function in PPPD with preceding balance disorders. Some previous articles have focused on the vestibular function in PPPD [5,21], including a few which have suggested specific laboratory findings for this disease [22,23]. For example, the functional head impulse test with optokinetic stimulation provoked more reading errors in patients with PPPD than in controls [22]. In addition, a significantly greater head-tilt perception gain in the head roll-tilt subjective visual vertical test was reported with PPPD compared to unilateral vestibular hypofunction and psychogenic dizziness [23]. Furthermore, phobic postural vertigo, a classical disease concept with similar clinical features to PPPD, has been reported to present worsening of staggering especially when viewing moving visual scenes, and increased sway in the 3.53–8 Hz frequency band [24–26]. However, to our knowledge, there have been no reports on the effect of prior balance disorders on the vestibular function of PPPD.

Here, we have found that the presence of preceding vestibular neuritis had a significantly positive association with abnormalities in caloric tests in PPPD patients, suggesting that vestibular dysfunction, especially dysfunction of the LSCC, is affected by this preceding disease. Vestibular neuritis is known to present hypofunction of the semicircular canal, which can be detected by the caloric test [27]. In accordance with this finding, all patients diagnosed with vestibular neuritis showed unilateral abnormal caloric response in our previous report [28]. Again, in this study, all PPPD patients with preceding vestibular neuritis showed unilateral abnormal caloric responses. It has been reported that patients who develop severe acute unilateral peripheral vestibular disorders suffer from postural instability even in the chronic phase and did not improve as much as normal subjects [29]. Even though some clinical symptoms in PPPD cannot be explained solely by preceding or other complicating diseases, persistent imbalance during upright posture is a symptom that is also observed in the chronic phase of peripheral vestibular disorders. Thus, our study suggests a residual effect of vestibular dysfunction caused by preceding peripheral vestibular diseases on persistent imbalance in PPPD. On the other hand, there was no significant association between the presence of vestibular neuritis and abnormalities in the LSCC vHIT. In vestibular neuritis, the abnormality rate of the caloric test was 100%, but that of the LSCC vHIT was only 50%. However, vHIT is reported to be less sensitive than caloric testing when assessing moderate vestibular dysfunction in vestibular neuritis patients [30]. Therefore, the difference in the abnormality rate between the two tests could be explained by partial recovery of vestibular function during a 3-month or longer duration which had elapsed from the onset of vestibular neuritis.

In addition, PPPD patients with preceding BPPV presented no oVEMP abnormalities, which was significantly lower than those with other preceding diseases. This reflects the stability of the utricle system in PPPD patients with preceding BPPV, suggesting a limited effect of BPPV on otolith function. In other words, compared to diseases such as

vestibular neuritis, sudden sensorineural hearing loss, and Ramsay Hunt syndrome that strongly impair vestibular function, the damage caused by BPPV is relatively small. We have previously reported that 30% of BPPV patients presented abnormal oVEMPs, which increased with age [31]. Although the prevalence of abnormal oVEMPs is much lower in this study, this may be explained by the considerably younger age of PPPD patients with preceding BPPV (55.6 ± 18.4 years old) than those of BPPV patients in our previous literature described above (63.0 ± 14.2 years old).

Meanwhile, patients with preceding unexplained vertigo did not present a significant association with vestibular dysfunction even though more than half of the cases presented abnormal cVEMPs. These patients were not examined by an otolaryngologist during the primary balance disorder before PPPD and were unable to reach a final diagnosis. Their preceding balance disorders were left undiagnosed, or otherwise may include clinically unestablished diseases. Among the 16 patients, 5 patients presented positional vertigo, a brief vertigo during head rotation, similar to those of BPPV. As mentioned above, these patients are less likely to present vestibular dysfunction due to the limited effect of BPPV on otolith function. On the other hand, the other 11 patients showed spontaneous vertigo, including 3 who experienced recurrent vertigo attacks lasting as long as several hours, but without any cochlear symptoms. The three patients may have been diagnosed with vestibular Ménière's disease (American Academy of Ophthalmology and Otolaryngology, 1972) or possible Ménière's disease (American Academy of Otolaryngology Head and Neck Surgery, 1995) [32] if they had been referred to an otolaryngologist at that time. The other eight patients with spontaneous vertigo presented single or brief vertigo, which is unlikely to cause vestibular dysfunction. Taken together, although preceding unexplained vertigo in PPPD patients failed to show a significant correlation with residual vestibular dysfunction, most patients presented cVEMP abnormalities, which is in correspondence with previous literature reporting frequent vestibular dysfunction in patients without a specific vestibular disease diagnosis prior to PPPD [5].

This study had several limitations. First, information and selection bias cannot be excluded because this was a retrospective study. The latter may also arise since this study was conducted at a tertiary research institution specialized in vertigo and dizziness. Second, although assumptions could be made, we cannot draw a clear conclusion as to why preceding vestibular neuritis was associated with abnormalities in caloric tests but not with VEMP testing and vHITs. Third, preceding balance disorders prior to PPPD may include undiagnosed or clinically unestablished diseases. Fourth, the onset of detected vestibular dysfunction in this study remains unknown, because most preceding balance disorders were diagnosed elsewhere, lacking an assessment on vestibular function at that time. Fifth, preceding diseases in some patients may be persistent, acting as a comorbid vestibular disease with PPPD. Thus, we cannot fully differentiate the sequela of the preceding vestibular disease with disequilibrium caused by an active balance disorder. Last, there was a lack of data in vHIT analysis because of the exacerbation of dizziness caused by head motion, a common characteristic of PPPD.

Nonetheless, our study indicates an influence of preceding balance disorders on vestibular function in PPPD. This highlights the importance of closely monitoring vestibular function with caloric tests, VEMP testing, and vHITs, based on the type of preceding balance disorders.

5. Conclusions

PPPD with preceding vestibular neuritis showed dysfunction of the lateral semicircular canal, suggesting the influence of residual vestibular damage on PPPD. Meanwhile, PPPD with preceding BPPV did not present any dysfunction of the utricular system, suggesting a limited effect of BPPV on otolith function. These results present the influence of preceding balance disorders on vestibular function in PPPD. This highlights the importance of closely monitoring vestibular function with caloric tests, VEMP testing, and vHIT, based on the type of preceding balance disorders.

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

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A Paradoxical Clinical Coincidence: Benign Paroxysmal Positional Vertigo and Bilateral Vestibulopathy

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Abstract: Benign paroxysmal positional vertigo (BPPV) and bilateral vestibulopathy (BVL) are two completely different forms of vestibular disorder that occasionally occur in the same patient. We conducted a retrospective review searching for that coincidence in our database of the patients seen over a 15-year period and found this disorder in 23 patients, that is 0.4%. More frequently they occurred sequentially (10/23) and BPPV was diagnosed first. Simultaneous presentation occurred in 9/23 patients. It was subsequently studied, but in a prospective manner, in patients with BPPV on all of whom a video head impulse test was performed to search for bilateral vestibular loss; we found it was slightly more frequent (6/405). Both disorders were treated accordingly, and it was found that the results follow the general trend in patients with only one of those disorders.

Keywords: Vestíbulo-ocular reflex; dizziness; vestibulopathy

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1. Introduction

The major categories of vestibular symptoms are vertigo, dizziness, vestibular-visual and postural. All were recently arranged in a taxonomy based on triggers and situational occurrence broad enough to cover most of what is clinically recorded during anamnesis, being purely phenomenological and avoiding topo-diagnostic implications [1].

Benign paroxysmal positional vertigo (BPPV) is an episodic vestibular syndrome triggered by head motion when performing positional changes. It is one of the most common diagnoses at outpatient clinics, and its frequency depends on the clinical context or specialty [2]. The criteria for its correct diagnosis have recently been delineated [3]. Vertigo elicited during positional maneuvers (Dix-Hallpike, supine head-hanging, or, in supine head roll to right or left) marks the suspicion that demands demonstration during the vestibular examination of coincidental nystagmus [4]. The pathophysiological explanation lies in the existence of otoconial debris that floats in the endolymph and moves to the affected semicircular canal or remains adhered to the cupula. Most cases occur as a primary and idiopathic disease with a rapid good response to treatment which means a very straightforward clinical procedure [5]. However, BPPV can occur as a secondary or comorbid disorder as in Ménière's disease, which is a type of disease in which vertigo occurs without any trigger: in 14% of the patients with definite Ménière's disease, some of the vertigo crises will be diagnosed as typical BPPV and treated accordingly [6]. Positional vertigo is also another form of clinical presentation in vestibular migraine [7]. Additionally,

both disorders (Ménière's and migraine) share an important overlap in which positional vertigo or nystagmus must be considered [8,9].

This finding is not restricted to BPPV and MD or Vestibular migraines. Previous authors have considered that different vestibular disorders are highly interrelated in 3.7% of the patients who receive at least two diagnoses to better define their clinical status [10].

Bilateral vestibulopathy or bilateral vestibular loss (BVL) is an untriggered chronic vestibular syndrome and, contrary to BPPV, is infrequent, representing less than 5% of the diagnosis at specialized clinics [11]. Recently, clear diagnostic criteria have also been laid down for BVL [12]. This is a differential diagnosis to be considered in any patient with chronic instability (which may become more severe when visual information is reduced, such as walking in darkness) and oscillopsia or movement-induced blurred vision. The abnormal ocular response during the right- and left-ward head-thrust test at the bedside [13] will be the red flag to pursue in the differential diagnosis of this entity [14]. In BVL there is an abrupt or progressive decline in the function of the vestibular periphery at the level of the receptor in the inner ear or the nerve; it can also occur after a period of vertigo crises and be associated with neurological symptoms. BVL shares some links with disorders such as vestibular migraine and Ménière's disease. Recurrent vertigo is also mentioned by 33% of the patients with BVL but it is not clear whether this is spontaneous or positional [15] and is more frequent (43%) in patients with dissociated BVL which indicates that the amount of vestibular deficit in one side is clearly different from that measured on the other side with any of the methods for vestibular testing commonly used. This form of presentation of the disorder represents 20.8% of BVL and, in that series, it is interesting to note that there was also one case diagnosed with BPPV [16]. This association (BPPV and BVL) had already been reported in four patients of a series of 240 patients with BPPV all of whom suffered from posterior semicircular canalolithiasis; in those, BVL was due to gentamicin-induced vestibular ototoxicity [17]. In a later and broader analysis of patients with BPPV affecting the posterior semicircular canal, BVL was found in 21/2847 patients who were considered to have a secondary form of BPPV [18].

The study aimed to analyze the prevalence of both disorders in a retrospective and prospective study. We were interested in not restricting the diagnosis of BPPV to posterior semicircular canalithiasis alone and in the amount of vestibular asymmetry found in these patients.

2. Material and Methods

This is a review work of the experience at one institution at two different centers (Pamplona and Madrid). The information in this paper pertaining to BVL was previously published but in a broader study on bilateral vestibulopathy [11]; no data on BPPV were mentioned in that paper. We present the results of a retrospective study in a single institution to address how frequently both disorders occur and of a prospective study to analyze how frequent BVL is when searched for systematically in patients with BPPV. Patients were seen between 1 September 2006 and 31 August 2021. This spans 15 years of work by three experienced neurotologists working part-time and full-time at one (RMH) or both (NPF) centers. All patients gave informed consent to the use of their correctly anonymized clinical data for research purposes.

2.1. Bedside Testing

This was carried out on all patients and included ocular motility (saccades and smooth-pursuit), spontaneous nystagmus with and without visual fixation (the latter with Frenzel goggles), the post-head-shake nystagmus or the skull-vibration induced nystagmus; positional tests: head-hanging or hyperextension in a supine position, head-roll to right and left in a supine position, and the Dix-Hallpike test to the right and left sides. Other tests were performed in accordance with clinical characteristics or ongoing findings during examination.

2.2. Bilateral Vestibulopathy

As this study was carried out partially with patients seen in a period before the current criteria were published [11], we checked that they all shared the same clinical characteristics: criteria A and B of the guidelines (Table 1). Regarding vestibular testing, some were diagnosed because of findings in the caloric and rotatory chair testing while others (those after 2011) were in the vHIT alone. The caloric test has, for years, been the gold standard for vestibular testing, and the rotatory chair test is the recommended evaluation to confirm BVL. Recently, the video head-impulse test (vHIT) has become the preferred evaluation both at the bedside and in the laboratory to test for vestibular function and allow the testing of the vertical canals, which was not possible with the beforementioned tests [19].

Table 1. Diagnostic criteria A and B of bilateral vestibulopathy, according to the consensus document of the Committee for the Classification of Vestibular Disorders of the Bárány Society (2017).

A.	Chronic vestibular syndrome with the following symptoms
	1. Unsteadiness when walking or standing plus at least one symptom from 2 or 3
	2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements
	3. Worsening unsteadiness in darkness and/or on uneven ground
B.	No symptoms while sitting or lying down under static conditions

Caloric test. The test was performed using two-channel VNG equipment (Ulmer VNG, v. 1.4 (SYNAPSYS, Marseille). Each ear was irrigated with water at different temperatures (44 °C and 30 °C). The induced nystagmus response was characterized by its slow-phase velocity during the duration of recording (2 min) or until it faded away. In this study, all patients diagnosed with BVL had a reflectivity or sum of the responses from both ears and each irrigation (4 stimuli) below 15 $^{\circ}s^{-1}$. This result was first confirmed with the ice water test in which when using water at 4 °C no response was obtained from each ear [20].

Rotatory chair test. This was performed using a CHARTR-RVT system (ICS Medical Corporation, Schaumburg, IL, USA). The rotatory chair is housed in an enclosure to perform the test in the dark. The head is positioned so that both horizontal canals are close to the plane of stimulus (i.e., at the gravitational horizontal). In the first impulsive rotational test, the patient was subjected to velocity steps to the right and left. The velocity steps involved the patient undergoing an angular acceleration of 100 s^{-1} for 1 s, rotation at a constant velocity for 60 s, and finally a deceleration to 0 s^{-1} within 1 s. This procedure was performed three times in a clockwise direction and three times in a counterclockwise direction, and the TC for each was averaged (TCave). In the sinusoidal harmonic acceleration test (SHA), the individual was subjected to sinusoidal oscillation about a yaw axis at various frequencies (0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz), with a peak angular velocity of 50 s^{-1}. From the chair velocity and slow-phase eye velocity, two parameters of the VOR were calculated: phase and gain. To confirm the findings of bilateral reduced response in the caloric test, the TCave had to be below 8 s and the SHA test, gain and phase had to be significantly lower than normal in at least three consecutive frequencies (Figure 1).

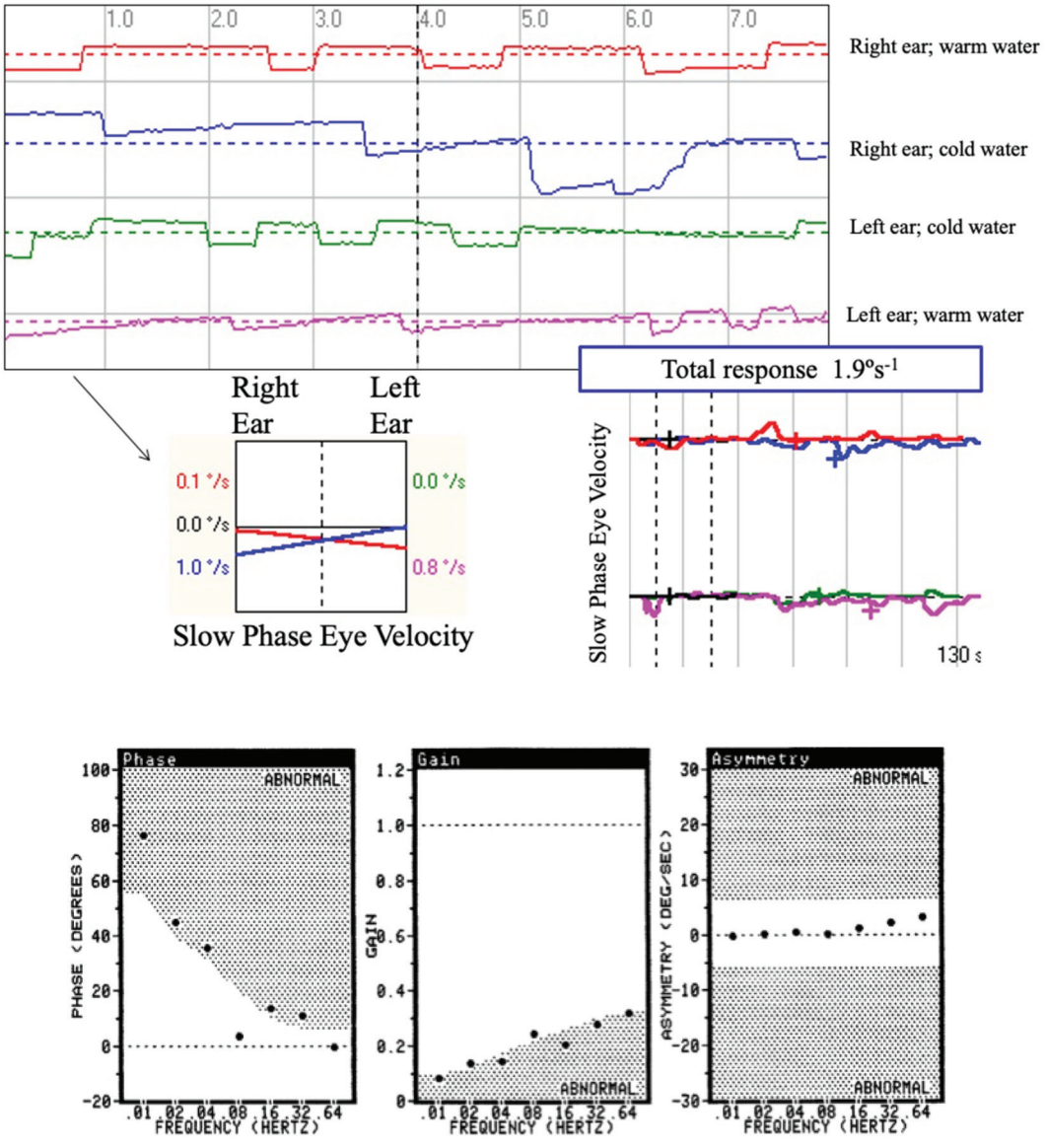

Figure 1. Vestibular test results in a patient diagnosed with bilateral vestibulopathy due to systemic gentamicin treatment. A: caloric test representation which shows a bilateral vestibular areflexia as no nystagmus response is obtained after stimulating each ear with cold and warm water and which has been confirmed in the ice water test in which no response was obtained from stimulating both ears. B: rotatory chair test which shows low gain and phase lag in the sinusoidal harmonic acceleration test.

Video-Head Impulse Test. This was performed using a vHIT system that allows the testing of all six semicircular canals (GN Otometrics, Denmark). For this test, the patient wears a pair of lightweight, tightly fitting goggles on which are mounted a small video camera and a mirror that reflects the image of the patient's right eye into the camera. The eye is illuminated by a low-level infra-red light-emitting diode. A small sensor on the goggles measures the head movement. Calibration is performed and the procedure of

vestibulo-ocular testing is initiated. Horizontal semicircular canals (right, RC, and, left, LC) are tested first: the clinician asks the patient to keep staring at an earth-fixed target 1 m. in front and gives the patient brief, abrupt, head rotations through a small angle (about 10–20 degrees), unpredictably turning to the left or right on each trial. At the end of each head turn, the head-velocity stimulus and eye-velocity response are displayed simultaneously on the screen. In a full test, at least 10 impulses are delivered randomly in each direction. The first pair of vertical canals is then evaluated: the patient's head is rotated 30° to the right while staring at the same earth-fixed target as before, but now out of the corner of his/her eye. Brief, abrupt, forward, and backward head impulses are then carried out, which allow stimulation of the left superior semicircular canal (LA) and the right posterior semicircular canal (RP) respectively. After a full test of at least 10 impulses in each direction, the second pair of vertical canals is evaluated: for this, the patient's head is rotated 30° to the left while staring at the earth-fixed target. Now, forward head impulses stimulate the right superior semicircular canal (RA) and backward impulses stimulate the left posterior semicircular canal (LP). A full test of at least 10 impulses in each direction is performed. At the end of each full test, all the head velocity stimuli and eye velocity responses are displayed on the computer screen, together with a graph of the calculated VOR gain (ratio of eye velocity to head velocity) for every head rotation (Figure 2). The gain was evaluated as normal or abnormal according to norms by age [21,22]. The second parameter is re-fixation saccades (RS) classified as covert and overt, the first being re-fixation saccades that take place during the cephalic impulse and the second taking place when the impulse has ended. A test was considered normal when the gain of the VOR was according to expected results consistent with age and there were no refixation saccades in any of the six canals evaluated. A test was abnormal when at least in the plane of 1 canal the response is lower in gain than expected and there are re-fixation saccades (Figure 3). In this study, in all the patients with BVL, the response was abnormal for the stimulation of the horizontal right and left superior, horizontal, and posterior semicircular canals as shown in the patient in Figure 4, and the gain in the horizontals was below 0.6.

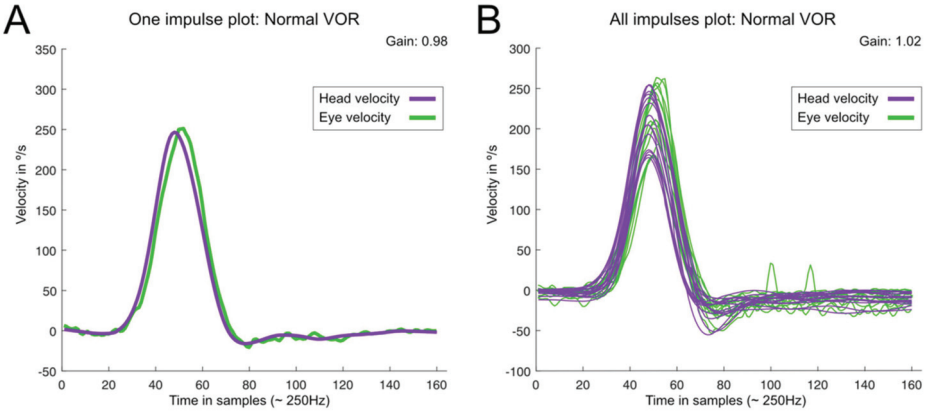

Figure 2. Graphical representation of a normal result in the video head impulse test (vHIT). (**A**): the result of a single head impulse; (**B**): the result of several impulses. In the former, the gain of the VOR was 0.98 and in the latter, the mean gain of the VOR was 1.02. This figure was obtained using a specific open-access program https://github.com/bendermh/HITCal (accessed on 9 March 2023) [23].

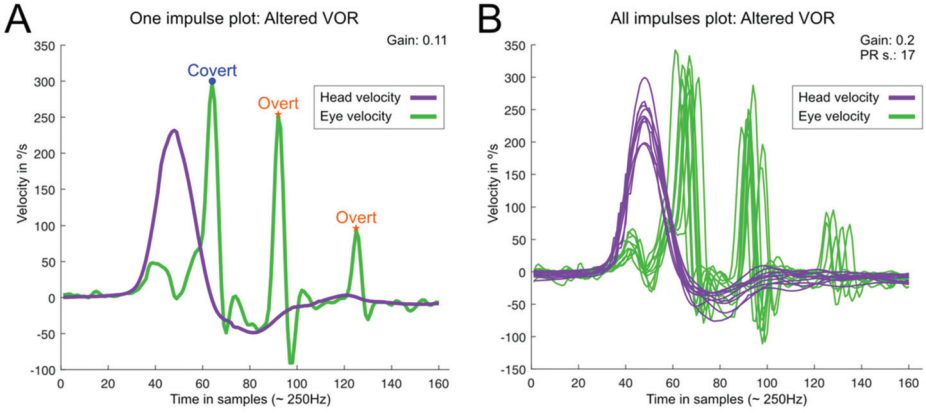

Figure 3. Graphical representation of an abnormal video head-impulse test result in a patient with bilateral vestibulopathy. This is the patient in Figure 1, and the analysis of the right horizontal canal stimulation is shown as an example and was performed with HITCAL software. The data shown correspond to horizontal rightward head impulses. (**A**): the result of a single head impulse; (**B**): the result of several impulses. In the former, the gain of the VOR was 0.11 and in the latter, the mean gain of the VOR was 0.2. In both corrective refixation saccades are shown and classified as covert (during the head impulse) and overt (once the head is stopped). This figure was obtained using a specific program obtained in open access https://github.com/bendermh/HITCal (accessed on 9 March 2023) [23].

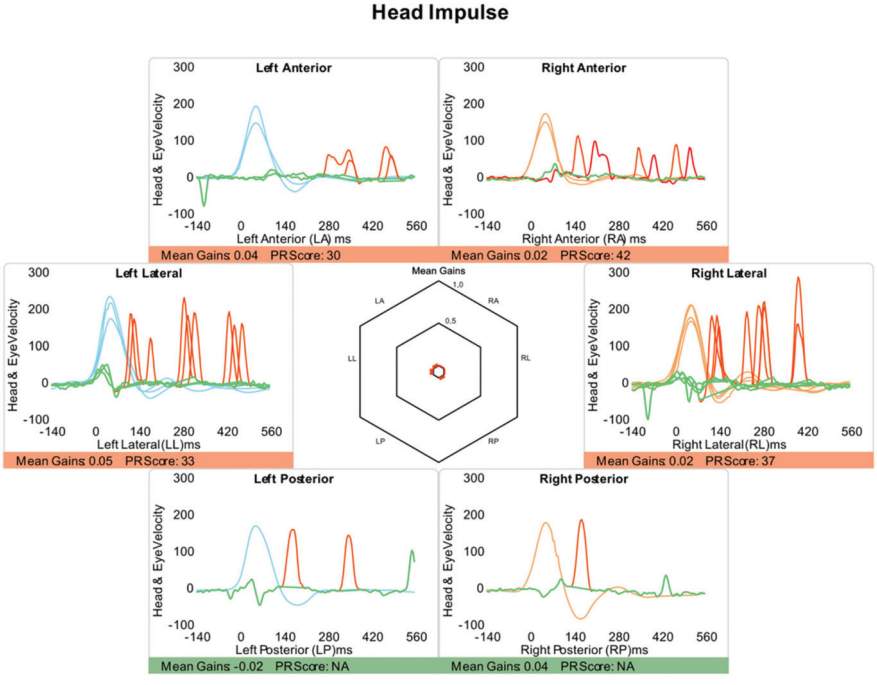

Figure 4. Result in the video head-impulse test of a patient with a posttraumatic BVL. This figure was obtained using a specific open-access program https://github.com/bendermh/HITCal (accessed on 9 March 2023) [23].

2.3. Benign Paroxysmal Positional Vertigo

Patients were seen for recurrent short (<1 min) attacks of vertigo induced by lying down, waking up, or turning over in the supine position, and certain position changes while performing activities during the day; this symptom was reproduced during testing and the duration of the attack was usually <1 min except in the case of horizontal canal involvement which was usually longer. In all cases under Frenzel goggles, nystagmus was elicited (after some latency) in the Dix-Hallpike test, supine roll test, or in head-hanging; in each, its characteristics will indicate (1) the side and canal affected (posterior, horizontal, or superior) and, (2) the mechanism: cupulolithiasis or canalithiasis. The patients were treated accordingly with the proper particle repositioning maneuver (PRM) and seen 30–60 min later to confirm resolution, persistence, or migration of the otoconia; in the latter two situations, the patient was treated again. All patients were seen 10–15 days later until the resolution of the BPPV.

In this case, only a vestibular bedside examination was done and, when considered by the neurotologist in charge, vHIT also. At one of the centers, vHIT was performed on all BPPV-diagnosed patients before the corresponding particle repositioning maneuver.

2.4. Inclusion Criteria

To be included in this work, after clinical and laboratory diagnosis several follow-ups were required to confirm the diagnosis in the case of BVP. In the case of BPPV patients, they were followed until the resolution of the initial symptom.

2.5. Statistical Analysis

For descriptive purposes, qualitative data are represented as absolute (n) and relative (%) frequency; for quantitative variables, data are shown as mean ± SD or mean (95% CI).

For demographic analysis, differences between normally distributed data were assessed with the t-student test or the one-way ANOVA test, and for non-normally distributed data the Wilcoxon test or the Kruskal–Wallis test was performed. Differences between percentages were determined by using Fisher's exact test.

All analyses were performed using R software v 4.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

3. Results

In the period of study, we were able to include in our database 5562 patients of which 3533 (63.6%) were female and 2029 (36.4%) male. Of them, 405 are part of a prospective study in which of all patients diagnosed with BPPV the vHIT was performed.

Of the total number of patients in 239 (4.3%) BVL was the main diagnosis and in 2297 (41.3%) BPPV. The mean number of follow-ups in the former was 2.3 and the number of PRM performed until resolution was 4179, which makes 1.9 PRM per patient.

Both diagnoses (BVL&BPPV) and the interest of this paper occurred in 23 patients, 0.4% of the total number of patients, and represents 10% of the patients with BVL and 1% of those with BPPV. They were 10 (43.5%) male and 13 (56.5%) female. Their mean age was 75 years [95% confidence interval (CI95): 64–82]. In 10 patients the first diagnosis was BPPV, in 4 BVL and, in 9 both were simultaneously done. When BPPV was first diagnosed the second diagnosis (BVL) was done 51 months (CI95 32–108) after and, when BVL was first diagnosed the second diagnosis (BPPV) was done 18 months (CI95 12–29) after. Those periods of time between diagnoses were significantly different (p = 0.034).

The cause of BVL was idiopathic in 11 patients, bilateral Meniere's disease in 6, bilateral vestibular neuritis in 3, systemic ototoxicity due to aminoglycosides in 2, and CANVAS in 1. In 20 patients we have the vHIT data and the mean gain of the VOR for the six canals is shown in Figure 5. BPPV was idiopathic in all cases and not related to antecedent ear infection or traumatism.

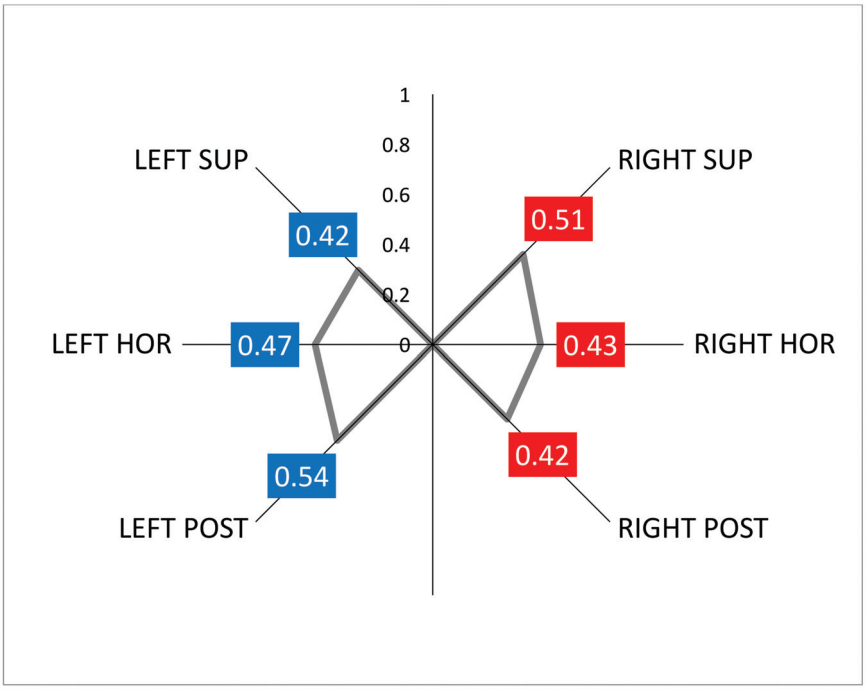

Figure 5. Graphical representation of the mean VOR gain in all patients tested with the vHIT.

The affected side with BPPV was the right in 13 (56.5%) patients and the left in 10 (43.5%). The affected canal was the posterior in 16 (69.6%) patients, the horizontal in 5 (21.8%) patients, the superior in 1 (4.3%), and, multiple canals in another 1 (4.3%) patient. According to physiopathology 20 were due to canalithiasis and 3 (all of them horizontal canals) to cupulolithiasis. In patients with BPPV, the mean gain of the VOR in the affected canal was 0.52 ± 0.16 while in the corresponding co-planar (and other ear) canal was 0.44 ± 0.23; differences were not significant ($p > 0.05$).

The specific PRM was performed immediately after diagnosis. The number of treatments performed to achieve a negative diagnostic test was only 1 in 13 patients; 1 additional PRM was performed in 5 patients and the rest, 5, needed 2.9 ± 1.1 PRM. There was an association between the initial diagnosis and recurrence such that in 8/10 of those first diagnosed with BPPV and then subsequently of BVL there was at least 1 recurrence that needed a new PRM. Recurrences were significantly lower when the first diagnosis was BVL or both (BVL and BPPV) simultaneous ($p = 0.006$).

In 18/23 patients once the diagnosis of BVL was done vestibular rehabilitation was initiated and all of them considered that to be beneficial.

At one of the centers, the vHIT was performed on all patients diagnosed with BPPV. They were 405 patients: the vHIT was considered abnormal in 86 (21.2%) but only in 6 (1.48%) a diagnosis of BVL was done.

4. Discussion

In this work we were interested in analyzing an *a priori* paradoxical situation occasionally found in clinical work as one of them, BVL, should mean the other was impossible, that is, BPPV, by making the vestibular receptor insensitive to any otoconial debris freely floating in the canal or adhered to the cupula. This review was prompted when examining a patient with a recent onset BPPV who was previously diagnosed with BVL after treatment with non-monitored systemic gentamicin due to renal disease. This is not an impossible

situation but is infrequent as it represents 1% of those with BPPV (in the prospective search that number was 1.8%) and 10% of those with BVL.

This finding firstly alerts on the need to perform a complete vestibular examination, in other words, the head impulse test (both at the bedside or in clinical form or with technology such as the vHIT) must be part of the vestibular examination in case of a suspected BPPV, and the Dix Hallpike test in a case of suspected BVL.

The rationale for the performance of the head-impulse test or its video-based method (the vHIT, here used) in patients with suspected BPPV (a mechanical disease) has been questioned by the results. Previous authors have not found any significant difference in patients with idiopathic BPPV between the gain of the VOR in the affected semicircular canal or in the asymmetry of VOR gain for co-planar canal pairs and, in none of the patients did they find refixation saccades when stimulating the affected canal [24]. On the contrary, in a prospective study the vHIT response (in terms of gain of the VOR) in patients with BPPV affecting the posterior canal was not found to be significantly different from that in normal controls but significantly different from that in the other ear of the same patient; this difference disappeared one-month after proper PRM treatment [25]. Both results provide two different messages: not to use the vHIT or to do so respectively during a vestibular examination of patients with typical BPPV. Our results are in line with the latest work and when combining the gain of the VOR and saccades registration the number of abnormal results increase in patients tested with the vHIT who were diagnosed with idiopathic BPPV. A recent meta-analysis concluded that otoconial debris could interfere with the normal functioning of the canal ampullae by biasing the cupula in the excitatory or inhibitory direction or by exerting some degree of pressure on the cupula which explains why only posterior semicircular canal BPPV most often displays abnormal VOR values as assessed in the vHIT [26].

In the case of BVL, the rationale for the performance of positional testing is well supported by previous works. BPPV has been found commonly among older adults with dizziness, including those not seeking medical care. According to different studies, 25% of these patients (>70 years old) mention unsteadiness or imbalance and not properly vertigo [27]. The resolution of positional nystagmus however does not always follow a significant recovery from unsteadiness.

We have found that BPPV can affect different canals irrespective of the diagnosis of BVL. This suggests that not only the Dix–Hallpike test but complete positional testing should be performed when BVL is suspected in order to verify whether positional nystagmus and vertigo could be part of the problem. The different forms of BPPV found in our work reflect what is found in other neurotology units where posterior canalithiasis is the most frequent finding [5]. In our work we decided not to include the "probable" and "possible" forms of BPPV given the difficulty of clinically dealing with them in the context of patients with BVL; those patients are in a dilemma when trying to reach a definite diagnosis and up to now are on follow-up.

We have found that BPPV and nystagmus occur in cases of moderate vestibular deficit and in our series most probably as coincidental diseases. It is not clear how much vestibular function must be preserved to induce a consistent nystagmus in examination, but, according to our findings, normal vestibular function is not the *sine qua non* for BPPV and nystagmus to occur. Post head-shake nystagmus [28] and skull vibration-induced nystagmus [29] are also closely dependent on the amount of vestibular hypofunction and degree of asymmetry between the normal and affected side; in the case of SVIN in vestibular neuritis when gain asymmetry is >31%, 95% of the patients show SVIN. However, in BPPV, induced nystagmus occurs because of otoconia stimulation of the hypofunctional receptor: the location, number, and size of the particles must also be considered [30]. The vHIT allows for a precise analysis of the VOR and we can say that at least when the gain of the VOR is 0.52, free-floating otoconia in the semicircular canal or attached to the cupula still exert a degree of pressure in the vestibular receptor and provoke a typical nystagmus response. It is a common experience in the final stage of Ménière's disease that some

patients still suffer vertigo episodes, and the caloric test shows a hypofunctional response and even no response at all with ice-water stimulation. The cessation of those crises after surgery indicates the existence of some controversy between clinical symptomatology and vestibular function tests results. In a large study, no correlation was found between disease duration (in years), stage of the disease (by hearing loss), and results in the caloric test and vHIT of the horizontal semicircular canals [31]. When the evaluation is extended to all semicircular canals and the vHIT is used then a trend to abnormal results was found for the vertical canals in that type of patients [32]. Saccular function as measured with the cervical vestibular evoked myogenic potentials (cVEMP) has clearly also shown abnormal results according to stage (as measured by hearing loss) showing a tuning shift to a higher best stimulation frequency [33].

Patients were treated following the usual methodology for each disorder and no specific or different procedure was considered, which also supports the idea of purely coincidental disorders. Taking into consideration the limitations of BPPV treatment in this particular elderly population [34], the results are similar to those shown by others. When both diagnoses were made at the same time (in 9/23 patients), the PRM was performed and, from the beginning, clearly identified the need for a further vestibular rehabilitation program; the treatment of BPPV did not result in a major change to chronic unsteadiness. On the contrary, BPPV was diagnosed in 4/23 patients, while in follow-up for their BVL, because of a major change in unsteadiness which alarmed them enough to come for follow-up, during clinical assessment for the first time they mentioned aggravation while moving the head up or down and getting in or out the bed or rolling to either side. The PRM was found to provide a significant amelioration of symptoms. The patients who were first diagnosed with BPPV and subsequently with BVL were seen because of an exacerbation in symptoms that went from typical spells to chronic unsteadiness which was slightly worse when performing positional changes; all patients (10/23) mentioned the "quality" change in symptoms as not being like those previously treated [35]. We were not able to track exactly when dizziness began, except that was not close to the latest PRM. However, BVL should return a differential diagnosis of residual dizziness, a commonly used term to characterize patients that report imbalance without positional vertigo after PRM treatment and resolution of nystagmus [36,37].

In conclusion, our findings support the need for a comprehensive bedside vestibular examination in patients irrespective of a suspected diagnosis or when the clinical follow-up shows a significant change in any given patient or only slight in the elderly. When BPPV and BVL are seen together, they should be managed as when seen alone. When chronic dizziness is the main clinical manifestation after PRM in patients with BPPV, it is important to consider BVL in the differential diagnosis.

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Systematic Review

Proprioceptive Cervicogenic Dizziness Care Trajectories in Patient Subpopulations: A Scoping Review

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Abstract: Proprioceptive cervicogenic dizziness (PCGD) is the most prevalent subcategory of cervicogenic dizziness. There is considerable confusion regarding this clinical syndrome's differential diagnosis, evaluation, and treatment strategy. Our objectives were to conduct a systematic search to map out characteristics of the literature and of potential subpopulations of PCGD, and to classify accordingly the knowledge contained in the literature regarding interventions, outcomes and diagnosis. A Joanna Briggs Institute methodology-informed scoping review of the French, English, Spanish, Portuguese and Italian literature from January 2000 to June 2021 was undertaken on PsycInfo, Medline (Ovid), Embase (Ovid), All EBM Reviews (Ovid), CINAHL (Ebsco), Web of Science and Scopus databases. All pertinent randomized control trials, case studies, literature reviews, meta-analyses, and observational studies were retrieved. Evidence-charting methods were executed by two independent researchers at each stage of the scoping review. The search yielded 156 articles. Based on the potential etiology of the clinical syndrome, the analysis identified four main subpopulations of PCGD: chronic cervicalgia, traumatic, degenerative cervical disease, and occupational. The three most commonly occurring differential diagnosis categories are central causes, benign paroxysmal positional vertigo and otologic pathologies. The four most cited measures of change were the dizziness handicap inventory, visual analog scale for neck pain, cervical range of motion, and posturography. Across subpopulations, exercise therapy and manual therapy are the most commonly encountered interventions in the literature. PCGD patients have heterogeneous etiologies which can impact their care trajectory. Adapted care trajectories should be used for the different subpopulations by optimizing differential diagnosis, treatment, and evaluation of outcomes.

Keywords: cervicogenic; cervical; proprioceptive; vertigo; dizziness; PCGD; whiplash

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1. Introduction

1.1. Background and Rationale

The prevalence of dizziness among people of working age (18 to 65 years old) is 20%–30% [1–4], and it is the number one reason for medical consultations for people over 75 years old [5]. Cervicogenic dizziness, cervical vertigo, and cervicogenic vertigo are interchangeable terms that refer to dizziness that is closely associated with neck pain, neck injury, or neck pathology. Many consider it to be one of the most common causes of dizziness, as it contributes to major social costs, insurance claims and handicap [3,6–8]. Throughout this manuscript, dizziness is understood as a non-rotatory illusion of movement, accompanied by disequilibrium and lightheadedness.

As a consequence of the absence of a gold standard testing procedure, cervicogenic dizziness's diagnosis is based on clinical presentation and the exclusion of other possible causes of dizziness [9–11]. However, researchers and clinicians should not only distinguish

this syndrome from other pathologies, but should also distinguish between the many potential etiologies that can lead to cervicogenic dizziness [11]. Indeed, patients with cervicogenic dizziness are not a homogeneous group, and have been classified into subgroups of individuals who share similar clinical characteristics. They were categorized to account for the differences in clinical presentation and care trajectory, as well as the notion that subgrouping improves disease knowledge acquisition [11]. The care trajectory refers to the itinerary of a patient through the healthcare system and among the different actors over a continuous period from the onset of the illness to its resolution [12]. However, even if the concept of subgroups has developed over the past two decades, it is still poorly understood, underused in the clinical and research setting, and has not yet been systematically examined. Before undertaking this review, a preliminary search using Medline (Ovid), Embase (Ovid), All EBM Reviews (Ovid), and CINAHL (Ebsco) for existing scoping reviews and systematic reviews on the subject was conducted on 5 May 2021. Most reviews were narrative and, although very informative, related to the general concept of cervicogenic dizziness, implying different subsets of patients and lacking systematic reporting of charting methods. The few systematic reviews were not scoping reviews. Therefore, this scoping review focuses on the care trajectory of the most common subset of cervicogenic dizziness in an articulated scope of inquiry, that of proprioceptive cervicogenic dizziness (PCGD) [9,11,13–15].

PCGD is experienced as non-rotatory vertigo, instability and disequilibrium associated with neck pain caused by abnormal afferent cervical proprioceptive activity [3,9,16]. It corresponds to what numerous authors would refer to as cervicogenic dizziness. The term PCGD will be used in this article, as proposed by Devaraja (2018), because it is more precise and eliminates other possible causes of cervicogenic dizziness, such as cervical vascular etiology [11,17]. Thus, this review will focus exclusively on the potential proprioceptive etiology of cervicogenic dizziness. PCGD is a diagnosis of exclusion [3,9–11,18] and exhibits a complex and heterogeneous nature. Different groups of patients are diagnosed with PCGD [11]. The specific proprioceptive mechanisms leading to PCGD may be different across individuals [9,11] and there is still confusion regarding this clinical syndrome. Indeed, encounters with dizzy patients should be distinguishing into vascular, vestibular, central, metabolic, pharmaceutical, orthopedic, iatrogenic, psychological, optometric and somatosensory pathologies [9–11]. Comorbidities are often encountered in this complex clinical context. Accordingly, there is inappropriate and insufficient diagnostic accuracy and treatment related to PCGD, which often results in lengthy care trajectories [8]. Differential diagnoses, diagnostic criteria, optimal treatment [4], and outcome measures must be mapped out to help shorten care trajectories for these complex patients.

1.2. Objectives and Review Questions

Hence, the objectives of this scoping review are to clarify the conceptual boundaries of PCGD and to map out the main research designs used to study PCGD and the key characteristics of affected patient populations. To do so, we will: (1) systematically identify the key characteristics of the literature and populations that have PCGD and (2) classify accordingly the knowledge contained in the literature in regard to interventions, outcomes and diagnosis.

Therefore, our review question can be summarized by the following: How has PCGD been studied, diagnosed, evaluated and treated in the pertinent literature, considering the key characteristics of patient subpopulations? This question implies the following interrogations: (1) What are the main research designs used to study PCGD? (2) Which subpopulations of patients does a PCGD diagnosis represent? (3) Which common differential diagnoses are associated with those subpopulations? (4) What evaluation tools are mentioned to identify the diagnosis? (5) What interventions have been considered by researchers for the management of PCGD? (6) What outcome measures have been used?

2. Materials and Methods

Protocol and registration: This scoping review was informed by the Joanna Briggs Institute methodology [19]. As such, Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA ScR) guidelines were followed to redact this systematic scoping review [20,21]. There was no a priori protocol published, because it was not recommended at the time of the beginning of the study.

Eligibility criteria: French, English, Spanish, Portuguese, and Italian articles were included in the review, as these languages are the ones fully understood by the reviewers. Randomized control trials, case studies, literature reviews, meta-analyses, and observational studies were included in this article. Expert advice, commentaries and letters were excluded to focus on higher evidence-level articles. Articles on animals were excluded because they cannot answer the research question. Research protocols were excluded as they do not yet contain a sample of patients and therefore cannot help to reach the scoping review's objectives. Conference abstracts were excluded as they can potentially contain mistakes and have not been properly peer-reviewed.

Types of participants: Articles concerning patients that have proprioceptive cervicogenic dizziness (PCGD) with or without associated conditions were included to identify all subpopulations and pertinent information on the specific characteristics and care trajectories associated with PCGD. Articles related exclusively to patients that did not present PCGD, with dizziness of vascular, central, vestibular or pharmacological causes, were excluded as they do not contain information about PCGD. Studies on healthy subjects were included if they were related to PCGD.

Concept: The relevant care trajectory elements to extract included differential diagnoses, diagnostic and predictive tools, and evaluative assessments to measure change and interventions.

Context: Articles written before 2000 were excluded. The recent introduction of new diagnosis entities with similar clinical presentations such as persistent postural-perceptual dizziness (PPPD) and vestibular migraine suggests that only the recent literature informed by those new diagnoses can have homogeneous samples of PCGD. Additionally, the separation of cervicogenic dizziness from proprioceptive etiologies (PCGD) and cervicogenic dizziness from other etiologies (i.e., vascular) was not suggested before 2000, to our knowledge.

Information sources and search strategy: A first limited search of MEDLINE (Ovid) and CINAHL to analyze the text words contained in the title and abstract of retrieved papers, and of the index terms used to describe the articles, was performed. The PsycINFO, Medline (Ovid), Embase (Ovid), All EBM Reviews (Ovid), CINAHL (Ebsco), Web of Science and Scopus databases were then searched using a Boolean strategy recommended by the university's research librarian. As an example, «((cervicogenic or cervical or proprioceptive) adj3 (vertigo* or dizziness)).ab,kf,ti.» was used to search Embase (Ovid). The rest of the strategies and corresponding databases can be consulted in Supplementary Appendix SA: SEARCH STRATEGY. The results yielded from this second step were exported in «.ris» format to the Covidence digital application to complete the review's methodology on 14 June 2021.

Evidence screening and selection: Both the title and abstract screening and the full-text review were carried out by two independent reviewers (including the main author) to identify potential literature and exclude irrelevant articles. Conflicts were settled by the main author and another independent researcher in consensus. Two separate reviewers extracted information from the articles, and consensus was reached with the main author of this scoping review. Additionally, cross-referencing was used to access primary sources concerning themes such as measuring tools, competing diagnoses, and epidemiology. A particular effort was made to find grey literature through contact with the main authors on the subject, but no unpublished literature was recruited with this approach.

Extraction and data charting process: A pilot testing of the extraction tool available in Covidence software was conducted by separate reviewers. This resulted in the modification

and personalization of the final extraction tool, which allowed for all relevant results to be extracted to meet the scoping review's objective (Supplementary Appendix SB).

Data items: Due to feasibility considerations, we limited the amount of data that we reported to study designs, subpopulations, differential diagnoses, diagnostic tools, interventions and outcome measures.

Synthesis of result: A descriptive quantitative synthesis of the evidence is provided by a tabulation and census of articles that relate each aspect of the care trajectory. Review articles are treated separately in some figures, and are not considered in other figures in order to give a true representation of the literature and to avoid double counting of data. A descriptive narrative of evidence is also presented.

3. Results

3.1. Extracting and Charting the Results

The aforementioned methodology yielded 1741 studies. A total of 797 articles were left after Covidence automatically removed articles recognized to be duplicates (n = 944). The selected articles were then screened by two independent reviewers based on title and abstract. Some 516 studies were excluded because they were found irrelevant based on inclusion/exclusion criteria. A total of 281 articles were assessed for eligibility in a full-text selection process by two independent reviewers. Some 125 studies were excluded following a full-text review based on the exclusion criteria (see Supplementary Appendix SC for the list and reason for exclusion). Conflicts were settled by consensus both in the title and abstract selection stage, and the full-text selection stage with the input of a third party (the last author of this paper). Finally, 156 studies were identified and selected for inclusion in the scoping review. A detailed search decision flowchart is presented in Figure 1.

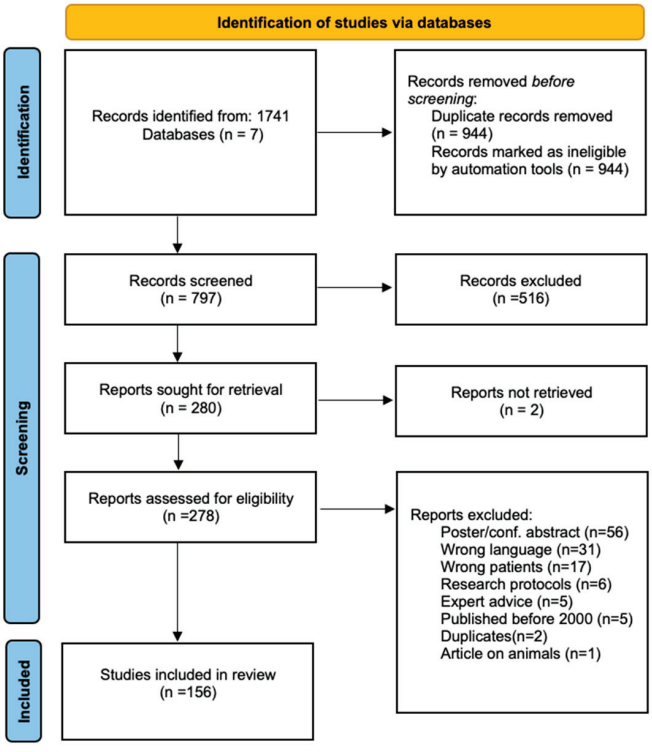

Figure 1. Prisma flow chart showing the identification of studies via databases.

3.1.1. Study Designs

A variety of different study designs were included: 17 randomized control trials (RCT) [22–38], 14 quasi-experimental studies [39–52], 84 observational studies of various designs (6 prospective cohort studies [53–58], 15 retrospective cohort studies [6,59–72], 20 case reports and case series [73–92], 33 cross-sectional studies [14,16,93–123], 10 case–control studies [15,124–132]), 9 systematic reviews [18,133–140], and 32 narrative reviews [1,3,4,7,9–11,141–165]. No qualitative studies, scoping reviews or pragmatic control trials have been published on PCGD. Figure 2 illustrates a quantitative synthesis of the study designs in the PCGD literature.

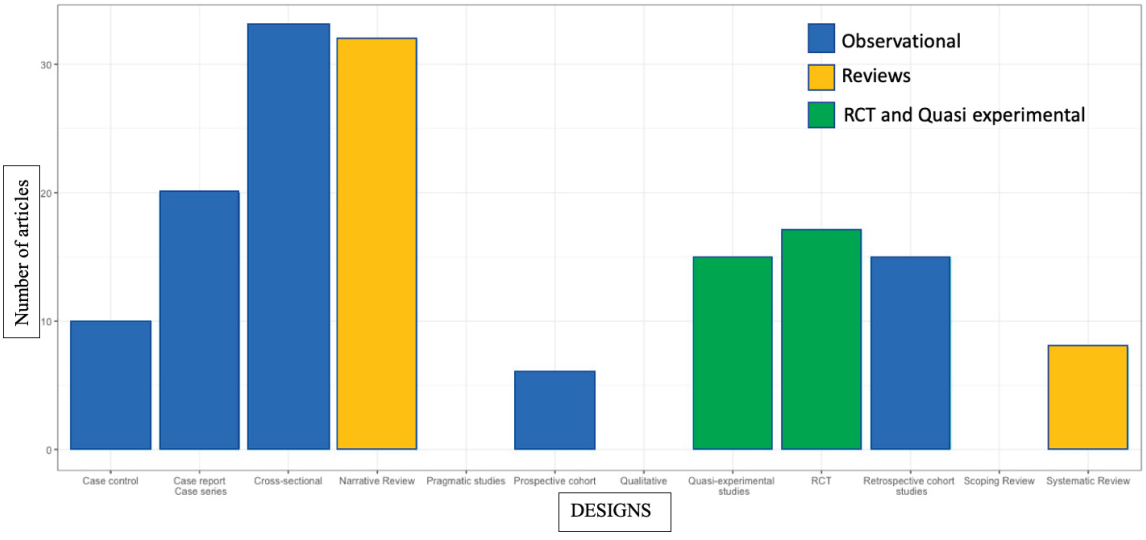

Figure 2. Research designs on proprioceptive cervicogenic dizziness. The number of articles selected by this scoping review is classified by study designs. RCT: randomized control trials.

3.1.2. Subpopulations of PCGD

A total of 81.9% of articles, reviews and other designs acknowledge at least one subpopulation in PCGD. Some 43.9% of articles acknowledge more than one subpopulation. A total of 28 of the 156 selected articles do not mention subpopulations in PCGD (18.1%). In total, four subpopulations of PCGD are identified in the literature: (A) chronic cervicalgia [7,13–15,22,24–26,28–31,34,36,37,41,45,46,50,56,58,60,61,63–66,68,73–75,77,78,81,82,84–86,89,90,92,95,98–100,109,110,115,116,118,120,124,126,142,146,148,153,163,166,167], (B) traumatic [1,6,7,9–11,13,16,23,24,29,31,37–39,42,45,50,55,62–66,69,75,77,81,82,86–88,90,95,96,98,99,103,106,107,109,112,114,116,119,124,125,127,137,138,140–143,145,148–150,152,154,157,158,162–164,168], (C) degenerative cervical disease [1,3,6,7,9–11,15,16,23,24,27,31,36,45,51,52,56,58,69,71,72,78–80,90,94,96,98,99,101,104,106,108,115,117,120,124,126–128,131,132,137,143,145,149,152–154,156,158,163,166,169,170], and (D) occupational postures and muscle fatigue or spasm [4,7,9,55,61,79,84,102,104,113–115,124,143,146,153,171] (see Table 1). Those potential etiological factors may alter in their specific ways the function of mechanoreceptors found in the smooth tissues (muscle, cartilage, tendons and ligaments) of the cervical region [4,16,146]. An illustrated quantitative synthesis of PCGD subpopulations' occurrence in the literature may be found in Figure 3.

Table 1. Subpopulations, clinical presentation and hypothesized etiological mechanism.

Subpopulations	Clinical Presentation	Hypothesized Etiological Mechanism
Chronic cervical pain	Patients with cervical pain for more than 12 weeks with no history of trauma or presence of muscle spasm that present dizziness.	Pain potentially alters proprioception
Traumatic	Patients have a history of [1] WAD or [2] PCS. Along with dizziness and cervical pain, patients may present the following symptoms: ataxia, unsteadiness of gait, postural imbalance, limited neck range of motion and potentially headache.	Pain, limitation of movement, and strains of joint capsules, paravertebral ligaments, and cervical musculature can alter cervical proprioception
Degenerative cervical disease	Mostly elderly populations presenting dizziness associated with degenerative cervical changes and cervical pain. Some patients may complain of headaches, or shoulder pain and some radicular symptoms or possible.	Histological changes and inflammatory processes can alter cervical proprioception
Occupational muscle spasm or fatigue	Sedentary populations that present dizziness associated with neck muscle fatigue or spasm without trauma. Patients could present limited cervical range of motion.	Muscle spasm may alter proprioceptive input

[1] WAD: whiplash associated disorders. [2] PCS: post-concussion syndrome.

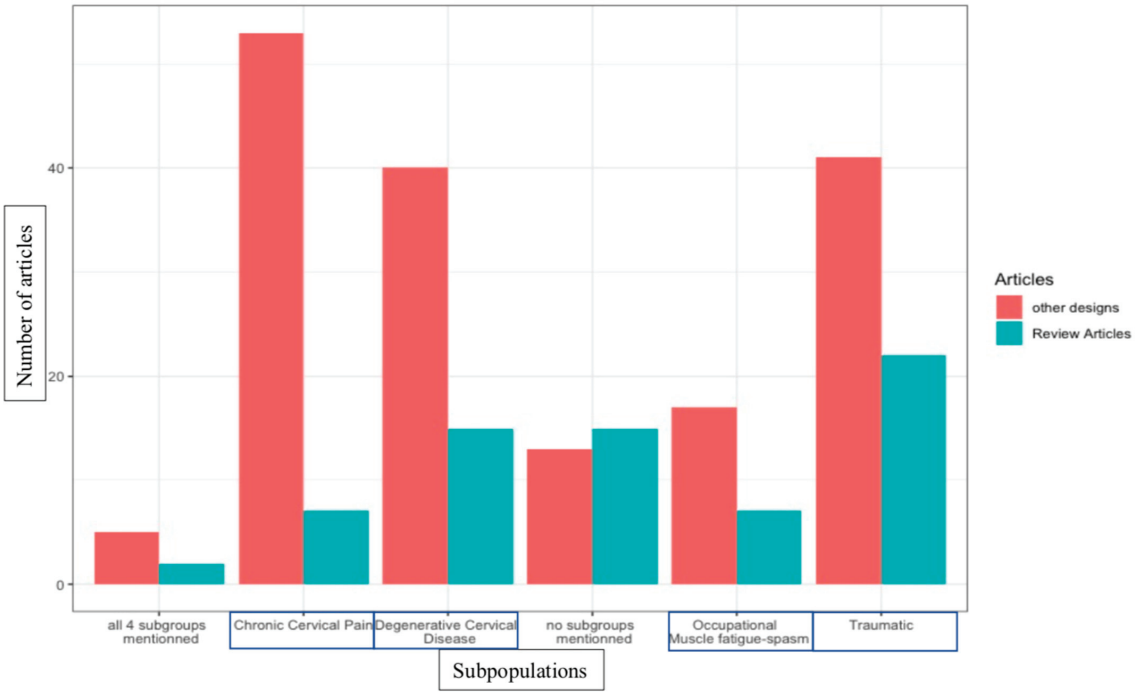

Figure 3. Quantitative synthesis of PCGD subpopulations' occurrence in the literature. Articles mentioning more than one subpopulation were counted in each pertinent category, except when all four subgroups were mentioned. No subgroups: no subpopulations are specified in the articles.

3.1.3. Assessments Used for the Diagnosis of PCGD

- Differential diagnoses and their assessment tools

As PCGD is a diagnosis of exclusion, the literature mentions 23 potential pathologies or group of pathologies to be ruled out. These are presented in a quantitative illustrated synthesis in Figure 4. Central causes [15,16,23,26,27,29–31,33–35,40–42,44,46,50,52,54,57–59,63,65–68,70,71,73,74,76,82,83,85,89,93,95,96,98,101–104,106–110,112,114,115,118,120,123,125,126,128,130–132,166], benign paroxysmal positional vertigo (BPPV) [15,16,22–26,29–32,39,42,54–57,59,63,65–67,70,74,76,82–84,86,88,90,99,101–104,107–112,114,115,125,126,132,156,166] and otologic pathologies [22–24,28,31–34,40,44,49,53,54,56,58–61,68,74–78,80–83,92,95,100,102,104,106–108,112,123,125,128,131] are the three most commonly occurring differential diagnosis categories in the literature on PCGD. The occurrence of differential diagnoses in articles mentioning different subpopulations of PCGD is presented in Table 2.

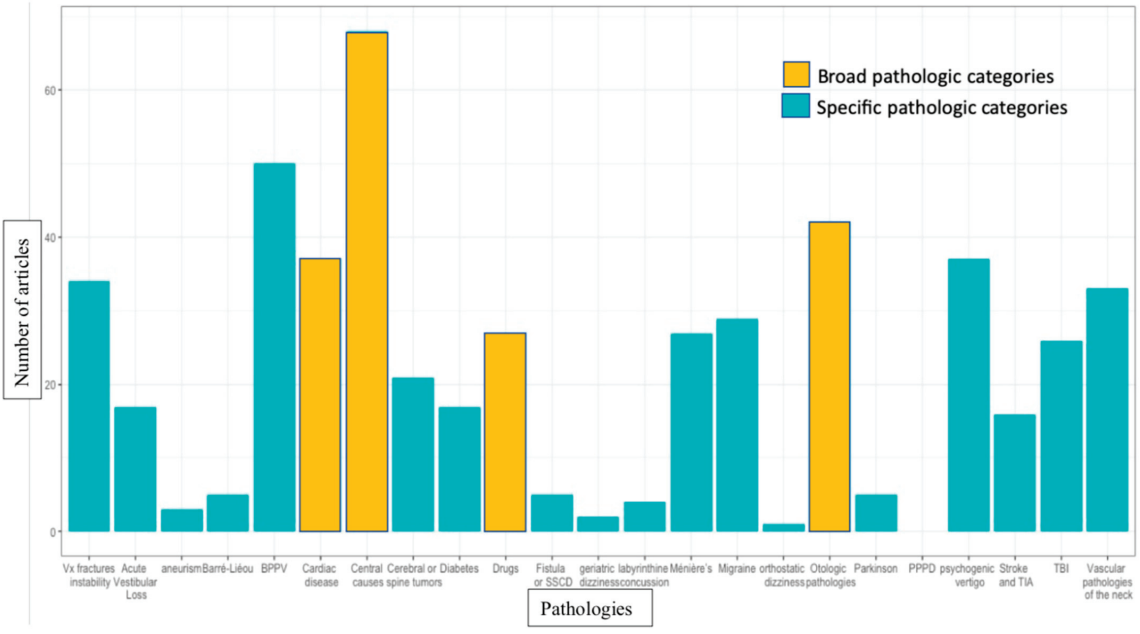

Figure 4. Pertinent differential diagnosis. SSCD: superior semicircular canal dehiscence syndrome; BPPV: benign paroxysmal positional vertigo; PPPD: persistent postural-perceptual dizziness; TIA: transient ischemic attack TBI: traumatic brain injury Vx: vertebral.

Furthermore, a total of 32 measuring tools contributing to the differential diagnosis process were mentioned in the literature. The most mentioned tools enabling this differential diagnosis process in the literature are presented in a quantitative illustrated synthesis in Figure 5. The Dix-Hallpike maneuver [10,15,16,22–24,26,29–31,35,38,39,42,55–57,59,65,66,75,76,81,82,84,86,90,99,101,104,107–109,112,115,123,125,128,130,132], magnetic resonance imaging (MRI) [6,31,42,56,58,60,67,70,71,78,81,82,86,90,92,93,95,98–100,106–110,114,115,117,126,128,132,166], cervical spine x-ray imagery (X-ray) [15,27,28,35,39,46,56–58,69–71,77,81,84,89,90,93,96,99,100,102,106,116,119,123,124,128,129] and audiological testing [15,41,42,47,51,55,56,58,60,62,67,69,70,74,81,82,93,95,98,99,101,106–110,114,123,125,129] are the four most reported tools to guide the differential diagnosis process. The Dix-Hallpike maneuver can identify BPPV, MRI can objectify some central causes, cervical x-rays can identify a vertebral fracture and audiological testing helps in the diagnosis of different otologic pathologies.

Table 2. Occurrences of differential diagnoses in articles mentioning different subpopulations of PCGD.

Traumatic	Degenerative Cervical Disease	Chronic Cervicalgia	Occupational (Muscle Spasm)
[1] BPPV (n = 22)	Central causes (n = 22)	Central causes (n = 28)	[1] BPPV (n = 11)
Central causes (n = 19)	Cardiac disease (n = 17)	[1] BPPV (n = 23)	Central causes (n = 9)
[3] Vx fracture instability (n = 17)	[1] BPPV (n = 16)	Cardiac disease (n = 20)	Cardiac disease (n = 8)
Migraine (n = 13)	[3] Vx fracture instability (n = 14)	[3] Vx fracture instability (n = 19)	Vascular pathologies of the neck (n = 7)
Psychogenic vertigo (n = 15)	Psychogenic vertigo (n = 13)	Migraine (n = 19)	Migraine (n = 7)
[2] TBI (n = 12)	Drugs and vascular pathologies of the neck (n = 11 for both)	Otologic pathologies (n = 18)	Drugs (n = 6)

[1] BPPV: Benign paroxysmal positional vertigo [2] TBI: traumatic brain injury [3] Vx: vertebral.

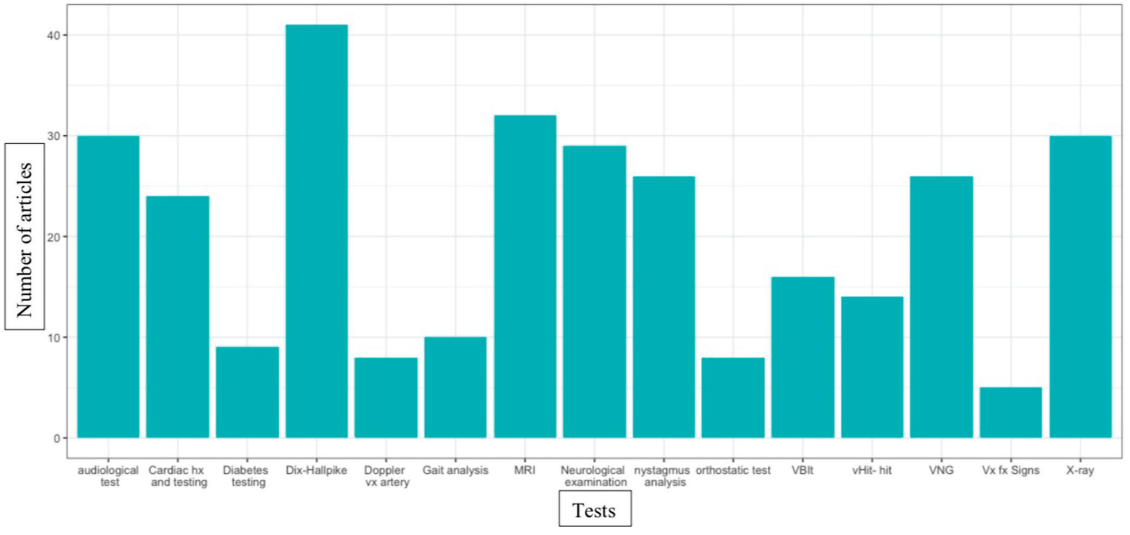

Figure 5. Pertinent tests for differential diagnosis. Cardiac hx: cardiac history, vx: vertebral, MRI: magnetic resonance imaging, VBIt: vertebrobasilar insufficiency testing, vHIT-hit: video head impulse test-head impulse test, VNG: videonystagmography, Vx Fx signs: vertebral fracture signs, X-ray: cervical spine X-ray imagery.

- Inclusive diagnostic tools (rule-in)

While exclusion diagnosis implies clinicians will «rule out» other pathologies, some clinical tests can also help to inform clinicians by trying to «rule in» PCGD. A list of the most often-cited tests is found in Figure 6. The two most cited clinical tests mentioned in the literature are palpation for segmental tenderness [6,10,16,23–26,28,29,34–36,40,43,45,51,55,60,61,66,73,74,76–78,81,84,85,87,90,93,95,98,100,103,104,107,109,120,126,128,129] and manual spinal evaluation [10,16,22,23,26–28,31,35,36,40,41,51,55,56,59,61,69,72–75,77,78,81,82,85,87,90,93,103,104,125,126,128].

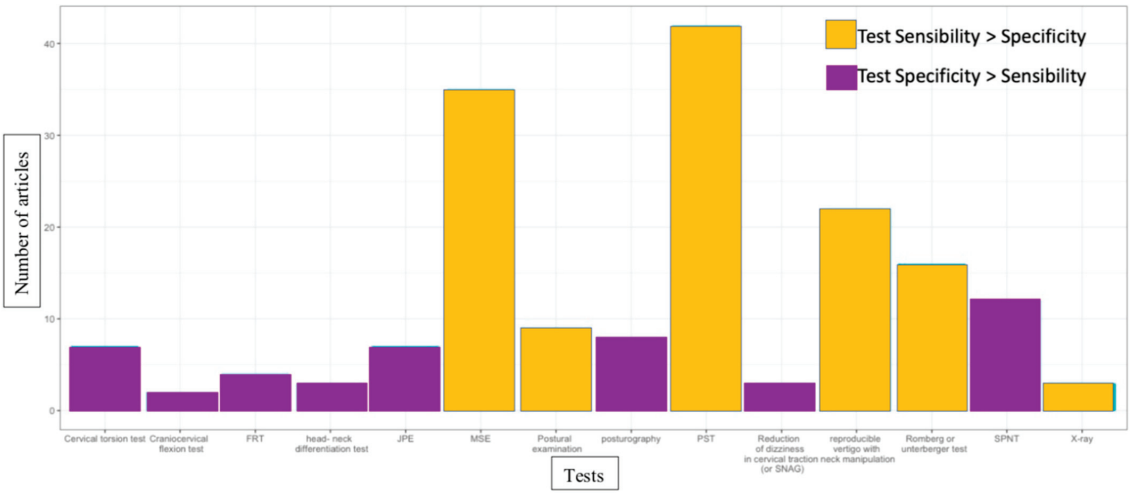

Figure 6. Clinical tests (to «rule-in») PCGD. FRT: flexion rotation test, JPE: joint position error test, MSE: manual spinal evaluation, PST: palpation for segmental tenderness, SNAG: sustained natural apophyseal glide SPNT: smooth pursuit neck torsion test.

3.1.4. Interventions and Outcome Measures

Many therapeutic interventions were found (n = 34) in the PCGD literature (see Table 3). These included modalities from physiotherapy, Chinese medicine, pharmacology, allopathic medicine, chiropractic medicine, and other approaches. Across subpopulations, exercise therapy [22,23,25–27,31,34,37,38,40,42,51,59,60,65,74,81,82,84,85,87,90,125,128,166] and manual therapy [22–28,31,33,36,38,40–42,46,59,60,76,78,79,82,84,87,90,101,107,124,128] are the most commonly encountered intervention in the relevant literature, as shown in Figure 7. The occurrence of interventions in articles mentioning different subpopulations of PCGD are presented in Table 4.

Table 3. Intervention modalities in Proprioceptive cervicogenic dizziness *.

Chinese Medicine	Physiotherapy	Pharmacology	Surgery-Injection
Acupuncture Tuina Acupressure Herbs	Manual therapy Transcutaneous electrical nerve stimulation Vestibular rehabilitation Dry needling Exercise therapy Sensorimotor rehabilitation Ultrasound Termal therapy Sustained natural apophyseal glide	Non-steroidal anti-inflammatory drugs Acetaminophen Analgesics Betahistine Muscle relaxant	Total disc replacement (TDR) Medial branch blocks (MMBs) Occipital nerve blocks (GON) Trigger point injections (TPI) Mepivacaine, bupivacaine Anterior cerical discetomy and fusion (ACDF) Percutaneous laser disc decompression (PLDD) and disc decompression. Botulinum toxin injection Coblation discoplasty Carbon fiber fusion cage (CIFC)

* Other modalities included are chiropractic adjustments; chuna manual therapy; helical patches; cervical traction; and patient education.

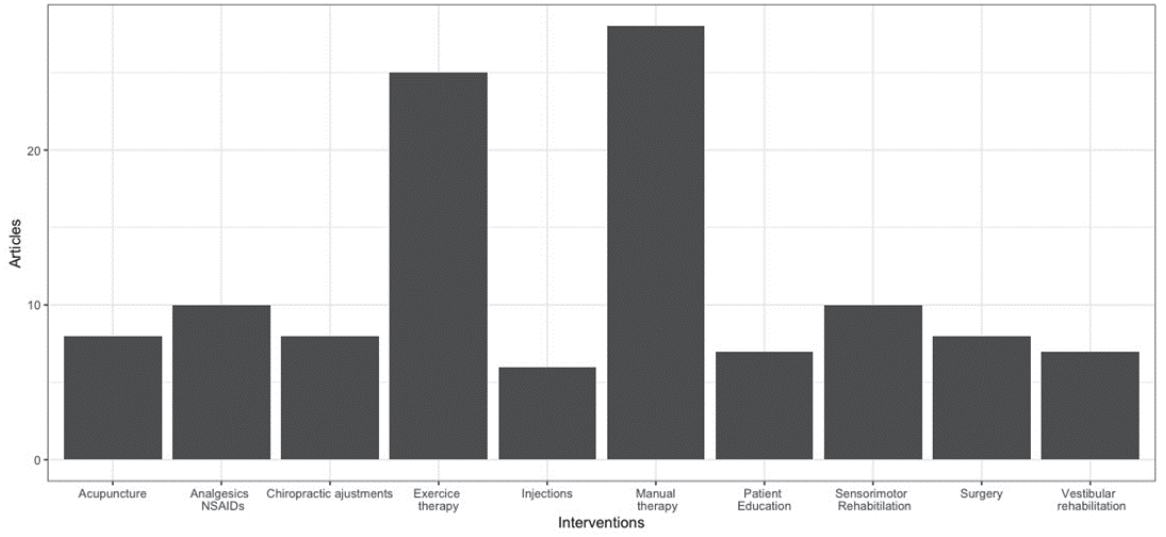

Figure 7. Interventions on PCGD in the literature.

Table 4. Occurrences of interventions in articles mentioning different subpopulations of proprioceptive cervicogenic dizziness.

Traumatic	Degenerative Cervical Disease	Chronic Cervicalgia	Occupational (Muscle Spasm)
Exercise therapy (n = 10)	Manual therapy (n = 9)	Manual therapy (n = 15)	Manual therapy (n = 4)
Manual therapy (n = 10)	Surgery (n = 8)	Exercise therapy (n = 13)	Exercise therapy (n = 3)
Sensorimotor rehabilitation (n = 6)	Analgesic NSAID [1] (n = 6)	Chiropractic adjustments (n = 7)	Patient education (n = 3)
Analgesic NSAID [1] (n = 5)	Exercise therapy (n = 6)	Injection (n = 5) Analgesic NSAID [1] (n = 5)	Analgesic NSAID [1] (n = 3)
Patient education (n = 5)	Acupuncture (n = 4)	Acupuncture (n = 5)	Chiropractic adjustments (n = 2)

[1] NSAID: Non-steroidal anti-inflammatory drugs.

While evaluating the efficiency of treatment, the 17 most commonly encountered outcome measures relevant to PCGD literature are presented in Figure 8. A total of 77 measuring tools were found in the literature. The four most cited measures of change were: dizziness handicap inventory (DHI) [16,23–35,42,56,66,68,76–78,81,85,89,90,95,98,104,107–110,117,120,128,130], Visual analog scale (VAS) for neck pain [16,23–27,30,31,34,40,41,51,54,60,64,68,71,73,74,76–78,81,84,86,90,100,106,109,110,116–118,126,128,166], cervical range of motion (CROM) [22–26,28,29,33,40,41,46,51,52,60,76,78,84,85,87,106,108,109,120,128] and posturography [16,23–26,29,33,34,39,40,43,46–48,62,85,95,106,107,110,119] (see Figure 8). Across subpopulations, measures of change used in trials are fairly similar (see Table 5). Dizziness is a multidimensional rehabilitation problem [172]. These dimensions should be considered when measuring treatment effectiveness. Figure 9 uses the International Classification of Functioning, Disability and Health to classify the most common health outcomes of functioning and disability found in the PCGD literature. The body function category (Figure 9) regroups many self-reported and performance-reported outcomes related to the many dimensions of PCGD: proprioceptive and sensorimotor performance (posturography, joint position error test (JPE) and Romberg), self-reported pain (VAS for cervicalgia and headaches), the amplitude of cervical movement (CROM), frequency and intensity of dizziness, level of self-perceived disability (DHI, neck disability index (NDI)), quality of life (SF-36), medical imagery of the cervical spine (X-Ray), and levels of anxiety and depression (Hospital Anxiety and Depression Scale (HADS)). Some self-reported outcomes measuring body functions also comprise items relative to activity and, to a much

lesser degree, to the participation category (DHI and SF-36). Indeed, dizziness can limit social participation and engagement and the ability to work, and may even exclude a patient from his profession [172]. DHI and SF-36 do not include specific items related to the social contribution of patients, such as their ability to work, their days on sick leave and the personal economic impact of the disease. In the literature, only one article reported on sick leave in PCGD [105].

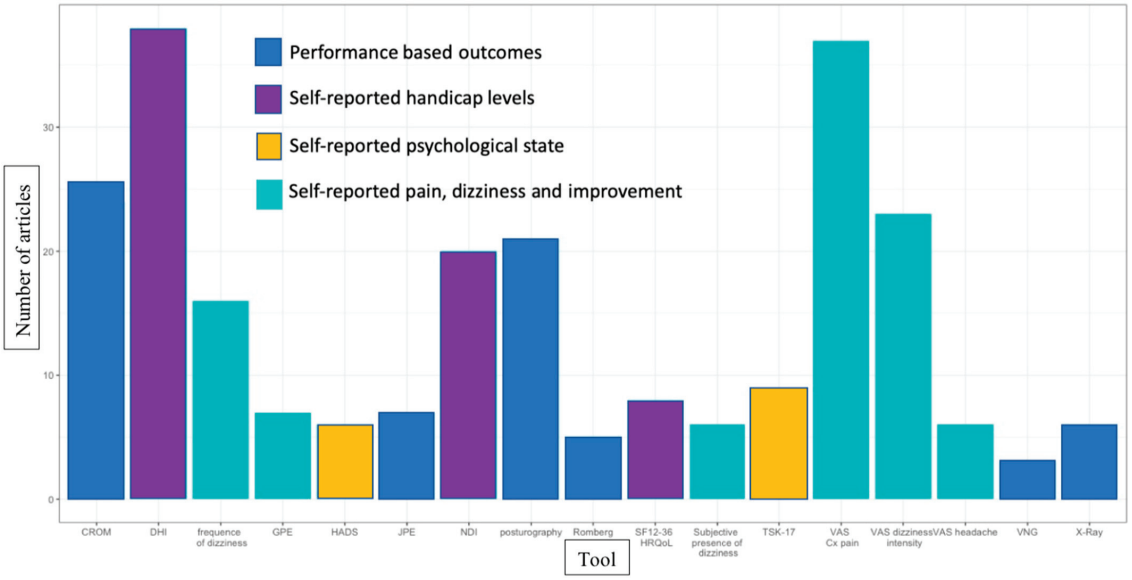

Figure 8. Tools to measure change CROM: cervical range of motion, DHI: dizziness handicap inventory, GPE: global perceived effect, VNG: videonystagmography, HADS: Hospital Anxiety and Depression Scale, JPE: joint position error test, NDI: neck disability index, HRQoL: health-related quality of life, TSK: Tampa Scale for Kinesiophobia, VAS: visual analog scale.

Table 5. Measures of change used across subpopulations.

Traumatic	Degenerative cervical disease	Chronic cervicalgia	Occupational (muscle spasm)
[1] DHI (n = 15)	[1] DHI (n = 16)	[2] VAS Cervical pain (n = 24)	[1] DHI (n = 5)
[2] VAS Cervical pain (n = 12)	[2] VAS Cervical pain (n = 16)	[1] DHI (n = 23)	[2] VAS Cervical pain (n = 5)
Posturography (n = 10)	[4] CROM (n = 9)	[4] CROM (n = 14)	[5] TSK-17 (n = 3)
[3] NDI (n = 9)	[3] NDI (n = 8)	[3] NDI (n = 13)	[3] NDI (n = 2)
[4] CROM (n = 7)	[2] VAS intensity and frequency of dizziness both (n = 8)	[2] VAS intensity and frequency (n = 13)	Posturography (n = 2) and [4] CROM (n = 2)

[1] DHI: dizziness handicap inventory; [2] VAS: visual analog scale; [3] NDI: neck disability index; [4] CROM: cervical range of motion; [5] TSK: Tampa Scale for Kinesiophobia.

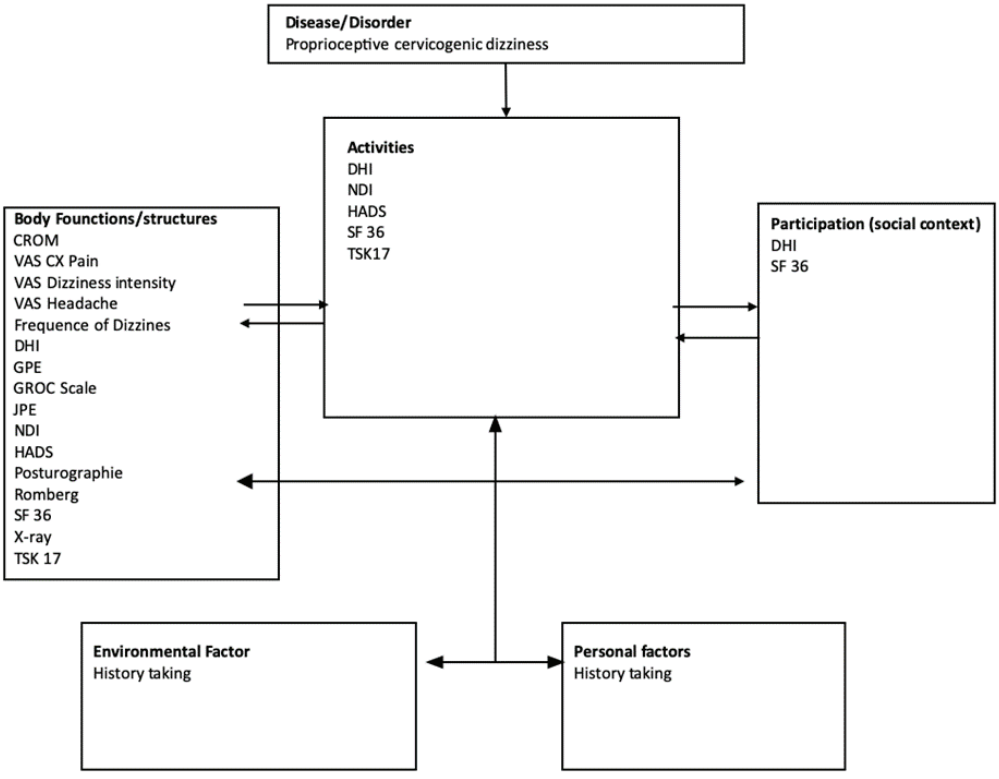

Figure 9. Measurement instruments in proprioceptive cervicogenic dizziness: an ICF classification (some measurement instruments are suitable in more than one ICF component). CROM: cervical range of motion, DHI: dizziness handicap inventory, GPE: global perceived effect, GROC-scale: global rating of change, HADS: Hospital Anxiety and Depression Scale, JPE: joint position error test, NDI: neck disability index, HRQoL: health-related quality of life, TSK: Tampa Scale for Kinesiophobia, VAS: visual analog scale.

4. Discussion

This article focused on the following central questions: (1) What are the main research designs used to study PCGD? (2) Which subpopulations of patients does a PCGD diagnosis represent? (3) What common differential diagnoses are associated with those subpopulations? (4) What evaluation tools are mentioned to identify the diagnosis? (5) What interventions have been considered by researchers for management? (6) Which outcome measures have been used?

To our knowledge, this is the first scoping review undertaken on the topic of PCGD. Four subpopulations of PCGD have been identified: chronic neck pain, degenerative cervical disease, traumatic and occupational subpopulations (muscle spasm). Central causes of dizziness and BPPV are the most often-mentioned potential diagnoses that compete with PCGD. The Dix-Hallpike maneuver is the most cited tool to inform differential diagnosis. Manual therapy and exercise therapy are the most studied interventions in the field. DHI is the most often-encountered measure of change used in this literature.

4.1. Designs

Many study designs were selected for this review (see Figure 2). Randomized control trials represent only approximately 10% of the selected literature. Observational studies are the most common designs. No qualitative protocols on the subject were found in any

database; this type of research should be encouraged because evidence-informed practice, value-based healthcare approaches and patient participatory paradigms require a more qualitative knowledge of the experience of patients suffering from PCGD in order to focus on what matters to them [173].

4.2. Subpopulations

Four subpopulations of PCGD have been identified that reflect the relatively heterogeneous population of PCGD. The reasons that some people develop PCGD and others do not, even though they are part of traumatic, degenerative cervical disease, muscle spasms or chronic neck pain populations, remain unknown [158]. Maybe differences in sensorial strategies between individuals could account for that. Patients keener on using proprioceptive input will be more at risk of developing PCGD in comparison with patients who rely more heavily on vestibular or visual cues for posture and gait. As patients can be part of more than one subpopulation of PCGD, research could investigate how cumulating etiological factors could predict poor prognosis [174]. Because PCGD pertains to different subpopulations, it is a «cross-cutting complaint» that concerns different specialties. As such, our results support the Bárány Society's recommendation to form multidisciplinary research teams to study PCGD [175], and their calls for interdisciplinary efforts in the clinic.

4.3. Competing Diagnoses, Differential Diagnosis and Comorbidity

Since PCGD is an exclusion diagnosis, central causes, cardiac disease and otological pathologies are among the four most cited pathological categories to be ruled out (see Figure 4). Unfortunately, these categories lack precision because they regroup numerous pathologies and are too elusive to effectively orient the differential diagnosis process and inform clinicians. BPPV, on the other hand, is the most cited specific diagnosis in this literature. It is also cited often as an important diagnosis to rule out, no matter what the subpopulation of PCGD is (see Table 2). It is therefore no surprise that the relatively simple Dix-Hallpike maneuver is the most cited test to rule out competing pathologies with PCGD (see Figure 5). Indeed, this test associated with adequate nystagmus analysis; paroxysmal presentation of symptoms and history taking can signal a BPPV diagnosis, but only for posterior canal issues. Lateral canal issues are not objectified with this test.

Knowledge of subpopulations could orient clinicians toward the most accurate and pertinent use of resources in terms of diagnostic tools. Indeed, certain differential diagnostic processes are more often encountered in articles recognizing specific subpopulations of PCGD.

In the literature on the traumatic subpopulation of PCGD, vertebral fractures and particularly traumatic brain injury are more often mentioned than in any other subpopulation. Additionally, there are relatively fewer mentions of the necessity to exclude cardiac diseases in the literature on the traumatic subpopulation of PCGD compared with other subpopulations. Clinicians could orient their diagnostic process toward a rather orthopedic direction rather than a cardiovascular direction in this subpopulation. While MRI, neurological examination and X-ray are cited in the literature on PCGD to help with differential diagnoses (see Figure 5), there are relatively few mentions of orthopedic examination for vertebral fracture signs and ligament testing. This could indicate that clinicians rely more on imagery than clinical testing, and could use clinical testing more, especially with the traumatic population.

In the literature on the degenerative cervical disease subpopulation of PCGD, cardiac disease and drug-induced dizziness are relatively more often cited than in any other subpopulation. This might be because the degenerative cervical disease subpopulation is more likely to be elderly, have cardiac conditions and be exposed to multiple drug issues [176]. Indeed, cardiac history and testing is the 7th most cited evaluation used in differential diagnosis (see Figure 5).

Incidentally, psychogenic vertigo is cited relatively more often in both the traumatic and the degenerative cervical disease subpopulations than in the other subgroups. This

could be explained by the potential psychological impacts related to trauma or ageing. Paradoxically, no mention of psychological assessment is present in the tests to inform differential diagnosis. More psychological testing should be carried out in a neurotological context, as vertigo and dizziness can also cause anxiety, panic and depression, and these could in turn also cause dizziness [177].

Other important aspects to discuss are persistent postural perceptual dizziness (PPPD) and vestibular migraine. PPPD was recognized by the International Classification of Diseases (ICD-11) only in 2017 [178], and vestibular migraine has been described by the members of the Bárány Society only since 2012 [179]. Although migraine is cited relatively often as a diagnosis of exclusion in PCGD, especially in the traumatic and chronic cervicalgia subpopulations, there is no golden standard to «rule in» migraine and diagnosis is based on clinical presentation [180]. This result supports the importance of controlling for migraine and developing subgroup analysis for migraine as a confounding factor in future interventional studies, as prompted by the Bárány Society's recent milestone article on 'Cervical Dizziness' [175]. Persistent postural perceptual dizziness is a common long-lasting cause of dizziness [178]. Paradoxically, it is not mentioned in the exclusion process of PCGD. Migraine and persistent postural perceptual dizziness are both exclusion diagnoses and can co-exist with other conditions. This situation adds to diagnosis uncertainty.

Early diagnosis and rehabilitation could optimize health outcomes for patients and add value to healthcare by reducing the social-economic burden of disease. One of the main issues with the lengthy care trajectory of PCGD is that despite being an exclusion diagnosis, it may also coexist with other disorders, and often does. Moreover, in elderly people at risk of falls, road accident victims suffering from post-concussion syndrome or whiplash, and patients suffering from neck pain or chronic headaches, 45.2% to 84% of patients have potentially one or more diagnoses in addition to PCGD [11,123,181]. In these subpopulations, dizziness is associated with higher levels of disability and more psychosocial consequences compared to patients in the same groups without dizziness [13,113,135,154,182]. This multimorbid situation makes the trajectory of care longer, and often results in therapeutic wandering for these patients, and a greater social and economic burden. There is a lack of a single gold standard test or accepted clinical prediction rule to limit diagnosis uncertainty [18]. Only one article has studied the possibility of combining different tests to shorten the exclusion process [16]. The issue of multi-morbidity calls for investigation of clinical prediction rules and the specificity of tests to «rule-in» PCGD. Indeed, while sensitive tests such as manual spinal evaluation and palpation for segmental tenderness are very often used in the literature, potentially more specific tests [10] such as cervical torsion [10,16,64,84,90,97,115], the head–neck differentiation test [10,97,123], joint position error test [10,16,50,65,87,90,98] and smooth pursuit neck torsion test [10,16,23,26,50,57,64,65,99,103,125,128] have a relatively lower rate of occurrence in the literature. Unfortunately, in comparison with the literature reporting tools to «rule out» other pathologies, the literature reporting clinical testing that is useful to «rule in» PCGD with more specific tools is scarce, and therefore should be encouraged (see Figures 5 and 6).

4.4. Measuring Change

In PCGD, many outcome measures are needed not only because of its multidimensional nature, but because self-reported outcomes and perceived level of handicap poorly correlate with the measurement of the level of sensorimotor performance [183]. This suggests they rely on other constructs [183]. The most commonly encountered outcome measures in PCGD are DHI, VAS for cervical pain, CROM and posturography (see Figure 8). Posturography and JPE are the only tests that can be found both among the tools for inclusion and for measuring change (see Figures 6 and 8), and this raises the question of their potential combined specificity and sensitivity to change. These six tools should be used to facilitate comparison between trials and meta-analysis of outcomes, and a psychological outcome such as HADS should also be included. Social engagement and personal economic impacts of disease should be reported in PCGD. As PCGD remains elusive in

its exact aetiopathogenesis, primary clinical outcomes and secondary «mechanistically based» outcomes should also help to establish a basis for hypothesized pathophysiological mechanisms [175].

4.5. Interventions

Manual therapy and exercise therapy are generally the most common interventions encountered in the literature. However, surgeries were considered more often for degenerative cervical disease subpopulations suffering from PCGD than in any other subpopulation (see Table 4). The reason for this might be that surgeries are aimed at degenerative changes and herniated disc issues rather than for dizziness itself, even if they may have an indirect impact on dizziness. In the same way, injections were mostly reported in the literature for the chronic cervical pain subpopulation, as they are a common treatment for chronic neck pain. Patient education was the third most studied intervention in the muscle spasm (occupational) subpopulation. Indeed, patient education about occupational habits aims to reducing muscle spasms, and indirectly could impact dizziness.

Knowledge of subpopulations' characteristics should also be reflected in the multimorbid context of PCGD. It enables the clinician to consider not only the type of intervention but the strategy of intervention that might be considered.

4.6. Limitations

Relevant sources of information may have been omitted in the literature written in languages that were not included in the review, notably Chinese and German articles. Another limitation of this study is that the proprioceptive etiology of cervicogenic dizziness is yet to be recognized by The International Classification of Vestibular Disorders. It is a working definition and is the most plausible cause of dizziness in cervicogenic dizziness, but still requires further investigation into its pathophysiological mechanism. In this scoping review, as no quality assessment of protocols was performed, the validity of the literature has not been put to the test. Care should be taken while interpreting the results.

In the differential diagnosis process, since some authors simply excluded general cardiac, central and otologic conditions without naming any particular pathology, specific conditions pertaining to those categories might be under-represented in our results in Figure 4. Additionally, relatively recent diagnoses in otology and neurotology make some pathologies unlikely to have been put forward in the differential diagnosis of PCGD before 2010, and even today. For example, a potentially relevant competing diagnosis such as PPPD might have been reported using other terms such as phobic postural vertigo or visual vertigo, but only two articles mentioned each pathology.

Some 43.9% of articles acknowledge more than one subpopulation. This introduces bias in subpopulation analysis. Particularly in the chronic cervicalgia analysis, 34 of the 53 articles also recognize at least one other subpopulation for PCGD, and in so doing, introduce bias to our data. For example, these articles could mention vertebral fractures or instability as a pathology to exclude, because the authors recognize the potential contribution of trauma or degenerative cervical disease subpopulations in PCGD.

5. Conclusions

This is the first scoping review of the literature on PCGD, to the authors' knowledge. Qualitative methods are inexistent in the literature on PCGD. The specific characteristics of PCGD patients differ according to their etiological categories. Subpopulation knowledge should inform subgroup analysis in PCGD trials and observational studies as well as clinical practice. Namely, there are four main subpopulations of PCGD: chronic cervical pain, traumatic, degenerative cervical disease and occupational. These subgroups have different care trajectories according to commonly encountered pathologies, probable comorbidities, usual red flags, and treatment strategies. This raised awareness will have important impact on future research in relation to subgroup analysis and in clinical practice, as it enables optimized differential diagnosis, treatment, and evaluation. Studies should also investigate

the reason that some patients from a single subpopulation develop PCGD and others do not; more randomized control studies are needed. Trials should use common outcome measures encompassing all dimensions of PCGD, including the social and economic categories, to facilitate future systematic reviews and elucidate pathophysiological mechanisms. Future studies should report on clinical testing to «rule in» PCGD.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12051884/s1, Appendix SA: Search strategy. Supplementary Appendix SB: Data extraction instrument. Supplementary Appendix SC: Sources excluded following full-text review.

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The Narrowed Internal Auditory Canal: A Distinct Etiology of Pediatric Vestibular Paroxysmia

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Abstract: Vestibular paroxysmia (VP) is a disorder encountered in the pediatric population that etiology has been attributed to neurovascular cross-compression syndrome (NVCC). The purpose of this study was to report a new probable pathological condition, the narrowed internal auditory canal (IAC), which appears to be involved in the development of a clinical picture of VP in the pediatric population. A retrospective descriptive comparative study was conducted to compare clinical, electrophysiological, radiological, and therapeutic outcomes in both etiologies. Overall, 16 pediatric patients suffering from VP were included and divided into two groups: patients with narrowed internal auditory (Group 1) were compared to those with NVCC syndrome (Group 2). Patients in both groups were similar in terms of auditory complaints, as well as hearing, vestibular, and electrophysiological status. A narrowed IAC was encountered in the adolescent age category and females, especially those with rapid growth. The diagnosis requires a careful analysis of the shape and diameters of the IAC. Radiologic measurements in the axial plane do not seem to be sufficient to confirm the diagnosis, and, therefore, an analysis of diameters in the coronal plane is required. Treatment with sodium-channel blockers drugs showed promising results not only by relieving vertigo but also by normalizing the electrophysiological findings. In conclusion, a narrowed IAC can be considered in patients suffering from VP.

Keywords: narrowed internal auditory canal; neurovascular compression syndrome; vestibular paroxysmia; pediatric vertigo; anticonvulsant drugs; cochleovestibular nerve

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1. Introduction

The prevalence of vertigo and balance impairment is estimated to be around 5–10% in the pediatric population [1–3]. Two peaks were reported by Brodsky et al.: the first one takes place during infancy and the second during adolescence [4]. In a recent search of the literature, Fancello et al. [5] identified vestibular migraine and migraine variants as the most common cause of vertigo (32.7%), followed by cochleo-vestibular disorders (23.9%). Vestibular paroxysmia (VP) is one vestibular disorder with unknown prevalence [6]. A definitive VP consists of at least ten recurrent, short (less than one minute), spontaneous attacks of stereotyped and self-limiting vertigo that respond to anticonvulsant drugs (carbamazepine/oxcarbazepine) [7]. Data on retrocochlear diseases in children are sparse [8,9],

but neurovascular cross-compression (NVCC) syndrome has been described [10], and VP has been attributed to NVCC syndrome [11]. The pathophysiology of these attacks relies on the "ephaptic theory" [12]: an electrical conduction between the proximal part of the partially demyelinated eighth cranial nerve (CN VIII) and neighboring vascular structures of the cerebellopontine angle (CPA) [13]. In fact, the vascular structures of the CPA can cause a direct effect on the surrounding nerves either by direct segmental compression or by pulsatile vascular effect and consequently lead to a dysfunction of the vestibular and/or auditory nerves [7,14].

In addition to the diagnostic criteria of VP defined previously [7], several findings may be helpful to consider a retrocochlear origin of VP. The hyperventilation maneuver can modify the direction of an initial spontaneous nystagmus or cause a hyperventilation-induced nystagmus (HVIN) [15]. The latter has been reported to be more common in retrocochlear pathologies compared to inner ear end-organ pathologies [7,16]. Electrophysiologic modifications with absolute values of interpeak latencies (IPL) I–III exceeding 2.3 ms in patients with normal pure tone audiograms are a strong indication of CN VIII involvement [17]. Vestibular dysfunction can vary among patients [18,19], and caloric testing discloses mild increases of a vestibular deficit over time [20]. MRI with high-resolution T2 weighted sequence (DRIVE/CISS/FIESTA) of the brainstem can support the diagnosis [7]. The exclusive presence of a neurovascular contact is not considered to be sufficient. A perpendicular contact along two different perpendicular planes leading to a deviation of the nerve path and generation of a weak point of the CN via pressure is essential for the diagnosis [21]. VP in NVCC responds to low doses of fast sodium channel drugs such as carbamazepine (200–600 mg/day) or oxcarbazepine (300–900 mg/day); it has shown to be effective in children [14]. Although a microsurgical decompression can be proposed in refractory cases [14], only one pediatric case of CN VIII surgical decompression was reported in the literature and succeeded to reveal tinnitus in a 15-year-old female [22].

A narrowed internal auditory canal (IAC) is another retrocochlear condition that can occur concomitantly with cochleovestibular nerve hypoplasia or aplasia [23–26]. It has also been reported that narrowed IAC can generate a local nerve damage or neuropathy, hence generating cochleovestibular and/or facial symptoms [27–30]. In the present study, we compared clinical, electrophysiological, radiological, and therapeutic outcomes of two pediatric groups matching the diagnosis criteria of probable VP: those with NVCC syndrome to those with a narrowed IAC. The goal of this comparison is to elucidate the existence of a distinct pathologic condition that appears to be, along with NVCC syndrome, at the origin of VP in pediatric patients.

2. Methods

2.1. Population

A retrospective descriptive comparative study was conducted to compare two retrocochlear pathologies. Over a two-year period, 704 patients were referred to our tertiary care department, after a preliminary pediatric otolaryngology and/or neurological consultation, for evaluation of vertigo or related balance complaints. After a thorough vestibular evaluation, patients whose clinical presentation met the criteria of probable VP, as defined by the Bárány society [7], were included. These patients underwent a radiologic evaluation with a cerebral and inner ear MRI, and, only when narrowing of the IAC was suspected, a high-resolution computed tomography (HRCT) of temporal bones was subsequently realized to confirm the diagnosis (for more details, see radiology sections below). Subjects younger than 5 years old and older than 18 years old were ruled out. Cases with a personal or a family history of headache or migraine, as well as motion sickness, were excluded. Children who are candidates for cochlear implantation were excluded, as well. Furthermore, patients with confounding variables such as previous ototoxic medication consumption, middle ear disease, neurological disorders, ophthalmic or vergence anomalies, psychological status, or systemic diseases were excluded.

Overall, 32 children with a narrowed IAC were selected. A total of 24 patients were opted out because of confounding variables, incomplete medical records, or loss of follow-up, and 8 remaining patients were included (Group 1). A comparative group including the pediatric population with NVCC syndrome was randomly selected (Group 2).

The investigation adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from the children's parents.

2.2. Cochleo-Vestibular Assessment

All children were subjected to cochleo-vestibular evaluation. A detailed medical and otological history was taken, and a complete otolaryngological and neurological examination was carried out by the same physician. Otoscopy and tympanometry were verified in each subject. The otoneurologic assessment included a battery of auditory and vestibular tests.

As part of an auditory evaluation, each child was subjected to a pure tone audiometry (PTA) and auditory brainstem-evoked responses (ABR). CN VIII involvement was suspected if the IPL I–III was prolonged to more than 2.3 ms on the interested side, as defined my Moller's ABR criteria [17].

As part of vestibular evaluation each child was subjected to a videonystagmoscopy to look for spontaneous nystagmus, a positional nystagmus, and HVIN. Spontaneous nystagmus was considered pathologic when its mean slow-phase velocity exceeded four degree per second [31]. We also performed cervical vestibular evoked myogenic potentials (cVEMPs), a rotational chair testing to assess the vestibulo-ocular reflex (VOR), and a video head impulse test (vHIT). Therefore, otolithic function was assessed by cVEMPs elicited in bone conduction (BC), as previously described [32]. Although the utricle may also respond to BC stimuli, the presence of cVEMPs indicates predominantly human saccular response function [33]. Latencies and amplitudes of the first positive–negative peaks (p13–n23) were defined as described by Fujimoto et al. [34]. Absent response was defined by an a non-reproducible p13–n23 over two attempts, and decreased response was defined by a reproducible p13–n23 with an asymmetry ratio above the normal upper limits. For the rotational chair test, a rotational chair (Nagashima Co. Ltd., S-II, Tokyo Japan) was accelerated to a maximum rotational velocity of 160°/s and then decayed by 4°/s. The test was performed once in a clockwise direction and once in a counterclockwise direction. Eye movements were recorded by ENG, and the duration and number of beats of per rotatory nystagmus were calculated for the evaluation of semicircular canals [35]. Vestibular function was defined by gain, phase, and symmetry, as described by several pediatric studies, and normative values were settled according to the age group [36–38]. For vHIT, the Ulmer II system (Synapsys®, Marseille, France) was used, with two experienced right-handed examiners. This device is a widely recognized validated non-invasive tool to assess high-frequency VOR in children [39], and it is used in routine practice for vestibular deficit screening. Each SCC is sensitive to endolymph displacement according to its specific anatomic orientation and, hence, to acceleration in that plane (see Rabbitt's mathematical model [40]). Five-to-ten acquisitions were made per SCC, beginning with the horizontal canal; examination time did not exceed 10 min. A normal response was defined by a gain value between 0.8 and 1.2, while a decrease in gain is defined by a value below 0.8 [41,42].

2.3. Radiological Assessment

All patients underwent a cerebral and inner ear 1.5 and/or 3 Tesla MRI to eliminate central pathologies and check for a cochleo-vestibular abnormality. Parasagittal images of the internal auditory canal demonstrate intact facial, vestibular, and cochlear nerves. The CN VIII course in the CPA and IAC was closely analyzed, and a sufficient nerve development was confirmed. When an NVCC syndrome was visualized with a normal IAC diameter, no further imaging was realized. Only when narrowing of the IAC was suspected did patients undergo an HRCT of temporal bones with measurements of the length, vertical diameter of the fundus (VDF), and vertical diameter of the porus (VDP) [43].

The normative measurements by CT among children, as defined by Marques et al., were as follows: length = 11.17 mm, VDF = 4.82 mm, and VDP = 7.53 [44]. In the present study, interpretations of the anteroposterior and craniocaudal diameters were assessed in both axial and coronal planes, respectively. A narrowed IAC was considered when an anteroposterior diameter measured less than 3 mm [44,45]. All the radiological analyses and measurements were carried out by the same radiologist.

2.4. Therapeutic Strategies

The efficacy of anticonvulsant drugs is one of the criteria that differentiate between a probable VP and a confirmed VP, among others [7]. In the present study, clinical observation was opted in patients with mild or moderate well-tolerated symptoms, and a probable diagnosis was defined. Treatment with anticonvulsant drugs was prescribed when symptoms were bothersome, recurrent, and incapacitating. The initial duration of treatment was set at six weeks, followed by a clinical evaluation at twelve weeks to assess the level and improvement.

3. Results

The demographic and clinical characteristics of both groups are shown in Table 1. The subjects' age refers to the time of the first vertigo attack; thus, the first attack ranged between 5 and 18 years. In Groups 1 and 2, 87.5%, and 50% of subjects were adolescents (≥10 years-old), respectively. Females were more commonly concerned: 75% in Group 1, and 62.5% in Group 2.

Table 1. Demographic and clinical data for Groups 1, 2, and 3. Abbreviations: F (female), HL (Hearing loss), L (left), M (male), and R (right), VP (Vestibular paroxysmia).

	Sex	Age (Years)	Vestibular Symptoms (Other than VP)	Auditory Symptoms	Pure Tone Audiogram	Spontaneous Nystagmus	Hyperventilation Maneuver
Group 1							
1	M	8	None	Absent	N	Absent	Absent
2	F	12	None	Absent	N	(L) horizontal	Absent
3	F	15	None	(R) Hypoacusis	(R) SNHL	(R) horizontal	Absent
4	M	15	Effort-induced vertigo	Absent	N	(R) superior	(R) inferior
5	F	16	Positional vertigo Effort-induced vertigo (L) Retro auricular pain	Absent	N	Absent	Absent
6	F	16	None	Absent	N	Absent	Absent
7	F	17	None	Absent	(x2) moderate HL	(R) horizontal	(L) Nystagmus
8	F	18	None	Bilateral tinnitus	N	(L) horizontal	(R) horizontal
Group 2							
1	M	5	Imbalance	Absent	(L) severe HL	Absent	Absent
2	F	6	Imbalance	Absent	N	Absent	Absent
3	M	6	None	Absent	N	Absent	Absent
4	F	8	Imbalance	Bilateral tinnitus	N	(R) horizontal	Absent
5	F	12	(L) Retro auricular pain	Absent	N	(R) horizontal	Accentuation of nystagmus
6	F	13	Imbalance	Absent	N	(R) horizontal	Accentuation of nystagmus
7	M	14	None	Absent	N	Absent	(L) nystagmus
8	F	16	Retro auricular pain	(L) fluctuating	(L) moderate HL	Absent	Absent

3.1. Clinical Data

In addition to VP, two patients (25%) with narrowed IAC described an effort-induced vertigo, and only one patient (12.5%) had retro-auricular pain. In patients with NVCC syndrome, imbalance was frequently mentioned (50%), followed by retro-auricular pain (25%).

Overall, although hypoacusis was not a common subjective complaint, hearing loss was more frequently documented. Two patients had sensorineural hearing loss (SNHL) in each group. While HL was unilateral in 50% of cases in Group 1, all cases of HL were unilateral in Group 2. Tinnitus was described in one patient in each group; both patients had normal hearing status.

On videonystagmoscopy, a spontaneous nystagmus was detected in 62.5% and 37.5% in Groups 1 and 2, respectively. Only one patient (Group 1) had spontaneous vertical nystagmus that could suggest a central cause, but it was well inhibited by fixation. The HVIN turned out to be positive in 66% of cases (three patients) for each group.

3.2. Cochleo-Vestibular Data

Cochleo-vestibular data for each group are described in Table 2. IPL I–III latencies were prolonged in eight ears in narrowed IAC (50%) and five ears (30%) in NVCC syndrome. Vestibular outcomes were variable. While assessing otolithic function via VEMPs, no dysfunction was documented in Group 1, and unilateral dysfunction was documented in 50% of cases in Group 2. When assessing the semicircular canals' function, Group 1 seemed to have decreased VOR in 37.5% of cases. In Group 2, the VOR deficit was evoked in two patients but was not coherent with the laterality of the vascular loop. Caloric testing, with a cutoff level 20% for caloric weakness [46], was realized among six patients in Group 1 and two patients in Group 2. While it was normal in 66% of cases in Group 1, it showed a deficit in 50% of cases in Group 2 which was ipsilateral to the NVCC. A decreased gain on VHIT was documented in 37.5% and 25% of cases in Group 1 and 2, respectively.

Table 2. Audio vestibular evaluation for Groups 1, 2, and 3. Abbreviations: ABR (auditory brainstem response), AC (anterior canal), L (left), LC (lateral canal), PC (posterior canal), R (right), VEMPs (vestibular evoked myogenic potentials), vHIT (video head impulse test) and VOR (vestibulo-ocular reflex).

	ABR I–III Interval		VOR	vHIT	VEMPs
	(R)	(L)			
Group 1					
1	2.12	2.28	N	Decreased gain (x2)	N
2	2.2	2.3	(R) decreased responses	N	N
3	2.42	2.46	N	Decreased gain PC (x2)	N
4	2.37	2.46	Bilateral decreased responses	N	N
5	2.27	2.37	N	N	N
6	2.5	2.5	N	N	N
7	2.04	No response	N	Decreased gain LAC & LLC	N
8	1.96	1.92	Bilateral decreased responses	N	N

Table 2. *Cont.*

	ABR I–III Interval		VOR	vHIT	VEMPs
	(R)	(L)			
Group 2					
1	1.83	2.25	N	Decreased gain LPC	Absent (L)
2	2.2	2.37	(R) decreased responses	N	Absent (R)
3	2.20	2.20	N	N	Absent (R)
4	2.50	2.10	N	N	Absent (R)
5	2.21	2.33	N	Decreased gain RLC	N
6	2.07	2.10	N	N	N
7	2.23	2.23	(L) decreased responses	N	N
8	2.36	2.36	N	N	N

3.3. Radiologic Data

Table 3 shows detailed radiological interpretations and measurements for both groups. While the neurovascular compression was unilateral in all cases in Group 2, the IAC narrowing was bilateral in all cases in Group 1, except for one case. A right-sided NVCC was more frequently encountered (62.5%) (see Supplementary Materials).

Table 3. Radiologic data and IAC measurements (in mm). AP (anteroposterior), L (length), CC (craniocaudal), H (height), MRI (magnetic resonance imaging), and VDP (vertical diameter of the porus).

Group 1				
	MRI	CT Scan of Temporal Bones + IAC Measurements (mm)		Conclusion
		Right	Left	
1	The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 7.2 Smallest AP diameter: 3.3 L: 10.9 - Coronal plane: Smallest CC diameter: 2.8	- Axial plane: VDP: 8.6 Smallest AP diameter: 2.9 L: 11.3 - Coronal plane: Smallest CC diameter: 2.2	Bilateral narrowing of the CC caliber of IACs, more marked on the left side.
2	The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 4.2 Smallest AP diameter: 4 L: 12.9 - Coronal plane: Smallest CC diameter: 2.3	- Axial plane: VDP: 5.8 Smallest AP diameter: 3.5 L: 13.1 - Coronal plane: Smallest CC diameter: 2.7	Bilateral narrowing of the CC caliber of IACs, more marked on the right side.
3	Bifid aspect of the left saccule. The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 4.6 Smallest AP diameter: 3.5 L: 10.9 - Coronal plane: Smallest CC diameter: 2	- Axial plane: VDP: 5.3 Smallest AP diameter: 4.3 L: 5.3 - Coronal plane: Smallest CC diameter: 3.4	Right narowing of the CC caliber of the IACs.
4	The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 4.6 Smallest AP diameter: 3.5 L: 13.7 - Coronal plane: Smallest CC diameter: 2.3	- Axial plane: VDP: 4.8 Smallest diameter: 4.1 L: 13 - Coronal plane: Smallest CC diameter: 2.3	Bilateral narrowing of the CC caliber of the IACs.

Table 3. *Cont.*

	Group 1			
	MRI	**CT Scan of Temporal Bones + IAC Measurements (mm)**		**Conclusion**
		Right	**Left**	
5	Narrowing of the IAC in their CC caliber more marked on the right.	- Axial plane: VDP: 5.4 Smallest AP diameter: 3.8 L: 10.5 - Coronal plane: Smallest CC diameter: 2.3	- Axial plane: VDP: 5.5 Smallest AP diameter 3.2 L: 10.6 - Coronal plane: Smallest CC diameter: 2.7	Bilateral narrowing of the CC caliber of the IACs, more marked on the right side.
6	The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 4.7 Smallest AP diameter: 4.1 L: 15.7 - Coronal plane: Smallest CC diameter: 1.5	- Axial plane: VDP: 8 Smallest AP diameter: 3.6 L: 16.3 - Coronal plane: Smallest CC diameter: 2.5	Bilateral narrowing of the CC caliber of IACs, more marked on the right side.
7	Bilateral IAC narrowing	- Axial plane: VDP: 4.5 Smallest AP diameter: 4.1 L: 12.4 - Coronal plane: Smallest CC diameter: 1.8	- Axial plane: VDP: 4.7 Smallest AP diameter: 3.4 L: 14.8 - Coronal plane: Smallest CC diameter: 2.3	Bilateral narrowing of the CC caliber of the IACs, more marked on the right side.
8	The internal auditory canals are small in size bilaterally.	- Axial plane: VDP: 3.2 Smallest AP diameter: 2.7 L: 9.7 - Coronal plane: Smallest CC diameter: 2.1	- Axial plane: VDP: 8.4 Smallest AP diameter: 2.5 L: 10.7 - Coronal plane: Smallest CC diameter: 1.8	Bilateral narrowing of the CC caliber of the IACs, more marked on the left side.
Group 2				
MRI				
1	Left PICA vascular loop in contact with the cisternal emergence of the left acoustic facial bundle.			
2	Vascular loop at the level of the left APC; close contact between the left AICA and the acoustic-facial bundle at this level.			
3	Vascular loop at the level of the right APC			
4	Arterial vascular loop of the right AICA having a double contact with the cisternal path of the right nerve VIII, especially at the porus, in RE Z zone, without deviation of the neural structure.			
5	Double contact between an AICA at the emergence of the VIII on the right.			
6	Neurovascular compression syndrome on the right-sided bundle of NC VIII with a moderate mass effect on the nerve structure (pathogenic appearance).			
7	Intimate contact of the APC between VII and VIII with right PICA.			
8	Vascular-nerve contact between the left AICA and the left acoustic-facial bundle at the level of the IAC porus. This contact is orthogonal with the G facial nerve and VIII G. Mass effect on VIII questionable in transitional zone.			

3.4. Therapeutic Data

Treatment with anticonvulsant drugs was prescribed to alleviate severe and recurrent incapacitating attacks [7,10]. Therefore, oxcarbazepine was prescribed in four patients for each group. All patients reported substantial improvement consistent with the onset of drug use, except for one patient in Group 2. Half of these patients described the reappearance of VP when treatment was withdrawn in the short term. In these cases, treatment was continued for longer periods.

3.5. Case Report

An 18-year-old girl has been suffering from recurrent attacks of vertigo consistent with paroxysmal vertigo for more than 2 years. She did not have any cochlear symptoms,

and her audiometry was normal. Her examination did not reveal a spontaneous or an induced nystagmus. Her cochleovestibular testing showed a normal otolithic function, symmetrical caloric responses, and normal gains on vHIT. On the rotational chair, her VOR was diminished. The ABR revealed a slight increase of the left-sided IPL I–III (2.37 vs. 2.27 for the right ear). When she underwent an MRI of the brain and inner ear, a narrowing of the IAC was suspected bilaterally, more specifically on coronal planes and more pronounced on the right (Figure 1).

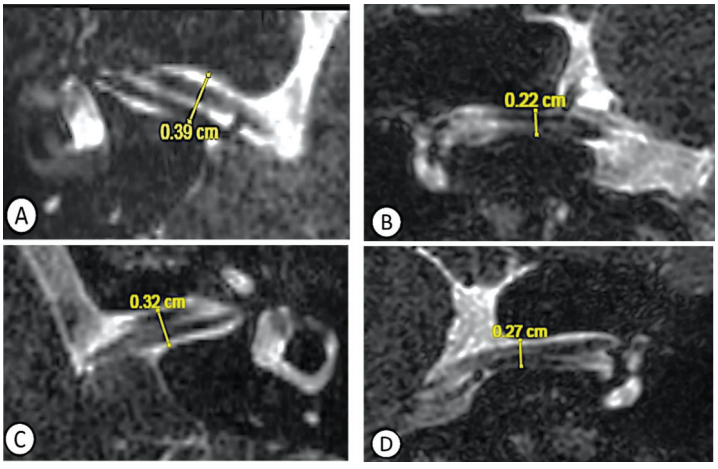

Figure 1. MRI of the inner ear (IAC sections) suggesting a bilateral narrowing of the IAC in the coronal plane, more pronounced on the right side: (**A**) right ear, axial plane; (**B**) right ear, coronal plane; (**C**) left ear, axial plane; and (**D**) left ear, coronal plane.

Consequently, an HRCT was performed. In the coronal plane, the smallest cranio-caudal diameter was estimated at 2.3 and 2.7 mm on the right and left side, respectively (Figure 2).

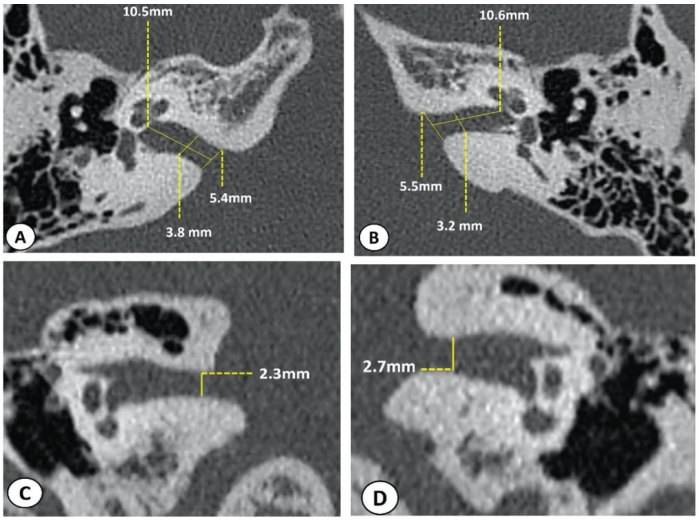

Figure 2. HRCT of temporal bones (IAC sections) confirming a bilateral narrowing of the IAC, in the coronal plane, more pronounced on the right side: (**A**) right ear, axial plane; (**B**) left ear, axial plane; (**C**) right ear, coronal plane; and (**D**) left ear, coronal plane.

In view of the recurrence and the disability of vertigo, preventing the patient from continuing her daily activity, a treatment with oxcarbazepine was prescribed at a dose of 300 mg. During treatment, the patient described a significant reduction of attacks. The IPL I–III was also normalized under treatment: 1.87 ms for the right ear and 2.07 ms for the left ear (Figure 3). Withdrawal of treatment was associated with a recurrence of symptoms, and this necessitated prolonging its duration.

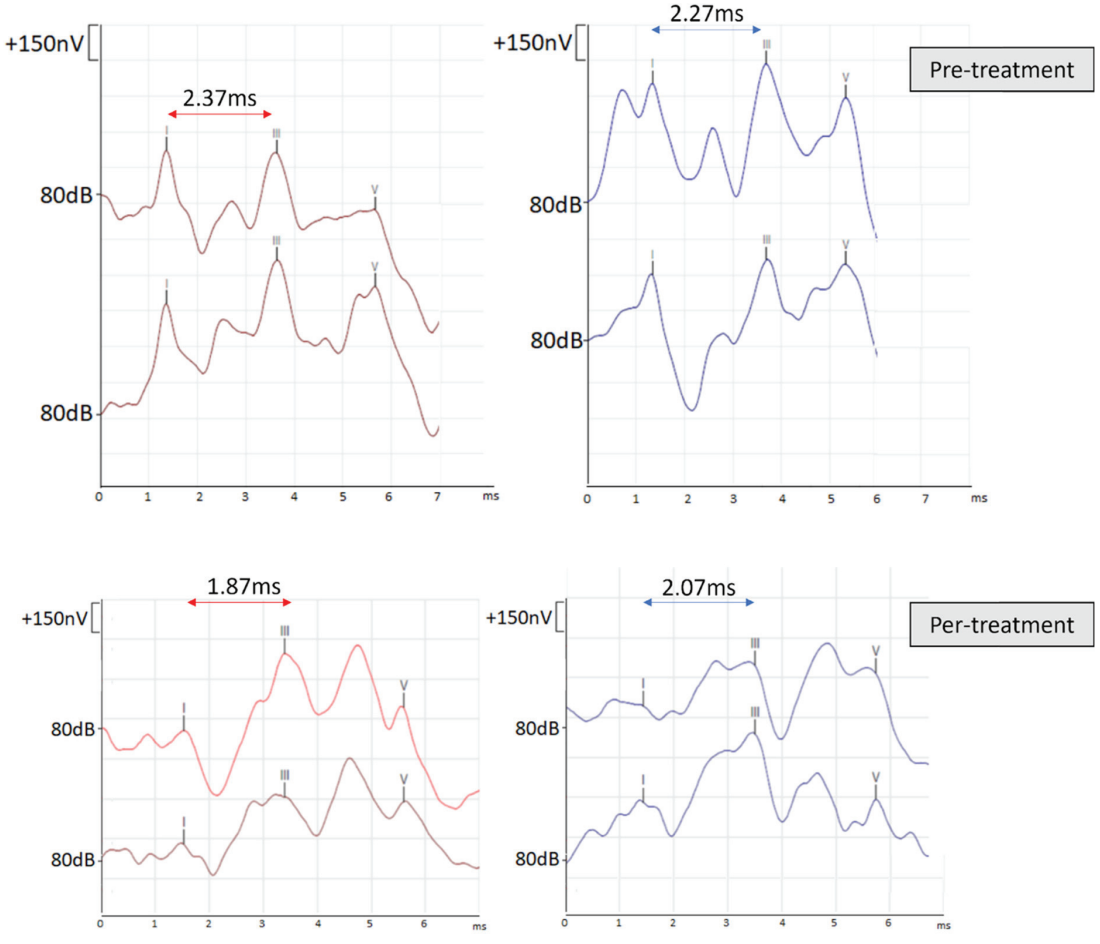

Figure 3. ABR and IPL I–III measures pretreatment and per treatment.

4. Discussion

4.1. The Narrowed Internal Auditory Canal

Our main objective of this paper is to emphasize a new etiology that can be considered among pediatric patients with VP. Our data suggest patients with narrowed IAC had similar clinical manifestations and cochleo-vestibular outcomes to those with NVCC. The IAC is a bony canal of the temporal bone that involves the CN VII (facial), the CN VIII (vestibulocochlear), and the labyrinthine artery, a branch of the anterior inferior cerebellar artery [47]. As stated earlier, it is assumed that a local compression of CN VIII can generate VP [29,48]. Furthermore, in the case of a narrowed IAC, we may assume that the cochleo-vestibular symptoms can be related to an entrapment-type local neuropathy similar to the pathology of the carpal tunnel or radiculopathies caused by the local compression [49,50].

In fact, congenital IAC stenosis can be responsible of various cochleo-vestibular and facial symptoms, but it is often associated with hypoplastic nerve [23,51,52]. In our study, radiologic evaluation confirmed sufficient nerve development, but a narrowed IAC. Previously, one case study reported cochleovestibular and facial nerve dysfunction secondary to IAC stenosis [53]. All of these data suggest that CN VIII compression, secondary to a small diameter of the IAC, may lead to local nerve damage, resulting in a possible ectopic excitation or inhibition of the involved cranial nerve fibers, as previously reported [54]. Therefore, a narrowed IAC might be considered in patients presenting a VP associated or not to auditory symptoms.

4.2. Morphometric Considerations

In the present study, our data suggested that a narrowed IAC is more commonly encountered in adolescence, as compared to childhood. Surprisingly, most of these adolescents had a noteworthy height growth (data not shown). On the one hand, growth happens in a craniocaudal direction with downward slanting of nerve roots [55]. On the other hand, the size and the shape of the IAC vary considerably among individuals; the wall length and porus diameter increase with age, but the diameter of the fundus remains stable [43,56]. The diameter and length increase significantly until the age of 1 year and 10 years, respectively [56]. A rapid height growth may be associated with an increased growth of the IAC length and consequently generate a nerve stretching, excitement, or damage of the nerves. In fact, an extensive development of a nerve tends to delay its neighbors, and a lack of development tends to excite them to a more active growth [57].

Another morphological criterion concerns the shape of the IAC, as it is not unique and can take several forms [44]. Hence, radiologic measurements, including opening width, longitudinal length, and vertical diameter, can be sufficient when the IAC is cylindrical. However, when IAC has a conical or a bud shape, these measurements may be insufficient, and one vertical measurement might be biased. Therefore, we elected to verify the smallest vertical diameter in addition to conventional dimensions in both the axial and coronal planes to avoid misdiagnosis. In fact, the association between otological symptoms and vascular loop are still controversial [58–62]. This relationship has been related to the loop location following Chavda classification [63]. While Yoo et al. reported that tinnitus was significantly higher when the loop lies within the cerebellopontine angle (Type I) and when the loop is extended within less than 50% of the IAC (Type II) [59]. Kim et al. found that tinnitus was significantly related to loops' extension more than 50% (Type III) [60]. Hearing loss was significantly associated with loops running between the CN VII and CN VIII [61]. Taken together, these data suggest that a narrowing of the shape-related smallest diameter of the IAC may generate cochleo-vestibular symptoms. It would be interesting to radiologically explore an associated lack of the protective property of the cerebrospinal fluid at the level of the suspected compression suggestive of a mechanical injury [64]. A grading of the internal auditory canal assessment, as per lumbar spinal stenosis [65], would strengthen radiologic practice and create a unified view of analysis and reporting system.

4.3. Therapeutic Considerations

In the present study, low doses of oxcarbazepine were prescribed for patients with invalidating symptoms, and it succeeded to relieve patients' symptoms. Oxcarbazepine's efficacy can somehow be secondary to its ability to bind to sodium channels and inhibit repetitive neuronal exciting firing [66]. Moreover, oxcarbazepine can inhibit glutamate, which is the most important afferent neurotransmitter in the auditory system [66,67]. So far, there are no randomized controlled trials for VP, but the response to treatment with carbamazepine/oxcarbazepine supports the diagnosis [14]. Although the long-term administration of anticonvulsant drugs in epileptic patients was reported to provoke delayed auditory conduction [68–70], a normalization of IPL I–III was noticed in our case. Thus, it is possible that the low doses of oxcarbazepine used in VP are less toxic than the higher doses usually required in epilepsy, resulting in a beneficial effect on the narrowed IAC-induced

neuropathy. Unfortunately, we were unable to control electrophysiological outcomes both pretreatment and per treatment in all patients; thus, further studies are required to support the efficacy of treatment in such pathologies. A conduction latencies modification needs to be evaluated in a larger population sample for its usefulness as a possible additional objective criterion to reinforce the diagnosis and evaluate the treatment's effectiveness.

4.4. Limitations and Further Research

In the present study, we report a distinct possible etiology that can be considered as the cause of VP in children. The results of this study should be considered in light of certain limitations. The sample size was small (n = 16), so it is too insufficient to obtain statistical data and to be generalized to the pediatric population. The results' estimates are based on retrospective observational data. They are therefore subject to bias. In addition, therapeutic data were scarce. Thus, a clear judgment on therapeutic response was missing. This topic, for which, to our knowledge, no previous studies have been conducted, requires further research. Additional studies with larger sample size, statistical data, therapeutic response, and long-term evaluations may be useful to consider the diagnosis broadly and generalize it to the pediatric population.

5. Conclusions

VP is a documented etiology of vertigo in the pediatric population and has been related to NVCC syndrome. In the present study, our data suggest that VP can also originate from a narrowed IAC. Clinical presentation and electrophysiological outcomes can be similar to those of NVCC syndrome. The diagnosis is suspected through MRI and can be confirmed by a supplementary HRCT of temporal bones with analysis of the shape, diameter, and opening width of the IAC in both axial and coronal plans. In the present study, we reported a systematic association between the narrowing of IAC diameter, especially in the coronal plane (less than 3 mm) and VP symptomatology, thus suggesting its involvement in the genesis of this pathology. This finding urges the concerned specialists to carefully assess the IAC diameter, not only in the axial plane, but also in the coronal plane. The latter can be evaluated initially on an MRI and, if deemed necessary, completed with a CT scan. Treatment with sodium-channel blockers drugs showed promising results. Although the present study is limited by a small sample size, it allows clinicians to become sensibilized to this VP's etiology. Further studies need to be conducted to assess the characteristics of this new clinical entity.

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"The Pupillary (Hippus) Nystagmus": A Possible Clinical Hallmark to Support the Diagnosis of Vestibular Migraine

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Abstract: (1) Background: Hippus (which in this paper will be called "Pupillary nystagmus") is a well-known phenomenon which has never been related to any specific pathology, so much so that it can be considered physiological even in the normal subject, and is characterized by cycles of dilation and narrowing of the pupil under constant lighting conditions. The aim of this study is to verify the presence of pupillary nystagmus in a series of patients suffering from vestibular migraine. (2) Methods: 30 patients with dizziness suffering from vestibular migraine (VM), diagnosed according to the international criteria, were evaluated for the presence of pupillary nystagmus and compared with the results obtained in a group of 50 patients complaining of dizziness that was not migraine-related. (3) Results: Among the 30 VM patients, only two cases were found to be negative for pupillary nystagmus. Among the 50 non-migraineurs dizzy patients, three had pupillary nystagmus, while the remaining 47 did not. This resulted in a test sensitivity of 0.93% and a specificity of 0.94%. (4) Conclusion: we propose the consideration of the presence of pupillary nystagmus as an objective sign (present in the inter-critical phase) to be associated with the international diagnostic criteria for the diagnosis of vestibular migraine.

Keywords: pupillary hippus; pupillary nystagmus; vestibular migraine; vertigo; vestibular examination

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1. Introduction

Vestibular migraine (VM) is characterized by recurrent vestibular attacks that are not associated with migraine headache. VM is now considered as the first cause of episodic vertigo in adults [1], and it is a common diagnosis in children [2]. The diagnosis is primarily based on clinical history, and international guidelines have been developed [3,4]. While the presence or history of migraine is essential for its diagnosis, the headache and dizzy symptoms do not need to temporally coincide. The instrumental examination of patients with VM shows normal results or variable and inconsistent abnormalities, but vestibular testing needs to be performed with the aim of excluding other disorders considered in differential diagnosis. This implies that it is necessary to spend time collecting the detailed clinical history of the patient who, however, is not always able to describe his symptoms exactly with the risk of omitting important details for diagnostic purposes.

Having an instrumental hallmark would be extremely useful, especially in cases where the clinical picture does not fully meet the international diagnostic criteria. In this paper, a sign that has been well known for years and whose origin has never been defined with certainty, so much so that it was classically considered a phenomenon without clinical value, was taken into consideration. It is a very characteristic behavior of the pupil, which dilates and contracts cyclically in the presence of constant lighting, independently of eye movements or change in illumination [5]. It has been called "pupillary hippus" (PH), "pupillary athetosis", or, in English-speaking countries, "pupillary unrest" or "dancing pupils", terms that seem, however, to be rather non-specific [6]. PH usually occurs in a physiologically drowsy state, and can range from 0.04 to 2 Hz [5], and the magnitude of

the pupil size variations range from not detectable to over 0.5 mm [7]. A precise definition of PH is lacking; the variety of techniques used to assess the pupil movements and the interindividual variation do not allow for validated parameters to consider PH as pathological. PH has been observed in patients suffering from epilepsy [7] or neurotic disorders [8], diabetic autonomic neuropathy [9] and is associated with disorders of the autonomic nervous system [10]. On the other hand, dysautonomia has also been reported to underlie migraine disease [11], and the presence of PH has also been reported in migraineurs [12,13]. In this paper we evaluated the presence of PH in patients suffering from VM with the aim of identifying an objective sign that may be potentially useful in helping the physician with the diagnosis of VM, especially when the criteria indicated by international guidelines are not fully met.

2. Materials and Methods

Two series of patients complaining of vertigo and dizziness were considered:

- 30 patients consecutively diagnosed as suffering from definite VM (mean age 52 years, minimum 6 years, maximum 77 years, 11 males and 19 females). The diagnosis of vestibular migraine was made based on international criteria [3]. We excluded from the study patients with probable VM and subjects who had received ear or eye surgery or other significant comorbidities.
- 50 consecutive patients (mean age 58 years, minimum 17 years, maximum 89 years, 23 males and 27 females) affected by vertigo and dizziness not attributable to VM, who constituted the control group. All the patients belonging to the control group did not suffer from migraine or other types of headaches.

The patients belonging to the control group were affected by paroxysmal positional vertigo (15), acute vestibular deficit (8), vascular vertigo (6), Meniere's disease (6), and acoustic neuroma (1). A total of 14 patients showed a normal examination, and the dizziness was attributable to diseases that were not strictly vestibular (such as pharmacological dizziness, orthostatic hypotension, and undiagnosed PPPD).

Patients underwent a thorough medical history, otoscopy, neurological evaluation (cerebellar tests and clinical evaluation of the cranial nerves), audiometry, evaluation of the spontaneous and positional nystagmus, and a head shaking test using infrared goggles. The instrumental examination consisted of performing video-HIT, functional-video-HIT, caloric testing, and cervical and ocular VEMPs.

During our experience, we have informally begun to call PH by the heterodox expression: "Pupillary Nystagmus"' (PNy). It is well known that no correlation exists between the pupillomotor response and the vestibulo-ocular reflex. From a semeiological point of view, PH could have some similarity with the well-known extra-vestibular nystagmus. Nystagmus is defined as "... a repetitive to and fro movement of the eyes that includes smooth sinusoidal oscillations (pendular nystagmus)" [14]. PH could be defined inductively as "... a repetitive to and fro change in the pupil diameter that includes smooth sinusoidal oscillations". The only difference is that this phenomenology affects intrinsic rather than extrinsic eye muscles. The semantic expression 'pupillary nystagmus' is intended only as a current, but suggestive, variant with the aim of referring to the common traits that the phenomenon of pupillary hippus has with extravestibular nystagmus.

The assessment of pupillary nystagmus (PNy) (presence/absence) was performed under Frenzel glasses, and a video (lasting at least 10 s) was taken. The examiner evaluated the visible amplitude of PNy during the whole observation period under Frenzel glasses. Patients entering the study did not report any other neurological or eye problems or significant head injuries. None of the patients took any drugs that could affect the autonomic nervous system. The presence or absence of pupillary nystagmus was assessed by two different examiners in a double-blind manner: each of them was unaware of the evaluations of the other, including the medical history and examination results. In no case was there a discrepancy in evaluation, demonstrating the ease of observation of the sign. All patients underwent contrast-enhanced brain nuclear magnetic resonance imaging.

A statistical evaluation was performed using a Pearson's chi-squared test, phi coefficient and Bayesian contingency tables—BF10 [GNU Project (2015). GNU PSPP (Version 0.8.5) [Computer Software]. Free Software Foundation. Boston, MA, USA; JASP Team (2022). JASP (Version 0.16.3).

Ethical review and approval by the local Institutional Board (Comitato Etico Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy) were waived for this study. Due to its retrospective nature, it was not set up as part of a research project. Furthermore, the study does not include new experimental diagnostic protocols, and the patients included in the study were diagnosed according to national guidelines. Written informed consent was obtained from all participants, and the study was conducted in accordance with the 1964 Declaration of Helsinki.

3. Results

Among the 30 VM patients, only two cases were found to be negative for pupillary nystagmus (Video S1, Supplementary Material). Among the 50 non-migraineur dizzy patients, three had pupillary nystagmus, while the remaining 47 did not. Table 1 shows the results obtained in the two groups.

Table 1. Prevalence of pupillary nystagmus in patients with vestibular migraine and in non-migraine patients. VM: vestibular migraine; No VM: dizzy patients not suffering from vestibular migraine; PNy+ patients presenting with pupillary nystagmus; PNy− patients who do not have pupillary nystagmus.

	VM	No VM	Total
PNy+	28	3	31
PNy−	2	47	49
Total	30	50	80

This resulted in a test sensitivity of 0.93% and a specificity of 0.94%.

The positive predictive value is 0.90, and the negative predictive value is 0.96.

A statistical evaluation was undertaken using the chi-square test, and showed a significant difference (X^2 value 60.25, $p < 0.001$, Phi 0.87, BF_{10} independent multinomial $8.598 \times 10^{+13}$). (Table 2).

Table 2. Bayesian Contingency Tables. Pny: pupillary nystagmus.

Contingency Tables			
	Migraine		
Pny	0	1	Total
0	47	2	49
1	3	28	31
Total	50	30	80
Bayesian Contingency Tables Tests			
			Value
BF_{10} Independent multinomial			$8.496 \times 10^{+13}$
N			80

Note. For all tests, the alternative hypothesis specifies that group 0 is not equal to 1.

4. Discussion

The diagnosis of VM is based quite exclusively on the history taking; there is no pathognomonic clinical sign for VM and there are no gold standard diagnostic tests for VM.

The availability of some clinical or instrumental test with a relatively high sensibility and specificity would be very useful, especially when the international criteria are not completely fulfilled. Only the functional video HIT performed with an optokinetic stimulation seems to provide some positive results in VM, indicating a visual dependence in VM patients complaining of visually induced vertigo, head motion–induced vertigo, and head motion–induced dizziness with nausea [15,16]. Usually, the diagnosis of VM is made by an audiologist, otolaryngologist or neurologist. It would be appropriate for the ideal sign associated with vestibular migraine to have all of the following characteristics:

- strongly suggestive (even if not pathognomonic) of the condition, therefore present in as many VM patients as possible and absent in most patients with vertigo or dizziness not migraine related;
- easily identifiable on otoneurological examination;
- present in the inter-critical phase, since it is difficult to examine a VM patient in the acute stage of the disease;
- ease of recording and archiving.

In the absence of changes in external influences such as luminance, mood, and fixation, the pupil is in constant motion. An exaggeration of this phenomenon is usually termed Pupillary Hippus: its frequency ranges from 0.04 to 2 Hz [5], and the magnitude of the pupil size variations usually do not surpass 0.5 mm [5]. It is more evident in pupils of medium amplitude and has a periodic pattern (the period measured was 5 seconds[5]) but the course may not be constant over time (Figure 1). The origin of pupillary hippus is believed to be related to an abnormal activity of the autonomic nervous system because it can be inhibited by pharmacologically antagonizing the parasympathetic system [5,10].

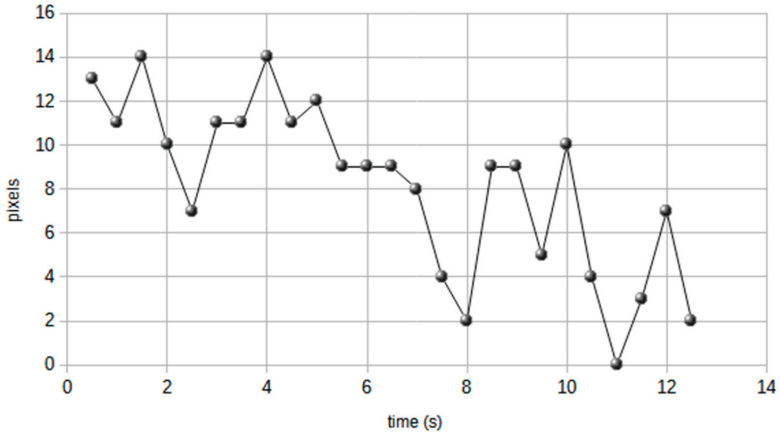

Figure 1. Pupil diameter trend in a migraine patient, shown by the measurement (pixels) performed on the video (by individual frame).

The disruption of the balance between the sympathetic and parasympathetic systems is considered a pathophysiological mechanism underlying migraine disease [13], and changes in pupillary function have been observed in migraine both in the headache attack and in the intercritical phase [17].

It has been reported that the left cerebral hemisphere is mainly involved in parasympathetic activity, and the right in sympathetic system activity. Parasympathetic stimulation in unilateral migraineurs causes significant skin phenomenology on the stimulated side, and sympathetic stimulation does not seem to influence this significantly. Activation in this case would occur through a trigemino-parasympathetic reflex, resulting in vasodilation and the increase in secretory phenomena [18]. There is evidence of a lower sympathetic activity in migraineurs, demonstrated by an increased latency to the light reflex, after apraclonidine

administration [19]. Reduced nocturnal activity of the parasympathetic system has also been demonstrated in migraine patients, especially in subjects with aura [20]. Furthermore, cardiac vagal responses via baroreceptors are reduced in migraine patients, but sympathetic system-related responses are not. As a consequence, it appears that the autonomic nervous system may play a role in the pathophysiology of migraine [21]. The pupillary hippus phenomenon can be extinguished with antagonists of the parasympathetic nervous system, whereas antagonists of the sympathetic system dilate the pupils without blocking the hippus: this suggests that the phenomenon originates in the centrally localized parasympathetic system and not in the sympathetic system [10]. Furthermore, parasympathetic activity contributes to the onset of pain in migraine by activating or sensitizing (or both) the intracranial nociceptors [10].

It seems well established in the literature that [10,18,19]:

- the pupil reacts to asymmetries in the balance between the sympathetic and parasympathetic through changes in its diameter, with particular dependence on vagal tone;
- An imbalance between the sympathetic and parasympathetic can contribute to the genesis of painful migraine pathology.

It has recently been shown that the pupillary cycle has specific characteristics in the migraine sufferer: in particular, the pupillary cycle period is longer in the migraine. This data allows the differentiation of a migraine patient from a non-migraine patient [21].

The pupillary cycle is a well-known phenomenon [22], and consists in the projection of a luminous dot onto the pupil, very close to the edge of the iris. The photomotor reflex causes miosis, which prevents the light beam from reaching the retina. Consequently, the pupil dilates, and the light reaches the retina again, giving rise to a new cycle. The frequency of the pupillary cycle allows for the evaluation of the sympathetic-parasympathetic balance and, consequently, the predisposition to migraine.

Our results recorded in a group of VM patients demonstrate a very high incidence of PNy (in contrast with the low incidence observed in patients suffering from vertigo and dizziness not migraine related) whose presence could be considered as a hallmark of the disease. The high sensitivity and sensibility of PNy makes this sign highly pathognomonic of VM, and it could be helpful in patients with possible VM. We have found PNy in the only child (six years of age) present in our series of patients suffering from VM. In children, the hippus frequency seems to be higher than it is in adults, suggesting the influence of the sympathetic branch of the autonomic nervous system on it that decreases with age and maturation [23]. For this reason, the presence of PNy in children must be considered with caution. Two patients in definite VM groups did not show PNy; analyzing their clinical and instrumental characteristics, we found no difference compared from those who showed PNy.

As it is not clear in the literature whether the phenomenon is also present in the dark, it is advisable to search for the sign under Frenzel's glasses or, in any case, in a permanently lit environment (Table 3). However, the use of a binocular system of evaluating the pupillary movements is recommended; a unilateral PH was described in migrainous patients. The search under infra-red video-Frenzel should be avoided entirely, or at least until evidence of the presence of pupillary nystagmus (even in the dark) is obtained.

Table 3. The modalities of observation of PNy.

1.	The patient is examined with the eyes open under Frenzel glasses
2.	Lighting must be constant
3.	Vergence movements and blink reflex should be avoided
4.	The observation must last at least 10 s
5.	A video recording of PNy is recommended

The sign was always detected in the inter-critical phase (none of the patients examined were in the acute vertiginous crisis phase or reported headache at the time of observation). Little time is required for the examination, as it is to be considered exactly like the 'bedside' search for a spontaneous nystagmus. However, it needs to focus specifically on the pupil if one wants to avoid losing the data. In our case series, pupillary nystagmus was present in the great majority of VM patients. It was also present in three patients considered non-migraineurs (6%), but we cannot exclude that in those cases the anamnesis was lacking, given the well-known difficulty in identifying headache crisis as migraine, which is often wrongly attributed to different causes (neck pain, neuralgia, sinusitis, etc.). As an alternative to the study of the pupillary cycle which is not complicated but which requires the help of the Ophthalmologist, we propose the direct search of this sign (using Frenzel glasses) in dizzy patients, especially when a VM is suspected.

The main limitation of this study is the small size of the sample and the heterogeneity of the control group. For this reason, we are planning a study with a large number of patients evaluating additional factors such as age, gender, and course of VM, in order to allow for more significant results. Moreover, the method we have proposed for evaluating the PNy is certainly less precise than an ophthalmological study of the pupillary cycle [21]. Using an infrared pupillometer would be more accurate than assessing pupil size under Frenzel goggles. Nevertheless, as a part of the bedside assessment of patients with suspected VM, this practical and simple evaluation of the pupil movements seems to be sufficiently valuable.

5. Conclusions

Even if our results need to be confirmed in a larger series of patients, we propose the observation of pupillary nystagmus as an objective sign helping the physician to diagnose vestibular migraine, being very common in the intercritical phase of this pathology and rarely encountered in dizzy patients that are non-migraine sufferers. This sign is easy to observe and is recordable with a camera or smartphone. We recommend the observation of PNy whose presence could be considered as a supplementary element to reenforce the diagnosis of VM based mainly on the clinical criteria suggested by a joint committee of the International Headache Society (IHS) and the Barany Society [4].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12051957/s1; Video S1: Patient suffering from vestibular migraine. The pupil cyclically dilates and constricts despite constant illumination (the video is taken under Frenzel glasses).

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Suppression Head Impulse Test (SHIMP) versus Head Impulse Test (HIMP) When Diagnosing Bilateral Vestibulopathy

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Abstract: The Suppression Head Impulse (SHIMP) test was introduced as an alternative to the Head Impulse Paradigm (HIMP) to overcome challenges in VOR gain calculation due to the interference of covert saccades. The objectives of this study were (1) to determine if SHIMP, compared to HIMP, reduces covert saccades in BV patients and (2) to define the agreement on diagnosing BV between SHIMP and HIMP. First, the number of covert saccades was compared between SHIMP and HIMP. Secondly, VOR gain was compared between SHIMP and HIMP. Lastly, the agreement between SHIMP and HIMP on identifying BV (horizontal VOR gain <0.6) was evaluated. A total of 98 BV patients were included. To our knowledge, this is the largest study population on SHIMP testing in BV patients. Covert saccades were significantly reduced, and a lower VOR gain was found during SHIMP compared to HIMP ($p < 0.001$). However, the clinical relevance of these statistically significant differences is small. In 93% of the patients, an agreement was found between the two paradigms regarding the diagnosis of BV, and both paradigms detect BV in the vast majority of patients.

Keywords: SHIMP; HIMP; VHIT; covert saccades; compensatory saccades; VOR gain; bilateral vestibulopathy

1. Introduction

The Head Impulse test (HIMP), first described in 1988, is nowadays widely used to assess the vestibulo-ocular reflex (VOR) function of all semicircular canals in the high-frequency domain [1]. During this test, the examiner performs fast head impulses (>120°/s) and passive head movements with a small amplitude (10–30°), unpredictable in timing and direction. Subjects are asked to fixate on an earth-fixed target at eye level in front of them. In the case of a normal VOR, the eyes will immediately move in the opposite direction of the head impulse to assure gaze stability on the target. In patients with a deficient VOR, the eyes will move slower than the head or even initially move along with the head. To correct for the loss of gaze fixation, a compensatory eye movement (saccade) is required. Therefore,

the appearance of saccades could indicate vestibular hypofunction. These saccades can appear after (i.e., overt saccade) or during (i.e., covert saccade) the head impulse. Overt saccades are often detected by the naked eye of the examiner. In contrast, this is mostly impossible for covert saccades [2].

The HIMP can also be performed using a device that allows for the quantification of the VOR and detection of all compensatory saccades: the video head impulse test (VHIT). This device tracks head and eye movements during the head impulse test. Different types of devices are commercially available, including systems with head-mounted lightweight goggles or an earth-fixed remote camera. The main outcome parameter is VOR gain, calculated as the ratio between eye and head movement. VOR gain will be close to one in healthy subjects and lower in patients with a deficient VOR [3]. For example, a bilateral horizontal VOR gain of <0.6 is one of the main criteria for the diagnosis of bilateral vestibulopathy (BV) [4]. Different algorithms can be used to calculate VOR gain. Covert saccades might challenge VOR gain calculation due to their interference with eye movements produced by the VOR [5]. This implies that VOR gain might not always perfectly reflect the VOR function. Current HIMP systems tend to overcome this issue by, for example, desaccading eye movements [6].

In 2016 the Suppression Head Impulse test (SHIMP) was introduced by MacDougall et al. as an alternative to HIMP to overcome challenges in VOR gain calculation due to the interference of covert saccades [7]. The main difference between SHIMP and HIMP is a head-fixed target instead of an earth-fixed target. The target is a laser dot projected by lightweight goggles. As a result, the target moves along with the head during the head impulse. In the case of an adequate VOR, the eyes will initially move in the opposite direction of the head. However, since the head-fixed target has moved during the impulse, these subjects need compensatory eye movements (saccades) to bring the eyes back on the target. Consequently, saccades during SHIMP represent (residual) vestibular function, while saccades during HIMP could indicate a vestibular loss [7]. Moreover, saccades in SHIMP testing will mainly occur after the head impulse (overt saccades) and not during the head impulse (covert saccades) [2]. However, studies show that predictability during SHIMP could still result in shorter latency of saccades and even covert saccades [8]. Hence, when properly performed, SHIMP testing could enable elimination over covert saccades and might facilitate a more precise VOR gain calculation than in HIMP.

Previous research demonstrated that SHIMP is a feasible test in healthy subjects and vestibular patients. In SHIMP, a lower VOR gain was found compared to HIMP. The underlying mechanism is not fully known, but several explanatory theories are preferred: less interference of covert saccades as described above (no desaccading of the traces necessary) or the influence of compensatory mechanisms that are possible during SHIMP (e.g., VOR cancellation/inhibition resulting in slower eye velocities) [7,9,10]. The presence of covert saccades is lower in SHIMP than in HIMP [7]. However, the clinical consequence of eliminating covert saccades when using SHIMP has not yet been determined comprehensively in a large group of BV patients.

Therefore, the objectives of this study were (1) to determine if SHIMP, compared to HIMP, reduces covert saccades in BV patients and (2) to define the agreement on diagnosing BV between SHIMP and HIMP. It was hypothesized that BV patients demonstrated fewer covert saccades and a lower VOR gain when tested with SHIMP compared to HIMP, but that these effects might not influence the diagnosis of BV in most patients.

2. Methods

2.1. Study Population

This study comprised patients diagnosed with BV at the Division of Balance Disorders at Maastricht University Hospital in the Netherlands and Antwerp University Hospital in Belgium, based on the diagnostic criteria for BV from the Bárány Society [4]. Inclusion criteria comprised (1) reduced caloric response (sum of bithermal maximum peak slow phase eye velocities of <6°/s on each side), (2) and/or reduced horizontal angular

VOR gain < 0.1 on a rotatory chair and a phase lead >68°, (3) and/or bilateral horizontal VOR gain < 0.6, obtained by the VHIT. Exclusion criteria comprised being unable to stop vestibular suppressants for one week (cinnarizine and all psychiatric medication) and the inability to undergo one of the vestibular examinations.

Study Design

A systematic approach was used. First, it was determined whether covert saccades were eliminated during SHIMP by comparing the number of covert saccades between SHIMP and HIMP. A custom-made algorithm detected saccades after strict trace evaluation to exclude artefacts as described in Section 2.3). Since the definition of covert saccades can be different between clinics, the latency of the first saccade (covert and/or overt) was also analyzed separately. Secondly, the VOR gain was compared between the two paradigms, and the influence of peak head velocity was determined. Lastly, the agreement between SHIMP and HIMP on identifying BV according to the diagnostic criteria (horizontal VOR gain <0.6) was evaluated. For this last analysis, the unfiltered data from the device were used, as will be the case in daily practice.

2.2. Experimental Setup

To reduce the artefacts to a minimum, two trained examiners (FL, BD) followed a strict experimental setup, as described in previous articles [11,12]. Every patient underwent testing in the same order (first HIMP, then SHIMP). All tests were performed using the ICS Impulse system (Natus, California, CA, USA). Distance to the target and room illumination were similar for all patients [13]. The right eye was tested in both SHIMP and HIMP paradigms. After calibration, the examiner nor the patient were allowed to touch the strap and the goggles. Patients were constantly kept alert by the instructions of the examiner. Fast (>120°/s), outwards, horizontal head impulses with a small amplitude (10–30°) were given, unpredictable in timing and direction [14,15].

2.3. Saccades

2.3.1. Saccade Detection

In order to determine saccades, first head and eye velocity traces were exported from the Otometrics system, and position and acceleration data were calculated using Wolfram Mathematica 11.3 (Wolfram Research, Champaign, IL, USA) [16]. Only traces that were accepted by the Otometrics system itself were exported. All traces were checked on artefacts. Traces were excluded from analyses when (1) peak head velocity was <120°/s, (2) the head velocity trace had a bounce >50% of peak head velocity after the head impulse, (3) head velocity never crossed zero after peak head velocity, (4) the head velocity trace contained missing values, (5) the head velocity trace differed from the standard shape, assessed by visual inspection and consensus between three authors (RB, DS, TD), or (6) when the mean head velocity of the interval of 80 ms prior and 120 ms after a peak head velocity was not in the range of $\pm$ 3 SD of the set of mean head velocities calculated in the same interval in all traces of one patient [17].

A custom-made algorithm was applied to extract saccades from the eye acceleration traces, yet every saccade was verified by visual inspection of the velocity and position traces. Two authors needed to achieve consensus (TD, DS) before a saccade was approved. Saccades were included when they (1) occurred after peak head velocity, (2) had a magnitude of more than 60°/s, and (3) the peak saccade velocity was recorded. The onset of a saccade was the point where eye velocity crossed zero or eye acceleration reached 2000°/s^2. The offset of a saccade was the point where eye acceleration crossed zero after eye velocity crossed zero, or acceleration was below 2000°/s^2 when velocity did not cross zero. A saccade was classified as "covert saccade" when onset occurred before head velocity crossed zero and as "overt saccade" when onset occurred after head velocity crossed zero. Head impulse onset was set on head velocity exceeding 10°/s. Head impulse offset was defined as head velocity crossing zero (Figure 1).

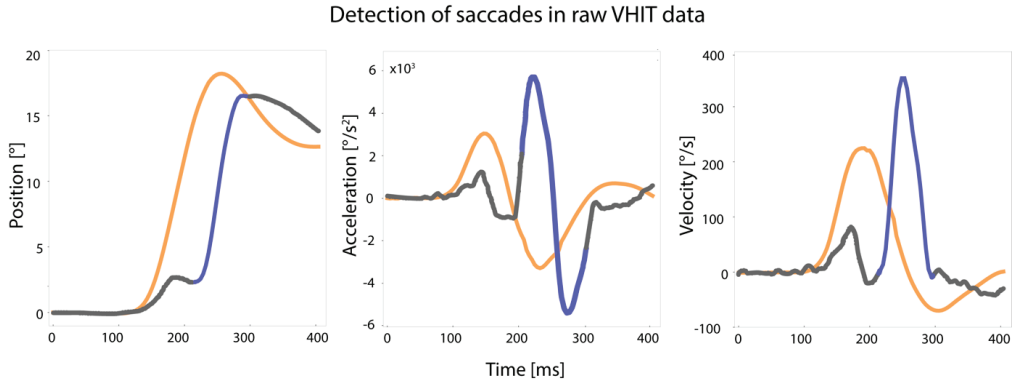

Figure 1. Detection of saccades in VHIT traces based on position, acceleration, and velocity of eye movement. The orange line illustrates the head impulse, the grey line represents the eye movement, and the blue line represents the saccade as included in the analysis. Raw data were exported from the Otometrics system (head and eye velocity traces). Position and acceleration data were calculated from these data. All traces were checked on artefacts and excluded if necessary. Saccades were extracted from these artefact-free traces using a custom-made algorithm. All saccades were verified by visual inspection. Definitions of artefacts and saccades are described in Section 2.3.

2.3.2. Presence of Covert Saccades

The presence of covert saccades for every patient was determined as the frequency of occurrence of at least one covert saccade per trial. Every trial consisted of seven artefact-free traces (as described above) [18]. Only the first saccade of a trace was used for analysis. As a result, every patient had a minimum of zero and a maximum of seven covert saccades per trial. The frequency of occurrence of a covert saccade was first registered as a binary outcome (yes/no) for every trace separately. From these data, a ratio (0–1) and percentage (0–100%) per patient were calculated.

2.3.3. Latency of Saccades

The latency of the first saccades was extracted from the original eye velocities in the Otometrics system. Both overt and covert saccades were included. Latency (in milliseconds) was registered as the onset of the saccade and was normalized to the start of the head impulse.

2.4. VOR Gain

For both HIMP and SHIMP, VOR gain was calculated by the Otometrics system itself over all traces accepted by the system. VOR gain was also calculated with a custom-made algorithm, using the raw data extracted from the Otometrics system. This VOR gain was calculated over the first seven artefact-free traces of every patient. Both methods (Otometrics system and custom-made algorithm) calculated the VOR gain by the ratio of the area under the curve of eye movement and head movement. The eye movement was desaccaded if needed [6]. To detect influences of head velocity on VOR gain outcomes in this study, peak head velocities were compared between HIMP and SHIMP.

2.5. Statistical Analysis

Data were analyzed using SPSS Statistics 25 (IBM, Armonk, NY, USA) for Windows and R (v.3.5.2.). The α-value was set at $p < 0.05$.

2.5.1. Statistical Analysis of Saccades

Covert Saccades

Marginal multilevel model analysis was applied with side (right/left) and test (HIMP/SHIMP) as independent variables and an unstructured covariance matrix of the residuals to detect a statistically significant difference in the frequency of covert saccades (ratio 0–1) in BV patients between HIMP and SHIMP testing.

Latency of First Saccade (Covert and/or Overt)

A two-sided paired t-test was used to compare the latency (ms) of the first saccade between HIMP and SHIMP. This analysis included the first saccade (i.e., both covert and overt saccades) of the first seven artefact-free traces in every patient. Logically, patients without a saccade in HIMP or SHIMP were not included in this part of the analysis.

2.5.2. Statistical Analysis of VOR Gain

Marginal multilevel linear regression with side (right/left), VOR gain, and test (HIMP/SHIMP) as independent variables and an unstructured covariance matrix of the residuals were performed to detect a statistically significant difference in VOR gain in BV patients between HIMP and SHIMP testing. VOR gain as calculated by a custom-made algorithm over the first seven artefact-free impulses was used for analysis.

2.5.3. Statistical Analysis of Peak Head Velocity

The difference in peak head velocities between HIMP and SHIMP was calculated with a two-sided paired t-test. Median peak head velocities (extracted from the raw traces of the VHIT system) of the traces used to calculate VOR gain were used for analysis.

2.5.4. Analysis of Agreement between HIMP and SHIMP Regarding BV Diagnosis

For this analysis, patients were excluded if diagnosed with BV solely based on VHIT outcomes since VOR gain obtained by the VHIT was used as the outcome parameter. VOR gain calculated by the Otometrics system (using all accepted traces) was used, as will be the case in daily practice. A HIMP VOR gain of <0.6 was classified as "bilateral vestibulopathy", and a VOR gain of $\geq$0.6 was classified as "no bilateral vestibulopathy" [4]. For SHIMP, two different cut-off values (<0.6 and <0.5) were used and separately analyzed. In case the paradigms (HIMP and SHIMP) showed a discrepancy in classifying BV, the patient was classified as "no agreement". In patients with "no agreement", visual inspection and descriptive analysis by two authors (TD, RB) were performed. This comprised inspecting the presence and timing of covert saccades, comparing VOR gain calculated by the system and the custom-made algorithm, and assessing if the traces showed characteristics of BV.

2.6. Ethical Considerations

This study was conducted following the legislation and ethical standards on human experimentation in the Netherlands and the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committee of Maastricht University Medical Center (NL52768.068.15/METC). All subjects provided written informed consent.

3. Results

3.1. Patient Characteristics

The study population comprised 98 BV patients from the Netherlands and Belgium: 56 males and 42 females. Mean age was 59 years old (SD 13 years). Definite and probable etiologies included: ototoxic effects of antibiotics (n = 12) or chemotherapy (n = 2); post-infectious due to Lyme disease (n = 2), cerebral malaria infection (n = 1), herpes infection (n = 1), meningitis (n = 6), or neuritis (n = 4); head trauma (n = 5); inherited by DFNA9 gene mutation (n = 13) or other gene mutations (n = 10); bilateral Menière's disease (n = 6); autoimmune disease (n = 2). In 34 patients, no etiology could be determined (idiopathic).

A representative sample of eye and head movements obtained with HIMP and SHIMP is illustrated in Figure 2. Further details of the VHIT characteristics (saccades, VOR gain, and peak head velocity) of all tested patients will be discussed below.

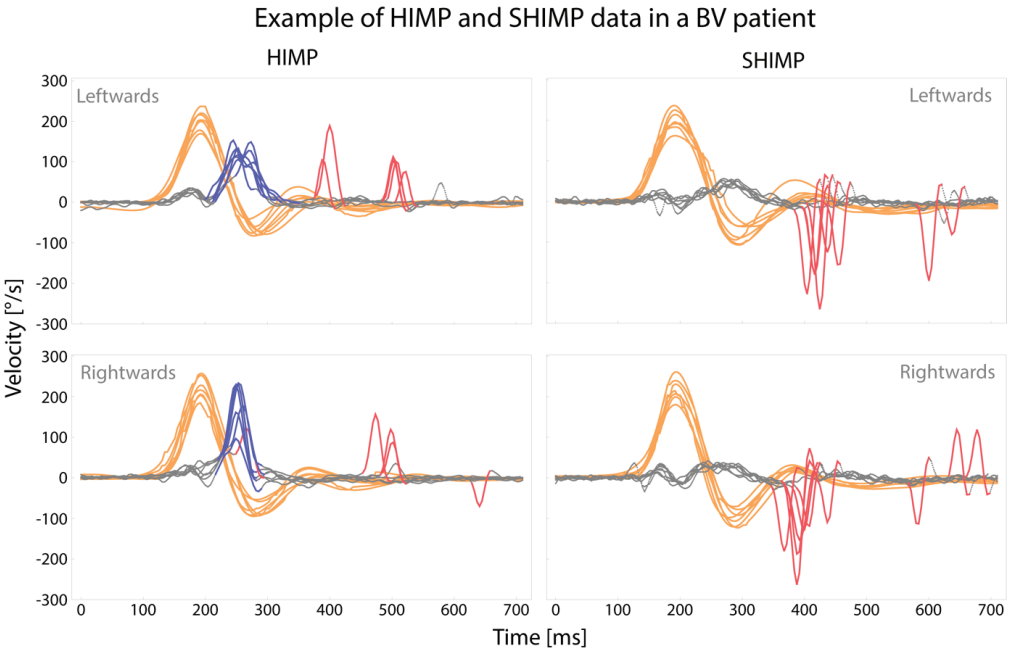

Figure 2. Raw eye and head movement data of one BV patient (patient 18), obtained by HIMP and SHIMP during two consecutive VHIT trials. Grey lines represent eye movements, orange lines represent head movements, blue lines represent covert saccades, and red lines represent overt saccades.

3.2. HIMP versus SHIMP: Presence of Covert Saccades

A statistically significant difference was found in the presence of covert saccades between SHIMP and HIMP ($F(1,97) = 86.314$, $p < 0.001$). During SHIMP testing, fewer covert saccades were produced compared to HIMP (estimated difference SHIMP-HIMP = −0.289 (−0.351, −0.227)). A covert saccade was present in 34–35% of the HIMP traces and 5–6% of the SHIMP traces (Figure 3A).

3.3. HIMP versus SHIMP: Latency of the First Saccade (Covert and/or Overt)

This analysis comprised 92 patients for leftwards impulses and 93 patients for rightwards impulses since patients without a saccade in HIMP or SHIMP could not be included. A statistically significant difference was found in the latency of the first saccade between SHIMP and HIMP ($p < 0.001$). Saccades appeared later (i.e., demonstrated a longer latency) during SHIMP testing. The mean latency of the first saccade was 276 ms for leftward head impulses and 274 ms for rightward impulses during SHIMP, and during HIMP, 193 ms for leftwards head impulses and 197 ms for rightwards head impulses (Figure 3B).

3.4. HIMP versus SHIMP: VOR Gain Differences

Mean VOR gain in SHIMP was lower compared to HIMP (estimated difference SHIMP-HIMP = −0.026 (−0.040, −0.012). This difference was statistically significant ($F(1,97) = 12.913$, $p < 0.001$). Mean VOR gains for rightward, and leftwards head impulses were, respectively, 0.32 and 0.33 in SHIMP and 0.35 and 0.35 in HIMP (Figure 3C).

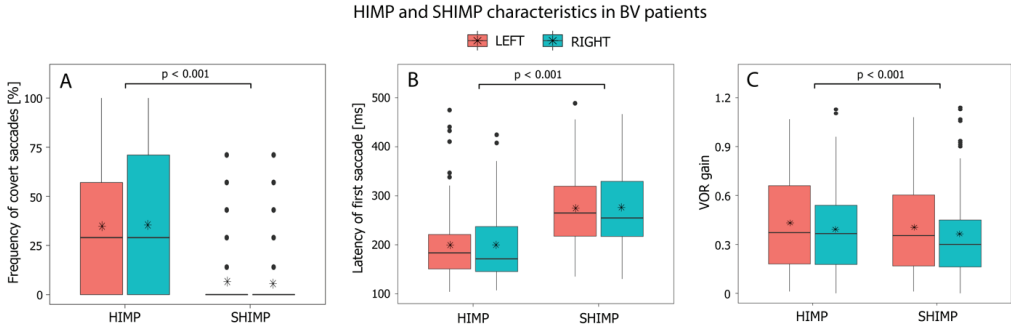

Figure 3. Characteristics of HIMP and SHIMP testing in BV patients for rightwards and leftwards head impulses: frequency of covert saccades (**A**), the latency of first saccade (covert and/or overt), (**B**), and VOR gain as calculated by a custom-made algorithm (**C**). Black horizontal lines represent median values; asterisks represent mean values for all patients.

3.5. HIMP versus SHIMP: Peak Head Velocity

Median peak head velocity was significantly lower during SHIMP compared to HIMP ($p < 0.001$) (Figure S1, Supplementary Materials).

3.6. Analysis of Agreement between HIMP and SHIMP Regarding BV Diagnosis

Six patients were excluded from this analysis since diagnosis of BV was solely based on VHIT outcomes, as described in paragraph 2.6.4. In 93% of the 92 patients, HIMP and SHIMP agreed on the diagnosis of BV (either "bilateral vestibulopathy" or "no bilateral vestibulopathy") when using the cut-off value of 0.6 for both paradigms (Table 1). In six patients (7%), the two paradigms did not agree on the diagnosis of BV. All these six patients were classified as "BV" with SHIMP and "no BV" with HIMP. However, in three out of these six patients, HIMP and SHIMP agreed when using the VOR gain calculated by the custom-made algorithm. In the other three patients with no agreement, the visual inspection did show pathological eye responses, but this was not reflected by a VOR gain <0.6. In case a SHIMP cut-off value of <0.5 was used, agreement on the diagnosis of BV increased to 97% (Table 1).

Table 1. Diagnosis of BV using HIMP and SHIMP (1a), and agreement between both paradigms (1b).

1a. Diagnosis According to VHIT Results (n = 92)	**HIMP (Cut-Off < 0.6)**	**SHIMP (Cut-Off < 0.6)**	**SHIMP (Cut-Off < 0.5)**
Bilateral vestibulopathy			
VOR gain <0.6 on both sides	64	70	65
No bilateral vestibulopathy			
VOR gain >0.6 on both sides	10	9	14
VOR gain >0.6 on one side	18	13	13
1b. Agreement on the Diagnosis of BV between HIMP and SHIMP			
HIMP (cut-off < 0.6) and SHIMP (cut-off < 0.6)		93%	
HIMP (cut-off < 0.6) and SHIMP (cut-off < 0.5)		97%	

4. Discussion

This study compared the outcomes of SHIMP and HIMP in a large group of 98 patients with bilateral vestibulopathy (BV), diagnosed according to the diagnostic criteria of the Bárány Society [4]. To our knowledge, this is the first study to compare SHIMP and HIMP in a patient population of this size.

SHIMP significantly reduced the number of covert saccades and VOR gain compared to HIMP. More importantly, in 93% of the patients, an agreement was found on the BV diagnosis between the two paradigms.

4.1. HIMP versus SHIMP: Covert Saccades

Significantly fewer covert saccades were produced by BV patients tested with SHIMP compared to HIMP (0.05 vs. 35%) (Figure 3). This "covert saccade killer" phenomenon is in agreement with previous studies on smaller populations of patients with a vestibular deficit [7,9,19]. The elimination of covert saccades should facilitate a more accurate gain calculation [7]. This is especially valuable in a BV population, in which patients often produce covert saccades [5].

4.2. HIMP versus SHIMP: VOR Gain

VOR gain in SHIMP was significantly lower than in HIMP. However, the clinical implication of the VOR gain difference is small: only a mean difference of 0.02 (leftwards impulses) and 0.03 (rightwards impulses) (Figure 3). This VOR gain difference between both paradigms is slightly smaller but comparable to previous results in smaller groups of healthy subjects and BV patients [7,9]. The underlying mechanism of a lower VOR gain in SHIMP is not fully known, but several explanatory theories are preferred. For example, the reduction of covert saccades could provide a more precise VOR gain calculation in SHIMP. However, a VOR gain difference (larger than in this BV population) between these paradigms was also demonstrated in studies with healthy subjects (without covert saccades in HIMP testing) [9,20]. This might be explained by VOR response suppression, in which subjects decrease their VOR response. VOR suppression in unexpected passive movements is observed within 60–90 ms after the start of head movement; therefore, it could be reflected in a lower VOR gain during SHIMP testing [10,21]. Furthermore, higher head velocities result in lower VOR gains [22]. In this study, peak head velocities were significantly lower during SHIMP testing, which could therefore not justify the lower VOR gains in SHIMP.

4.3. HIMP versus SHIMP: Agreement on the Diagnosis of BV

Agreement between HIMP and SHIMP on the diagnosis of BV (VOR gain < 0.6) was found in 93% of this population (Table 1). This suggests that the significant differences observed between both paradigms (presence of covert saccades and VOR gain) probably have minor clinical consequences since both paradigms detect BV in the vast majority of the patients.

The six patients in which HIMP and SHIMP did not agree on the BV diagnosis (when using a SHIMP cut-off value of <0.6) were all diagnosed as BV by SHIMP and not with HIMP. These discrepancies could be attributed to gain calculation and cut-off values. Regarding gain calculation, a custom-made algorithm and visual inspection of the traces did show severe vestibular hypofunction in these cases in both paradigms. Although, it must be stressed that also, with the custom-made algorithm, no agreement was found between both paradigms in 5 out of 92 patients. This demonstrates the need for a standardized approach for evaluating and interpreting head impulse testing outcomes. This should include a universal gain calculation algorithm combined with an assessment of the raw traces [5,8]. Regarding cut-off values, two cut-off values were used for SHIMP in this study (VOR gain <0.6 and <0.5). Although no official cut-off values have been published for SHIMP, it was previously proposed to state a lower cut-off value, considering the lower VOR gain values during SHIMP [23]. In this study, lowering the SHIMP cut-off value to 0.5 increased the agreement between HIMP and SHIMP to 97%. However, an increase in the agreement does not imply an increase in the correctly made BV diagnoses. After all, fewer patients were diagnosed with BV after lowering the cut-off value to 0.5, while BV was already demonstrated by caloric testing and/or rotatory chair testing. This implies that future research is needed to determine the proper cut-off value for SHIMP in BV.

4.4. HIMP versus SHIMP: The Daily Practice

Both HIMP and SHIMP were well tolerated by all patients, and some of them reported that SHIMP testing felt more like a game than a medical test. Unfortunately, the current clinically available SHIMP software does not include testing of vertical semicircular canals. Therefore, when testing of all six semicircular canals is needed (e.g., in a research setting, such as vestibular implant research), HIMP testing is preferred [24]. Nevertheless, since SHIMP was demonstrated to be a "covert saccade killer", SHIMP could be an alternative in clinical settings which do not have the financial means to obtain a VHIT system. A less expensive diagnostic headband could be used during head impulses while the examiner observes the presence or absence of overt saccades [25].

4.5. Limitations

Testing was not randomized. SHIMP was always tested after HIMP since these tests were part of a whole testing day. However, if more coverts were produced during the second test (SHIMP) due to a learning effect, it would only underestimate the significant decrease of covert saccades in SHIMP. Moreover, previous studies with BV patients and healthy subjects showed no difference in covert saccades and/or VOR gain when tested repeatedly [11,16]. Therefore, it can be expected that randomization would not have significantly influenced the study.

5. Conclusions

To our knowledge, this is the largest study population on SHIMP testing in BV patients. Covert saccades and VOR gains were significantly reduced during SHIMP compared to HIMP. However, the clinical relevance of these statistically significant differences is small, and both paradigms detect BV in the vast majority of patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm11092444/s1, Figure S1: Peak head velocities during HIMP and SHIMP.

Author Contributions: Conceptualization, R.v.d.B. and V.V.R.; methodology, T.v.D. and D.S.; formal analysis, D.S. and M.J.; data curation, T.v.D., F.L., B.D., D.S. and M.J.; writing—original draft preparation, T.v.D. and R.v.d.B.; writing—review and editing, F.L., B.D., D.S., M.J., N.G., A.P.F., H.K., V.V.R. and R.v.d.B.; visualization, R.v.d.B. and V.V.R.; supervision, R.v.d.B. and H.K. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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Reliability of Monothermal Caloric Test as Screening Test of Vestibular System

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Abstract: This retrospective study completed at a tertiary care center aimed to assess the monothermal caloric test (MCT) as a screening test, using the bithermal caloric test (BCT) as a reference. Additionally, it attempts to measure the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a fixed inter-auricular difference (IAD) value for both cold and warm stimuli using water irrigation. Medical records of 259 patients referred for vestibular symptoms who underwent BCT with water irrigation were reviewed. Patients with bilateral vestibular weakness and caloric tests using air irrigation were excluded. BCT showed 40.9% unilateral weakness. Two formulas were used to determine the monothermal caloric asymmetry (MCA-1 and MCA-2). The measurement of agreement Kappa between the two formulas in comparison with BCT revealed moderate agreement at 0.54 and 0.53 for hot and cold stimulation, respectively. The monothermal warm stimulating test (MWST) using MCA-2 showed better results, with a sensitivity of 80%, specificity of 91%, PPV of 83.1%, and NPV of 89.2%. Thirty-four patients had horizontal spontaneous nystagmus (HSN) with a mean velocity of 2.25°/s. These patients showed better sensitivity but lower specificity after adjustment of HSN using the MCA-2 formula at warm temperatures. Therefore, they should complete the caloric test with cold irrigation to perform the BCT. MCT is efficient as a screening test if the warm stimulus is used with the MCA-2 formula fixed at 25%. If present, HSNs should be adjusted. Negative IAD (normal) in the absence or presence of adjusted HSN or slow-phase eye velocity $\leq 6°/s$ at each right and left warm stimulation should be accomplished by the BCT.

Keywords: caloric test; vestibular test; bithermal; monothermal; vestibular paresis; caloric paresis; vertigo

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1. Introduction

The bithermal caloric test (BCT) assesses the function of the lateral semicircular canal by generating thermal variations within the external auditory canal. This variation in temperature changes the density of the endolymph fluid within the lateral semicircular canal and leads to a convection current that stimulates sensorial cells located in the lateral ampullary crest.

Thermal variation in the standard BCT is achieved by four irrigations (cold and warm stimulation for the right and left ear) using water or air stimulation that are warmer or cooler than the body temperature. The slow-phase eye velocity (SPEV) of nystagmus is generated by stimulation of the lateral semicircular canal with water irrigation. Then, the unilateral weakness (UW) and direction preponderance (DP) are calculated using the Jongkees formulas [1]. Caloric tests and video head impulse tests are the gold standard tests for evaluating the function of the vestibular system in vertiginous patients [2,3]. However, the caloric test is the most uncomfortable vestibular test because it can induce nausea and vomiting, and some patients refuse to complete the test. Furthermore, the BCT is

time-consuming, taking at least 40 min depending on the operator, patient compliance, and laboratory protocol.

The monothermal caloric test (MCT) assesses the function of each lateral semicircular canal by using single-temperature irrigation. Compared to BCT, MCT is more economical, less time-consuming, and offers less patient discomfort during the test. To be considered a screening test, MCT must have high sensitivity and acceptable specificity. Monothermal caloric asymmetry (MCA) was calculated by many authors using the following formula: MCA = (right ear − left ear) × 100/larger stimulated side [4]; another formula is also used: MCA = (right ear − left ear) × 100/(right ear + left ear) [5] where the peak SPEV of the response following the temperature irrigation is reported for each side.

Barber et al. investigated the efficiency of a monothermal warm screening test (MWST) in 1971 [6]. He used the results of BCT on normal subjects as the gold standard. He found a false negative result of MWST equal to 0.7% if the inter-auricular difference (IAD) was less than 23% and each of the irrigations induced a caloric nystagmus with a SPEV greater or equal to 11°/s (SPEV ≥ 11°/s) (1). Many authors have proven that MCT is an invalid screening test because of the high false negative predictive value reaching 29% [7–9] and high false positive predictive value ranging from 48% to 78% [9,10]. On the other hand, many authors found that MCT is a valid test with warm water irrigation after excluding the failure criteria [11,12] that could increase the false negative rate; therefore, it needs to be completed by a BCT; these failure criteria are: (1) IAD lower than 15%; (2) SPEV less than 8°/s for each warm irrigation [13]; (3) horizontal spontaneous nystagmus (HSN) of 4°/s or higher [5,12,13]. Different study group sizes, different failure criteria for pathologic BCT, variations in test procedures, and stimulus types will result in conflicting results and different conclusions. The aims of this study were (1) to confirm the reliability of the MCT as a screening test using the BCT procedure as a reference in patients with and without HSN, and (2) to assess the correlation between the two formulas used to measure the MCA in comparison to the BCT results. In addition, we measured the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in all patients with the IAD value for both warm and cold stimuli using water irrigation.

2. Materials and Methods

This retrospective study was conducted at our tertiary care center for a one-year duration. This study was approved by the institutional review board of our institution. The BCT is a standard screening test used to evaluate the function of the vestibular system. We reviewed the medical records of all patients with signs and symptoms of vestibular system dysfunction. Bilateral vestibular weakness and caloric tests using air irrigation were excluded from the study to decrease bias. Bilateral vestibular weakness was defined as a peak SPEV lower than 6°/s at each of the four caloric irrigations [14]. Patients with HSN will be included and studied separately to avoid bias in the results and conclusions.

A caloric test using water irrigation was used in combination with videonystagmography (VNG) to test patients with dizziness and vertigo. The VNG evaluates the oculomotor system, which includes the saccadic, gaze, optokinetic, and pursuit systems. It also includes spontaneous, positional nystagmus, and the caloric test. Caloric stimulation was performed using an open-loop water irrigation unit. Water irrigation was performed with subjects in the supine position and heads in flexion at 30°, using warm 44 °C and cold 30 °C in each ear for 20 s for a total volume of 250 mL. In all patients, an alternating ear sequence was used, starting from the right ear in the following order: right warm, left warm, right cold, and left cold. A minimum interval of 5 min was allowed between the caloric subtests.

Bithermal caloric asymmetry (BCA) was calculated using the Jongkees formula: BCA = [(Right Cold + Right warm) − (left cold + left warm)] × 100/(right cold + right warm + left cold + left warm), where the peak SPEV of the response following temperature irrigation is reported for each side [15].

MCA for both warm and cold conditions was calculated as MCA-1 = (right − left) × 100/larger stimulated side [4] or MCA-2 = (Right − Left) × 100/(Right + Left) [5].

The unilateral vestibular weakness (UVW) is defined in BCA, MCA-1, and MCA-2 as IAD $\geq$ 20% [14], $\geq$25% [10], and $\geq$25% [3], respectively. We fixed the cutoff point of UVW for these values based on the reported references.

2.1. Horizontal Spontaneous Nystagmus Adjustment

It is expected that a patient with an acute unilateral peripheral lesion will have spontaneous nystagmus with a constant slow-phase velocity with their eyes closed. Spontaneous nystagmus skews the results of the caloric test and must be accounted for by adding (or subtracting) the numeric value of spontaneous nystagmus from each caloric subtest (note that some software systems are automatically corrected for spontaneous nystagmus). Spontaneous nystagmus is almost always "direction-fixed" and will therefore "add" to the responses opposite to the direction of the spontaneous nystagmus fast phase and "reduce" the responses in the same direction of the fast phase. For example, a 4-degree right-beating spontaneous nystagmus adds 4°/s to the value of both the right warm and left cold responses. Therefore, for adjustment, 4°/s should be subtracted from each of the peak SPEV values to not report a direction proportional to what was actually due to spontaneous nystagmus. Likewise, for the right cold and left warm responses, the effect would be the opposite (i.e., 4°/s would be added to each subtest to correct for spontaneous nystagmus).

2.2. Statistical Analysis

Kappa was used to define the agreement between the MCA-1 and MCA-2 formulas with the Jongkees formula of BCT. Then, the measurement of agreement Kappa was used to study the agreement between the BCT and MCT (MWST and MCST: monothermal cold stimulation test). Pearson's product-moment coefficients were used to examine the correlation between the BCT and MCT. The area under the ROC curve was calculated to show the correlation between the sensitivity and specificity of the MWST and the MCST. ROC curves displaced into the upper left corner of each panel indicate an excellent screening test with high sensitivity and specificity. We also measured PPV and NPV. All analyses were performed using SPSS version 24. p value greater than 0.05 is considered statistically significant.

3. Results

A total of 259 patients with VNG studies were included; 60.1% were female and 39.1% were male; the median age was 50.4 years;

The patients included in this study were presented to the neurotology clinic to rule out the causes of vestibular dysfunction. The study group showed 40.9% UVW and 59.1% without vestibular asymmetry (healthy controls), as shown in Figure 1. The female sex was the majority in both groups (Table 1).

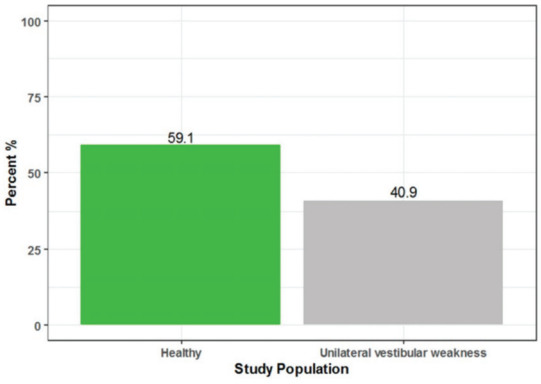

Figure 1. Patient with unilateral vestibular weakness and healthy controls.

Table 1. Descriptive analysis for baseline patients' demographic.

Patients' Demographics N = 259		Healthy Controls N = 153 (59.1%)	Unilateral Vestibular Weakness (UVW) N = 106 (40.9%)	*p*-Value
Age (years) *	Mean ± SD	47.8 ± 14.1	53.8 ± 13.1	0.001
Gender	Females	92 (60.1%)	70 (66.0%)	0.404
	Males	61 (39.9%)	36 (34.0%)	

* Data are presented as mean ± SD and frequency (n [%]). SD: standard deviation

When the formulas MCA-1 and MCA-2 were fixed at 25% and BCA was fixed at 20%, the measurement of Kappa agreement for the inter-rater reliability between the three screening tests was 0.54 for hot stimulation and 0.53 for cold stimulation, indicating a moderate agreement between the three screening techniques. Table 2 shows the results of both the MWST and MCST in comparison to the BCT results as a reference gold standard using both the MCA-1 and MCA2 formulas among 225 patients without HSN. The MCA-2 formula showed higher sensitivity (80%) and specificity (91%) in the MWST, with high positive and negative predictive values of 83.1% and 89.2%, respectively. At both temperatures, the MCA-1 formula showed better sensitivity than the MCA-2 formula, but with lower specificity. Furthermore, the MCA-1 formula showed a lower PPV in both the MWST and MCST than the MCA-2 formula. The NPV was high for both formulas and both the MWST and MCST, as shown in Table 2. The false PPV and false NPV for the MCT were lowered by using MCA-2 in hot stimulation and were 16.9% and 10.8%, respectively.

Table 2. Results of MCT for both warm and cold stimulation in comparison with BCT among non-HSN patients.

Caloric Weakness Cutoff Points			MCT	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Patients without HSN (N = 225)	BCA (20%)	MCA-1 (25%)	MWST	91.2% (85.1–97.4)	58.6% (50.6–66.6)	54.9% (46.4–63.3)	92.4% (87–97.8)
			MCST	85% (77.2–92.8)	67.6% (60–75.2)	59.1% (50.1–68.1)	89.1% (83.3–94.9)
		MCA-2 (25%)	MWST	80% (71.2–88.8)	91% (86.4–95.7)	83.1% (74.7–91.5)	89.2% (84.2–94.2)
			MCST	58.8% (48–69.5)	93.1% (89–97.2)	82.5% (72.6–92.3)	80.4% (74.3–86.4)

BCT: Bithermal caloric test, BCA: Bithermal caloric asymmetry, HSN: Horizontal spontaneous nystagmus, MCA: Monothermal caloric asymmetry, MCT: Monothermal caloric test, MWST: Monothermal warm stimulating test, MCST: Monothermal cold stimulating test.

The ROC curve results for the sensitivity and specificity of the MCT for both warm and cold conditions in patients without HSN were better using the MCA-2 formula. The MWST performed better under the curve (85.5% using the MCA-2 formula) than the MCST (75.9%) (Figure 2). The MWST and MCST in the MCA-1 ROC curve results of patients without HSN were 74.9% and 76.3%, respectively. The *p*-values for the ROC curve for both the MCA-1 and MCA-2 formulas were significant ($p < 0.001$) at hot and cold temperatures.

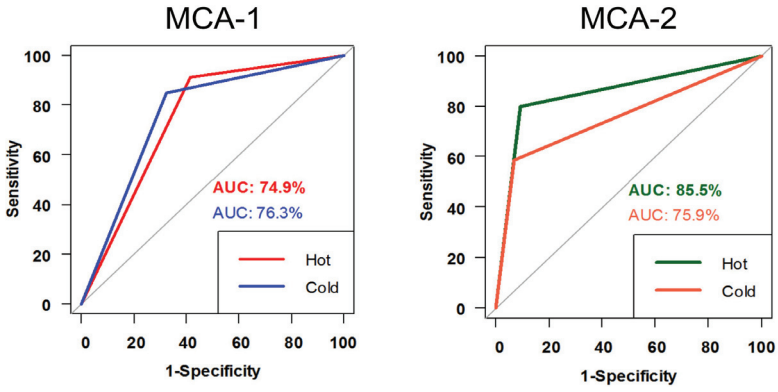

Figure 2. ROC curve for MCT for both warm & cold stimulation among non-HSN patients by using the two formulas: MCA-1 and MCA-2. (ROC curve: receiver operating characteristic curve, MCT: monothermal caloric test, HSN: horizontal spontaneous nystagmus).

A total of 34 patients had HSN with a mean velocity of 2.25°/s (2.25 ± 1.6°/s). Sensitivity, specificity, PPV, and NPV with and without adjustment of the HSN using the MCA-2 formula to measure the MCA showed better results than the MCA-1 formula (shown in Table 3). The sensitivity was better after the adjustment of the HSN for both cold and warm stimulation. The specificity was better only in cold stimulation with an adjusted HSN. With HSN adjustment, NPV was higher for both cold and warm stimulation. As the cold stimulation showed better results with HSN adjusted, the false PPV and false NPV in cold stimulation with HSN adjusted were 20% and 35.7%, respectively.

Table 3. Evaluation of the screening effect of MCT for both warm and cold stimulation compared to the BCT in patients with horizontal spontaneous nystagmus (HSN) with and without HSN adjustments using the MCA-2 formula.

HSN Patients N = 34	Caloric Weakness Cutoff Points		MCT	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Without HSN adjustment	BCA (20%)	MCA-2 (25%)	MWST	61.5% (42.8–80.2)	75% (45–105)	88.9% (74.4–103.4)	37.5% (13.8–61.2)
			MCST	73.1% (56–90.1)	62.5% (29–96)	86.4% (72–100.7)	41.7% (13.8–69.6)
With HSN adjustment	BCA (20%)	MCA-2 (25%)	MWST	81% (64.2–97.7)	53.8% (26.7–80.9)	73.9% (56–91.9)	63.6% (35.2–92.1)
			MCST	76.2% (58–94.4)	69.2% (44.1–94.3)	80% (62.5–97.5)	64.3% (39.2–89.4)

BCA: Bithermal caloric asymmetry, MCA: Monothermal caloric asymmetry, MCT: Monothermal caloric test, MWST: Monothermal warm stimulating test, MCST: Monothermal cold stimulating test.

The ROC curve results for the sensitivity and specificity of MCT in patients with HSN, with and without adjustment for both warm and cold stimulation, are shown in Figure 3. The results for both the formula and both warm and cold stimulations were better after the adjustment of HSN. The MCA-2 with cold stimulation showed the best result under the curve after adjustment of the HSN, with a result of 72.7%. The *p*-value for the ROC curve for MCA-2 using cold stimulation before adjustment for HSN was 0.037 and became more significant after adjustment for HSN at 0.005. The *p*-value for the ROC curve for MCA-2 using hot stimulation before the adjustment of the HSN was 0.039 and became more significant after the adjustment of the HSN at 0.02.

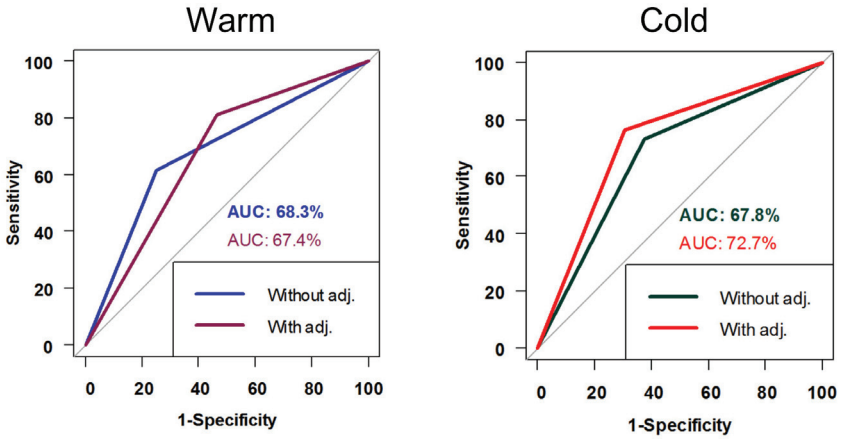

Figure 3. ROC curve for MCA-2 with and without HSN adjustment for both warm and cold stimulation.

4. Discussion

This study aimed to confirm the reliability of MCT in differentiating healthy individuals from individuals with UVW. Our study group showed that 40.9% have a unilateral right or left vestibular weakness. MCT has an advantage over BCT as it offers less discomfort to the patient, is less time-consuming, and is more economical. On the other hand, it has to be as reliable as a BCT, with high sensitivity and acceptable specificity for use as a screening test in specialized neurotology clinics. The DP results of BCT were not included in the study, as it requires four irrigations to be calculated, it does not represent asymmetry, such as UW, and it could deviate to either side without the presence of HSN [10–13,15,16]. Previous studies using water caloric tests have shown that the sensitivity of the MWST is higher than that of the MCST, and the specificity is nearly similar [5,7,8,11,12,17,18]. In contrast, Enticott [10] and Cunha et al. [16] found the sensitivity and specificity of the MCST to be more reliable than those of the MWST. Our study showed that the sensitivity, specificity, PPV, and NPV were higher in the MWST (80%, 91%, 83.1%, and 89.2%, respectively) than in the MCST (58.8%, 93.1%, 82.5%, and 80.4%, respectively) using the MCA-2 formula and in patients without HSN. This thermal variation could be explained by the fact that warm irrigation will produce an action potential due to the stimulation of the sensorineural cells in the crista ampullaris of the lateral canal, generating depolarization, whereas the MCST shifts the cell membrane to close the potassium channel, thus resulting in hyperpolarization. Therefore, depolarization resulted in more pronounced nystagmus, which increased the sensitivity of the test.

Patients presenting with a history and physical examination of vestibular weakness, and a normal MWST result (<25% IAD) should complete the caloric test with cold irrigation, as the MCT is less sensitive for subgroups with less severe disease [7,19]. A diagnosis with UVW is valid if IAD in MWST is equal to or higher than 25% by using the MCA-2 formula, as it showed higher sensitivity and specificity (80% and 91%, respectively). Furthermore, the false PPV was 16.9% using the MCA-2 formula in MWST, lower than the reported studies of 48–78% [9,10] and the false NPV was 10.8% using the MCA-2 formula in MWST, lower than the reported studies of 29% [7,8]. This indicates that MCT results are a valid screening test in patients without HSN and with warm stimulation using the MCA-2 formula.

HSN is a failure factor that decreases the sensitivity and specificity of MCT [11,12,18–21]. A positive HSN of >4°/s in the VNG is considered an indication of BCT [5,6,13]. Other studies found the presence of HSN regardless of its velocity, which is an indication of BCT [11,18,19]. We studied 34 patients with HSN (mean, 2.25°/s) to analyze their effects on the final results. The calculations were performed with and without HSN adjustment. We found that the sensitivity increased using the MCA-2 formula and after HSN adjustment.

Furthermore, the HSN affects the MCA results because the specificity was lower than expected in all formulas; we conclude that all patients with HSN and with an IAD < 25% after adjustment should complete the caloric test with cold irrigation to perform the BCT.

In some patients, the caloric responses in both ears were very weak or absent. When each of the four caloric irrigations had a peak slow component velocity lower than 6°/s, bilateral weakness was present [14]. The diagnostic algorithm for MWST is shown in Figure 4.

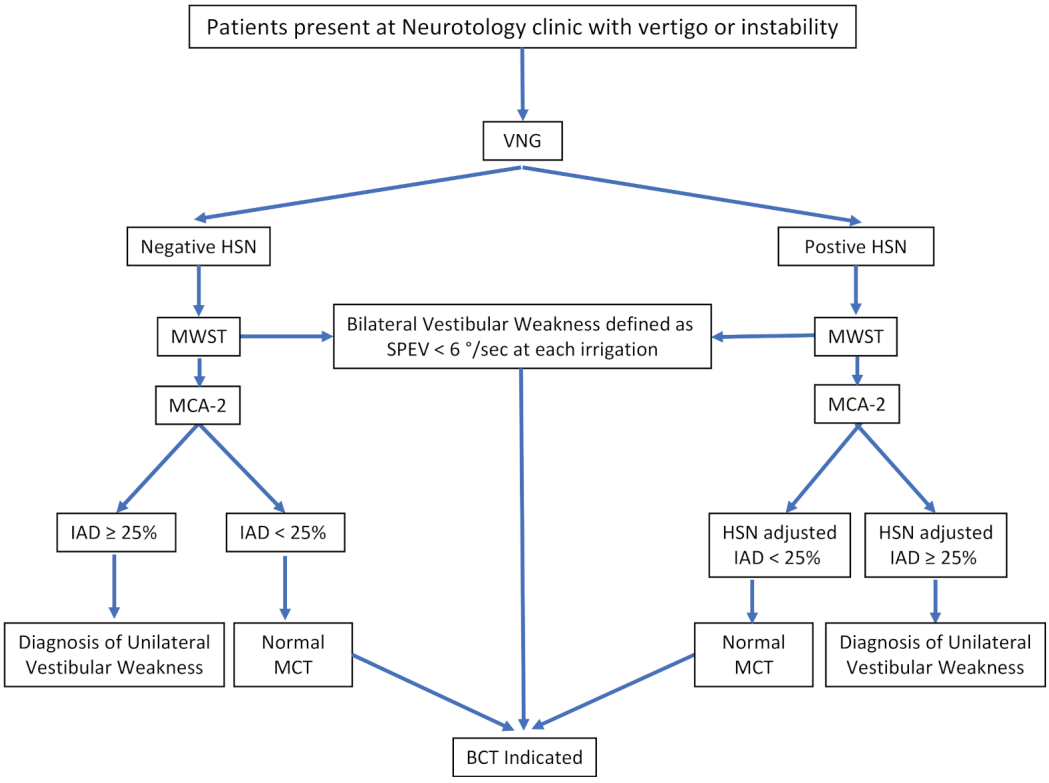

Figure 4. Diagnostic Algorithm of monothermal warm stimulating test. VNG: Videonystagmogram; HSN: Horizontal Spontaneous Nystagmus; MWST: Monothermal Warm Stimulation test; MCA: Monothermal caloric asymmetry; MCA-2 formula: MCA-2 = (Right − Left) × 100/(Right + Left); IAD: Inter-auricular Difference; SPEV: Slow-Phase Eye Velocity; BCT: Bithermal Caloric Test; MCT: Monothermal caloric test.

We studied the correlation between the two formulas used to measure MCA in comparison with BCT results. The Kappa agreements between the three formulas indicate moderate agreement, which is statistically acceptable. The MCA-1 formula is faster to apply than MCA-2 for those who calculate the IAD manually, but the MCA-2 formula showed better sensitivity, specificity, PPV, NPV, and ROC curve in MWST. This eventually makes the MCA-2 formula better for calculating the MCT.

Limitation of the Caloric Test

Depending on the clinical and physical examinations, other vestibular and otolithic diagnostic tests can be performed to evaluate dizzy or vertiginous patients. The caloric test is non-physiological as it stimulates the lateral semicircular canal at 0.003 Hz with angular movements. The caloric test, both bithermal and monothermal, assesses only the

function of the lateral semicircular canal; it will not provide information about the function of the vertical canals, saccule, or utricle. Furthermore, symptoms of UVW originating from the inferior vestibular nerve will not be detected by caloric testing. These patients need a video head impulse test (vHIT) that will test each canal separately and vestibular evoked myogenic potentials (VEMP) to assess the integrity of the saccule and utricle [2,22]. In addition, monothermal caloric test is unable to identify the directional preponderance of caloric nystagmus.

5. Conclusions

MCT is efficient as a screening test if the warm stimulus is used with the MCA-2 formula fixed at 25%. If present, HSNs should be adjusted. Negative IAD (normal) in the absence or presence of adjusted HSN or SPEV equal to or less than 6°/s at each right and left warm stimulation should be accomplished by the BCT. The vestibular work-up completed with other vestibular tests, such as the vHIT and VEMP tests, is recommended as it will assess the vestibular system as one unit and help in offering the patients an appropriate diagnosis.

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Dynamic Visual Acuity Results in Otolith Electrical Stimulation in Bilateral Vestibular Dysfunction

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Abstract: (1) Background. Patients with bilateral vestibular disease (BVD) experience oscillopsia with a detriment to visual acuity (VA). This VA is driven mainly by the VOR that has two components: rotational and translational. VA can be tested by using dynamic visual acuity (DVA) on a treadmill because both systems are activated. The aim of this study is to compare VA before and after chronic electrical stimulation of the otolith organ. (2) Materials and Method. Five patients suffering from bilateral vestibular dysfunction (BVD), previously implanted with a new vestibular implant prototype, were included in this study with the aim to check VA with and without vestibular implant use (W and W/O) in static, 2 km/h and 4 km/h walking situations. DVAtreadmill was measured on a treadmill with a dynamic illegible E (DIE) test in static and dynamic conditions (while walking on the treadmill at 2 and 4 km/h). The DVA score was registered in a logarithm of the minimum angle of resolution (LogMAR) for each speed. In addition, every patient completed the oscillopsia severity questionnaire (OSQ) and video head impulse test (vHIT) before and after activation of the vestibular implant. (3) Results. The analysis shows a significant difference in OSQ scores and DVA with an improvement in dynamic conditions. Organized corrective saccades during the use of a vestibular implant with no changes in gain were also detected in the video head impulse tests (vHIT). (4) Conclusion. The vestibular implant with otolithic stimulation offers changes in the response of DVA, which makes this paper one of the first to address the possible restoration of it. It is not possible to rule out other contributing factors (presence of covert saccades, somatosensory system, . . .). More work seems necessary to understand the neurophysiological basis of these findings, but this implant is added as a therapeutic alternative for the improvement of oscillopsia.

Keywords: bilateral vestibular disease (BVD); dynamic visual acuity (DVA); vestibulo-ocular reflex (VOR); oscillopsia severity questionnaire (OSQ); vestibular implant

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1. Introduction

Patients with bilateral vestibular injuries experience an illusion of visual movement during head movements, known as oscillopsia, one of the main symptoms of the syndrome, which causes a reduction in their quality of life. Our movements in daily life have both translational and rotational components. In order to compensate for this situation, the central nervous system (CNS) keeps a stable image on the retina with compensatory movements, mainly driven by the vestibulo-ocular reflex (VOR) [1]. The retinal slippage, representing the degree of movement of the image through the retina, should not exceed 2°/s, to avoid VA loss [2]. According to the type of head movement, two types of VOR are distinguished: the angular VOR (aVOR), which responds to the angular acceleration

detected by the semicircular canals (CSC), and the translational VOR (tVOR), related to the linear movement detected by the otoliths [3].

The aVOR generates compensatory eye movements for head rotation in both vertical and horizontal planes during slow movement and head accelerations up to 10 Hz or 4000°/sec^2, but with the increase in the speed and frequency of head movements, the translational VOR (tVOR) is recruited to maintain gaze generating eye movements during head translation [4]. Although this tVOR has not received as much attention because the equipment to induce controlled and repeatable passive stimulation is expensive, we now know some aspects: at 2 Hz and at near distances, the gain of the compensatory tVOR is significantly increased [5] and there are decreases in the conjugate retinal image slip of the near target versus a distant background with the goal of minimizing the relative motion of one with respect to the other, and the binocular disparities during active or passive movements are minimized [6]. These eye movements complement and work synergistically with visuo-motor reflexes (ocular following reflex) [7].

Visual acuity can be tested by various functional vestibular tests such as the dynamic visual acuity (DVA). All DVA testing protocols evaluate horizontal and/or vertical semicircular canals in active or passive head movements. However, when walking, all vestibular sensors are stimulated indirectly, especially the vertical canals (head tilt movement) and otoliths (rebound—movement of the head up and down). The DVA test on a treadmill [8,9] involves head movements in the vertical plane at relatively low speeds (maximum peak 30°/s) and at a relatively low frequency (approximately 2 Hz). It has been established in previous studies that, at all walking speeds, it reaches frequency values of 2 Hz and this figure or higher is necessary to establish an exclusive gaze stabilization of the vestibular system without the influence of other oculomotor systems [3,10].

Although today there is no definitive solution for patients with bilateral vestibular dysfunction, some teams around the world have recently generated attempts to artificially restore the functionality of the vestibular system through implants that perform electrical stimulation of the vestibular afferent pathway, as reflected in previous articles.

Our research team, as reflected in previous articles, has developed a vestibular implant that performs direct stimulation on the otolithic organ, having proven benefits and promising results in various vestibular tests: Dizziness Handicap Inventory (DHI), Dynamic Gait Index (DGI), vestibular evoked myogenic potential (VEMPS), Subjective Visual Vertical (SVV), and posturography [11]. Based on these results, the present study aims to find out if there is an effect on oscillopsia after performing this stimulation. For that, oscillopsia was quantified objectively by dynamic visual acuity on a treadmill, approaching a physiological situation [8,11,12] and subjectively by the oscillopsia severity questionnaire (OSQ).

2. Patients and Methods

Five patients were included in this study with bilateral profound hearing loss and BVD according to Criteria Consensus of the Classification Committee of the Bárány Society and had received a new research vestibular implant (VI) [13]. The exclusion criteria for this study comprised: being unable to provide consent personally, not matching cochlear implantation criteria, ossification or other inner ear anomalies that prevent full insertion of electrodes, retrocochlear or central origins of hearing impairment, medical contraindications for surgery, chronic depression, dementia and cognitive disorders, cerebellar ataxias, downbeat nystagmus syndrome, peripheral neuropathies, Parkinson's disease, atypical Parkinson's syndromes, multiple system atrophies, central gait disorders due to normal pressure hydrocephalus, frontal gait disorders, lower-body Parkinson, subcortical vascular encephalopathy or multiple sclerosis.

The vestibular implant is a custom-modified cochlear implant with two arrays: a full-band straight electrode, CI24RE(VEST), from Cochlear Ltd. (Cochlear Ltd., Lane Cove, NSW, Australia) with three active electrodes for VI stimulation (Figure 1). Full-band electrodes were selected to assure that the electrodes were facing the closest area of neural

tissue related to the saccular area. For the cochlear stimulation, a perimodiolar array with 19 active electrodes (Cochlear Ltd., Sydney, NSW, Australia) was used in all of them.

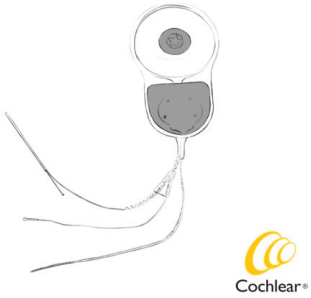
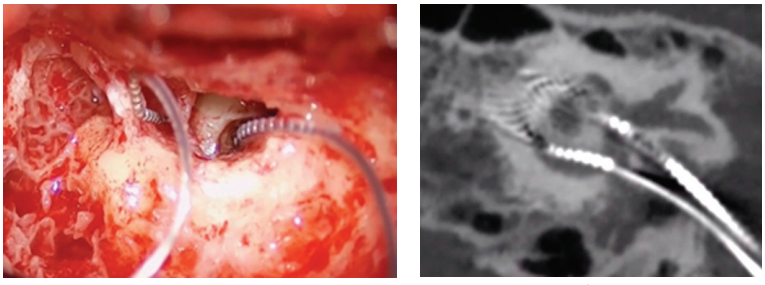


Figure 1. Cochleo-vestibular implant CI24VEST and external processor.

All test were performed one month after activation. Patients used the implant every day, and except for sleeping hours patients used the implant between 8 and 16 h per day.

2.1. Surgery

The same surgeon performed all procedures (A.R.M.). Enlarged retroauricular approach was performed. Then, after identifying the temporalis muscle, a flap was developed following the same principles as in standard CI surgery. As cochlear implantation was performed simultaneously, posterior tympanotomy was performed at this time with a clear exposure of the long process of incus, stapes and oval window. CI was inserted first. Once it was inserted and tested, VI was inserted. Opening of the vestibule was performed by performing a 0.5 mm stapedotomy medial and inferior to the anterior crura of the stapes in order to reach the closest area to inferior vestibular nerve afferent near the saccule macula, inserting the 3 first contacts of the vestibular component (Figure 2a).



(**a**) (**b**)

Figure 2. (**a**) Surgical image of electrodes' position; (**b**) CT postoperative electrode position.

During the surgical procedure, the facial nerve was monitored with the Nerve Integrity Monitor 2tm system (Medtronic, Minneapolis, MN, USA). Fixation of both electrodes was made independently. A vestibular response telemetry (VRT) was carried out intraoperatively (Python Software Foundation, version 2.4, Wilmington, DE, USA) in order to obtain electrically evoked action potentials (ECAPs) from the vestibular nerve [11].

During the postsurgical stay, CT scans and 3-D reconstruction were performed to check the placement and orientation of both electrodes (Figure 2b).

2.2. DVAtreadmill

DVA was assessed on a treadmill [14] (Domyos RUN 100), which includes a safety key to stop in case of a fall, with a screen placed at 2.8 m from the subject. The test was performed in front of a dynamic illegible E (DIE) test in order to repeat test without

memorization [15]. The VA scale was adapted to the test subject distance, which was 2.8 m for all measurements. The chart was positioned at eye height. Patients were tested in static condition (while standing still) and in dynamic conditions (while walking on the treadmill at 2 and 4 km/h) with the vestibular implant turned on or off. Testing started with optotypes presented at a LogMAR of 1.0. When all optotypes were recognized correctly, the corresponding LogMAR was considered achieved and the last one obtained corresponded to the DVA score. A patient with a score of 1 or more line differences between static and dynamic acuity was defined as having an abnormal DVA. Every condition was tested once and a rest period of 1 min was inserted between each condition while the treadmill was stopped. If the patient was unable to keep a certain speed, the test was stopped and registered as "drop-out". The speed of letters per row in each condition was calculated, as well as the decrease in LogMAR between static and dynamic conditions. DVAtreadmill was considered abnormal when a VA difference of more than 1 line was recorded at static, 2 and 4 km/h with and without vestibular implant.

When carrying out the test, it is essential to always use the same conditions, regarding the reading distance, brightness and ametropia correction. If the patient wears lenses (contact or glasses), the examination is performed with them, except in cases of progressive lenses where the test is performed without correction

2.3. Oscillopsia Severity Questionnaire (OSQ)

Every patient completed the oscillopsia severity questionnaire (OSQ) developed by the Division of Balance Disorders in Maastricht [8]. The OSQ includes nine questions about the patients' experience of oscillopsia in daily life. Every question can be answered by one of the following five options: Always (=5), Often (=4), Sometimes (=3), Seldom (=2) or Never (=1). The outcome of every separate question was registered and the mean value for every patient was calculated. A mean value of three or more was considered as moderate to extreme oscillopsia severity.

2.4. VHIT

We also measured horizontal angular VOR gain and saccades by vestibular head impulse test (VHIT) (ICS Impulse type 1085 from GN Otometrics A/S, Taastrup, Denmark) with and without vestibular implant in the same visit to reduce the effect of learning over repeated trials. We also tested vertical canals, but we based our results only on horizontal ones because VOR gain of the verticals for the diagnosis of BVP has to be further evaluated [13].

2.5. Electrical Stimulation

The basic profile of electrical stimulation to obtain the vestibular response consists of an ACE (RE) coding strategy with MP1+MP2 stimulation, a maximum of 8, with a stimulus speed between 900 and 1200 Hz and a pulse width of 25 μs, depending on the patient's response characteristics. Electrodes 1, 2, and 3 were used with the same C value and a dynamic range of 1, based on responses obtained intraoperatively.

In the patients, activation was achieved when reaching 80% of the intraoperative response value.

The programming of the cochlear part was carried out as established by the usual protocols 4 weeks after surgery, using 19 electrodes in this case. As a fitting method we use both electrodes' arrays alternatively. After that, patients use both electrodes simultaneously for chronic electrical stimulation.

2.6. Ethical Considerations

This study was conducted in accordance with the guidelines contained in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. This work was approved by the Ethical Committee of our hospital (Id: CEIM 2017/956,

CEIM 2020-020-1-). The patients/participants provided their written informed consent to participate in this study.

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Significance was set on $p < 0.05$. Scores of each item of the oscillopsia severity questionnaire were compared for patients with and without vestibular implant using Kruskal–Wallis test (IC 95% $p < 0.05$ for all comparisons). VA registered in logMAR and timings in each condition were also measured with a Student *t*-test ($p < 0.05$ for all comparisons).

3. Results

In the present study, five patients, all males with BV, were included. The mean age was 45 years (SD 9.41). The duration of illness varied between 5 and 20 years. Etiologies included Cogan syndrome, head trauma, bilateral Meniere disease, cholesteatoma and meningitis (Table 1).

Table 1. We describe in this table demographic characteristics of patients and the DVA on a treadmill result in LogMAR with vestibular implant on and off in each condition.

Patient	Etiology	Sex	Age (Years)	Evolution (Years)	Years of Implantation	VA STATIC	VA 2 km/h	VA 4 km/h
P1 ON	Meningitis	Male	49	5	2018	0.40	1.00	
P1 OFF						0.40	1.00	
P2 ON	Cogan Syndrome	Male	47	6	2020	0.40	0.40	0.40
P2 OFF						0.40	0.40	0.89
P3 ON	Trauma	Male	48	20	2021	0.17	0.40	0.40
P3 OFF						0.17	0.40	0.48
P4 ON	Meniere Syndrome	Male	36	15	2021	0.00	0.10	0.10
P4 OFF						0.00	0.48	0.30
P5 ON	Cholesteatoma	Male	64	8	2022	0.0	0.10	0.10
P5 OFF						0.0	0.17	0.17

In the present study, the subjects were used as their own controls so that the results with and without the implant were compared in the same visit to reduce a learning effect, and thus analyze if immediate changes were produced.

Four patients were able to complete the procedure at their own maximum safe walking velocity (2–4 km/h), and only one (Patient 1) was not able to complete 4 km/h with and without the vestibular implant. Absolute VA values obtained in each condition are presented in Table 1. VA differences between static, 2 and 4 km/h conditions were only normal in two patients (Patients 4 and 5) who had a normal VA difference with the vestibular implant at all three velocities (no more than one line of differences between the static and dynamic conditions). Most of the subjects were tested at 6 km/h as well, but we decided to reduce the examinations to just 4 km/h in order to prevent the falling risk for some of them.

Moreover, changes were evident during the DVA on the treadmill with the use of the implant, reflecting significant differences in logMAR with the vestibular implant on and off at 2 ($p = 0.048$; $p = 0.043$) and 4 km/h ($p = 0.014$; $p = 0.033$) ($p < 0.05$) (Figure 3). An analysis of the time per row to answer each line was also carried out, and a significant improvement ($p < 0.05$) resulted from the vestibular implant being on in the dynamic conditions, especially for the most difficult situation (4 km/h) (Figure 4)

The comparative study of OSQ results shows that the mean in most of the items is greater than or equal to 3 (8/9) and the result is reduced in the condition with the vestibular implant on. Significant differences were found using the patients themselves as controls ($p < 0.05$) (Table 2).

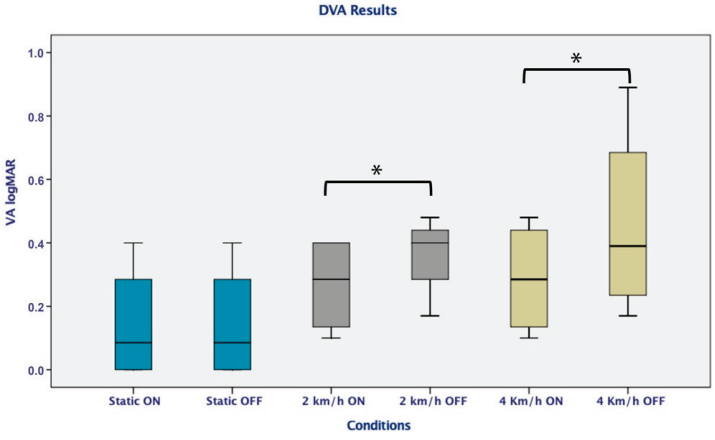


Figure 3. DVA on a treadmill with the vestibular implant on and off reflecting a significant difference in logMAR on 2 km/h and 4 km/h condition ($p < 0.05$). * Indicates significant differences between conditions.

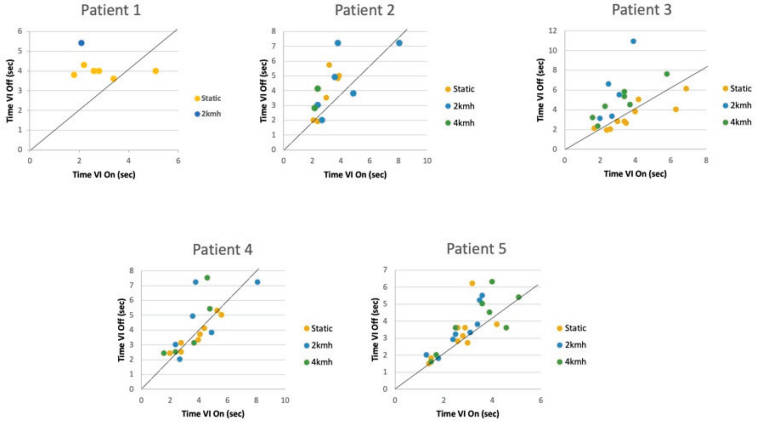


Figure 4. Timings per row for static and 4 km/h conditions in DVA on a treadmill with vestibular implant on and off in each patient. At 2 and 4 km/h, significant differences were acquired ($p < 0.05$).

Table 2. Oscillopsia severity questionnaire with vestibular implant on and off with significant differences $p < 0.05$ in almost all the items (6/9). * Indicates significant differences.

	Oscillopsia Severity Questionaire				
	Vestibular Implant Condition	**N**	**Media**	**SD**	**SIG**
OSQ ITEM 1	VI OFF	5	4.60	0.894	0.09
	VI ON	5	3.20	1.483	
OSQ ITEM 2	VI OFF	5	5.00	0.000	0.1
	VI ON	5	4.40	0.894	
OSQ ITEM 3	VI OFF	5	4.80	0.447	0.04 *
	VI ON	5	3.00	1.581	
OSQ ITEM 4	VI OFF	5	5.00	0.000	0.005 *
	VI ON	5	2.00	1.000	
OSQ ITEM 5	VI OFF	5	4,20	1.789	0.04 *
	VI ON	5	3.00	1.581	
OSQ ITEM 6	VI OFF	4	5.00	0.000	0.03 *
	VI ON	4	4.00	1.414	

Table 2. *Cont.*

	Oscillopsia Severity Questionaire Vestibular Implant Condition	N	Media	SD	SIG
OSQ ITEM 7	VI OFF	5	5.00	0.000	0.05 *
	VI ON	5	3.60	1.673	
OSQ ITEM 8	VI OFF	3	5.00	0.000	0.2
	VI ON	2	4.00	1.414	
OSQ ITEM 9	VI OFF	5	5.00	0.000	0.04 *
	VI ON	5	3.40	1.673	

Regarding the VHIT study of the five patients, a gain restoration was not achieved, although an immediate saccadic reorganization process was obtained in two of the patients (Patients 1 and 2) that suggests an absence in the stimulation in the six semicircular canals, as expected, but changes in VOR were reflected in VHIT with a substantial improvement in the DVA (Figure 5).

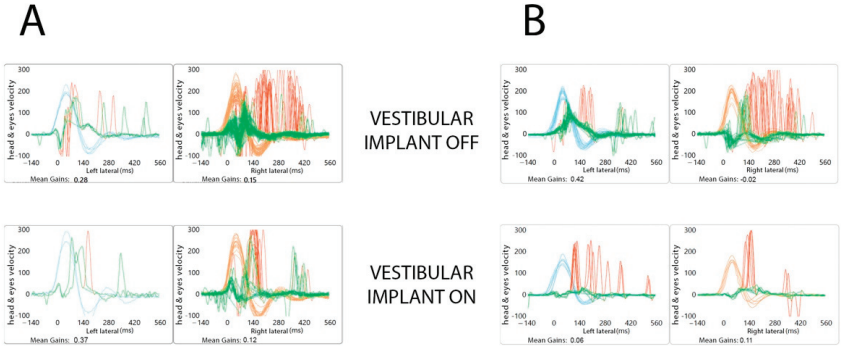


Figure 5. VHIT with an immediate saccadic reorganization process obtained in two of the patients (**A**,**B**).

4. Discussion

In this research we wanted to quantify oscillopsia in BVD patients who use a new vestibular research implant CI24RE(VEST) and to compare the variations in VA with the device. We wanted to provide information on the otolithic involvement in the VOR since the role of the otoliths in humans (utricle and saccule) in the global vestibular function has not been widely studied and it is difficult to determine.

It is important to take into account that the subjects included in this study presented reduced vestibular activity before implantation, both at the otolithic organs and in the semicircular canals (tested by absence in VEMPS response, gain on VHIT < 0.4 and areflexia in caloric test), which ruled out the possibility of assuming outcomes in this study based on residual effects. In addition, no changes in VHIT gains were observed with the device, so it presumably indicates that the VA effect could be attributed to translational VOR.

One possible way to analyze reliable and sensitive VA in BVD patients is the evaluation of walking on a treadmill at controlled velocities because with frequency ranges around 2 Hz the VOR contribution in gaze stabilization is predominant [3,10]. Guinand et al. demonstrated a rise in test sensitivity for BVD by up to 97% by combining the three speeds of 2, 4 and 6 km/h (8). However, it should be taken into account that in patients with BVD, it has been described that up to 22% were not able to complete the DVA test on a treadmill (drop-out) [9], which coincides with our results since in one of the patients it was not possible to reach a speed of 4 km/h. The results that have been achieved in this study are promising; however, visual acuity that is considered normal has not been achieved at the moment, which can be justified by multiple factors, although one of them could be the lack of restoration of a VOR.

However, we must bear in mind that the DVA is a functional outcome of the multisensory system. A central processing of visual, vestibular and oculomotor inputs exists, and patients can use adaptation and compensation mechanisms to improve gait or gaze [16]: saccades, the vestibulo-collic reflex, automatic spinal locomotor programs [17], compensatory walking strategies with a reduction in walking speed or stride length [18], and that somatosensory system [7].

Although the aim of our implant was not the analysis of semicircular canals, interesting findings were obtained during the analysis of vHIT. In some of the patients, a reorganization of the saccades was observed on both sides when using the device, a finding that did not present when we repeated the test with the vestibular implant off. Recovery saccades with shorter latency would have resulted in the target landing on or near the fovea before it was extinguished, and this may have allowed for better DVA performance. [1,19,20]. This suggests that the reorganization of the refixation saccades influences the amount of vestibular disability [14]. The lack of improvement in VHIT gain and these saccades can represent the activation of a central compensating mechanism. The studies established so far have allowed theorizing that the constant electrical stimulation generates a barrage of action potentials in the saccular nerve, which replaces the reduced or absence of saccular afferent action potentials in these patients with BVD [21]. Theses action potentials are continuously arriving at the vestibular nuclei and the midline of the cerebellum and other structures, but we still do not know completely where saccular afferents are projected. These new pieces of information obtained in some of our patients, allow us to speculate that these central projections are not limited exclusively to motor control systems but are also associated with corrective saccades.

On the other hand, the OSQ of our patients shows similar results to those of Guinand 2012 [8]. Before using the implant, in static conditions, the subjects presented oscillopsia, even in the patient with the longest evolution of the disease (20 years) for whom it was supposed that he would have established central adaptation mechanisms for the tolerance of the retinal slip. However, this situation improved from extreme to moderate or soft oscillopsia severity with the use of the implant in many of the items. We consider this sensation of a certain degree of oscillopsia to be the result of an absence of a VOR restoration.

These findings in the DVA on a treadmill, coupled with the OSQ and the appearance of corrective saccades in the VHIT, make us assume that the inputs generated by the vestibular implant through the afferent pathways act on the central nervous system favoring a response that improves the adaptation and compensation mechanisms, and ultimately improving the patient's visual acuity and thus their quality of life.

Despite of the lack of DVA test specificity, it is one of the few tests that evaluates the function of the otolithic organs close to reality and its widespread use allows us to perform comparatives with other research groups. We therefore hope with this research to provide information on vestibular stimulation, and the knowledge will be the start of continued research in the field with many unknowns still to be resolved.

5. Conclusions

The vestibular implant with otolithic stimulation offers changes in the response of the DVA, which makes this research one of the first to address the possible restoration of the tDVA, although it is not possible to rule out other contributing factors (presence of covert saccades, somatosensory system, . . .). More work seems necessary to understand the pathophysiology of these findings, but this implant is added as a therapeutic alternative for the improvement of oscillopsia.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Long-Term Evolution of Vestibular Compensation, Postural Control, and Perceived Disability in a Population of Patients with Vestibular Neuritis

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Abstract: Objectives. The aim was to analyze and compare the compensatory process, vestibular dysfunction, postural control, and perceived disability in a population of patients with vestibular neuritis (VN). Material and Methods. This is a prospective and longitudinal study of 67 patients diagnosed with VN. Inclusion criteria were sudden onset of vertigo, unidirectional spontaneous horizontal nystagmus, and impairment in vestibular test. Exclusion criteria were imaging or clinical findings of any neurotologic disorder. All vestibular tests were performed; vHIT, vestibular evoked myogenic potentials (VEMPs), caloric test and computerized dynamic posturography (CDP), dizziness handicap inventory (DHI), and visual analogue scale (VAS) were also performed at every follow up. Results. We observed a correlation between the composite score of CDP and baseline vestibular function elicited either by caloric test, VEMPs, or vHIT. There was a significant correlation between baseline vestibular function and first visit questionnaire scores. The main gain recovery for the horizontal canal was 0.1 ± 0.04 for the first three months. After that, the gain recovery significantly decreased. The presence of covert and overt saccades', latency and amplitude decreased, respectively, after the 6-month period, when compared to the baseline results. We also observed a decrease in the PR score from 3 months after the vestibular insult until the last follow up. We observed a significant decrease in DHI and VAS from the first visit until the last one. Those patients with an initial HC gain below 0.5 had significantly higher DHI and VAS scores at every follow up. Conclusions. There are different measurements that could become a complete measurement of the state of compensation, postural control, and disability of the patients. There is a time window in which the vestibular restoration could give us clinical insights regarding the management of VN patients.

Keywords: vestibular neuritis; vestibular compensation; disability; unsteadiness

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1. Introduction

Vestibular neuritis (VN) is the main cause of acute vestibular syndrome, which causes long-lasting, continuous, and spontaneous vertigo. It is assumed to be of viral origin [1], because of possible reactivation of latent herpes virus simplex type 1. The main alternative cause postulated is vascular ischemic origin, a theory based on the recurrent finding that vascular risk factors are more prominent in these patients [2]. The viral hypothesis is more contrasted because, currently, there is genetic and radiological evidence of inflammation in the acute phase of VN [3,4].

Simply based on symptoms, VN presentation overlaps with that of a great variety of disorders such as a potentially serious ischemic stroke or minor gastroenteritis [5]. Therefore, the diagnosis should be based on clinical history and physical examination, following the HINTS protocol [6].

The horizontal and superior semicircular canals are more commonly affected in VN [7]. However, in a minority of patients, a complete or a selective involvement of the posterior canal takes place [8]. Although a major vestibular dysfunction in VN is expected, recent studies report some cases with a final diagnosis of possible vestibular neuritis with mild or no objective deficit in vestibular function [9].

For these reasons, it is well known that after VN, the ipsilateral VOR and its pathway are affected. This is evidenced, either by caloric, rotatory testing, vHIT, or VEMPs.

A vestibular lesion induces changes in the gain and time constant of the VOR system [10]. The gain of the VOR is an indication of the intensity of vestibular response and, therefore, of the vestibular compensation process. Some restoration and adaptation changes are usually described in these patients, a finding usually interpreted as a "compensatory system" [11].

Patients who suffer from vestibular neuritis tend to develop a persistent long-term disability in their daily activities. Some clinical variables such as the initial vestibular deficit, an enhanced visual dependence, or the level of anxiety may, to some level, predict outcomes in VN patients [12]. Although previous evidence reported that neither caloric test paresis nor VOR gain of vHIT predicts symptom outcomes in vestibular neuritis [13] other authors suggest that saccadic organization seems to participate in visual target retention and ocular compensation during head impulses in vHIT studies [14,15]. So far, there is no evidence of a relationship with vestibular function parameters, postural control, and perceived disability in vestibular neuritis.

The aim of this study is to analyze and compare the compensatory process, the evolution of vestibular dysfunction, postural control, and perceived disability in a population of patients with vestibular neuritis over time.

2. Materials and Methods

This was a longitudinal and prospective study. In all, 67 patients were recruited consecutively from the Department of Otorhinolaryngology in the University Hospital of Getafe from January 2017 to May 2020. Patients were admitted to the emergency unit due to acute vestibular syndrome and were finally diagnosed with vestibular neuritis. All patients were thoroughly assessed by a multidisciplinary team consisting of otorhinolaryngologists and a neurologist. Complete anamnesis, as well as otological and neurological examinations, were applied to every patient. In the emergency unit, all patients received the following treatment: prednisone (1 mg/kg in decrescent dose for 12 days) and antipsychotic (sulpiride 50 mg/8 h for maximum 3 days). After 3 months of follow up, when needed, vestibular rehabilitation therapy was offered to improve the imbalance.

The inclusion criteria for VN were (1) a single sudden onset of sustained vertigo, (2) unidirectional spontaneous horizontal nystagmus to the healthy side following Alexander's law, (3) reduced caloric response (canal paresis > 25%) or VOR dysfunction in vHIT test, and (4) absence of neuro-otologic signs or symptoms suggestive of other peripheral, vestibular, or central disorders including hearing loss.

Exclusion criteria were (1) history of neurotologic disorders or otologic surgery, (2) medically ill condition or malignancy that can cause immunocompromised status, and (3) brain magnetic resonance imaging (MRI) that revealed acute infarction or other acute/chronic brain lesions, including cerebellopontine angle tumors.

This project was approved by the institutional review board (CEIm). Informed consent was obtained from every patient.

Patients received follow-up assessments 1 week, 1 month, 3 months, 6 months, and 1 year after the onset of vertigo. All tests necessary to analyze vestibular impairment and the process of recovery and compensation were performed from the initial visit until the end of the follow up. These included vHIT, cervical and ocular VEMPs, and bithermal caloric test. DHI and visual analogue scale were performed as well to know the disability perception of every patient.

Data were processed with SPSS version 22.0. For the evolution of continuous quantitative variables, the ANOVA test was used. Duncan's post hoc test was used considering first-visit results as a reference. For qualitative variables, Chi^2 test was performed. A study of multiple regression was performed to analyze the evolution of vHIT parameters, CDP, and disability questionnaires. Statistical significance for all tests was 0.05.

2.1. Vestibular Testing

Baseline vestibular responses were obtained with conventional bithermal caloric testing (30.5 °C and 43.5 °C) and a 10 s ice-water caloric test, when indicated. We used a video-based system (Ulmer VNG, v.1.4, SYNAPSIS®, Marseille, France) for the acquisition and analysis of the eye response. The maximum velocity of the slow phase of nystagmus evoked in each ear was analyzed to identify unilateral weakness and directional preponderance as determined by Jongkees' formula. A mean unilateral paresis exceeding 25% indicated vestibular hypofunction.

We also evaluated the dynamic function of the horizontal semicircular canals using the vHIT (GN Otometrics; Copenhagen, Denmark). Fast, short, and unpredictable head impulses were performed in random horizontal directions while the subject was seated in front of the ground-fixed target and was instructed to maintain his/her vision continually fixed on the target during the test. Eye and head velocities were acquired with a sampling frequency of 250 Hz, and we calculated the hVOR gain from an average of 20 head impulses performed over a range of velocities from 100 to 250°/s.

To evaluate the function of vertical canals, the patient's head was rotated 40° to the right to align it with the left-anterior–right-posterior plane. Patients were directed to continue staring at the same earth-fixed target as before. Brief, abrupt, forward and backward head impulses were made to stimulate the left anterior semicircular canal and the right posterior semicircular canal, respectively. After 20 impulses in each direction, the second pair of vertical canals was evaluated.

The presence or absence of saccades and their latency, and amplitude were registered for each exploration. To assess the dispersion of the saccades' latency values, we used the PR score [16].

PR score is a quantitative variable that ranges between 0 and 100; when PR is close to 0, saccadic responses are described as gathered, and when it is nearing 100, they are described as scattered.

VEMP was performed for all patients using standard BERA equipment (SmartEP® Intelligent Hearing Systems®). Each subject was tested while sitting down and turning their head away from the stimulated ear to contract the sternocleidomastoid muscle (SCM). The active electrode was placed in the middle of the upper third of the SCM and a reference electrode was placed on the chin. The ground electrode was placed on the forehead. Acoustic stimuli were presented through inserted earphones. Acoustic stimuli were 500 Hz tone bursts presented five times/second. The rise–plateau–fall time was 1–2–1. VEMP threshold and response amplitude were measured at a stimulus of 90 dB HL. The EMG from each side was amplified and bandpass filtered (10 Hz to 1.5 kHz). Results from 200 repetitions in each ear were averaged. The peak-to-peak amplitude (μV) was measured for P13–N23 potentials. To estimate the relative response in both ears, we used the interaural difference (IAD) ratio, calculated as (right ear amplitude − left ear amplitude) ÷ (right ear amplitude + left ear amplitude) × 100. A mean IAD ratio exceeding 40% indicated abnormal VEMP.

Computerized dynamic posturography (NeuroCom® International, Inc., Clackamas, OR, USA) was carried out with the sensory organization test (SOT) battery. In this test, the patients were asked to maintain their balance under six different conditions. The first three conditions (SOT1, SOT2, and SOT3) provided accurate, uninterrupted foot support surface information. The visual information provided is different in each of these conditions. In SOT1, the patients keep their eyes open, whilst in SOT2, they must have their eyes closed. In SOT3, the patients must keep their eyes open, but the surroundings move in

a pattern referred to by the patient antero-posterior (A-P) swaying movements. In SOT conditions 4, 5, and 6, the visual information is the same as those described for SOT1, 2, and 3 respectively, but the A-P sway movement of the patient drives the movement of the supporting surface in an axis parallel to the ankle joint. For every SOT condition, three trials were performed; in each of them, the A-P sway was measured and calculated relative to the sway of 12.5° (which is considered the maximum A-P sway about the ankle joint in normal subjects). In terms of general performance, a composite score (CS) was given as an overall estimate of postural stability, which is a weighted average of the results in different trials with special emphasis placed on the conditions SOT3 through SOT6.

2.2. Handicap Measurements

We used the DHI questionnaire [17], while vertigo severity was assessed using the visual analogue scale (VAS).

In the DHI, the patient had to answer "yes", "sometimes", or "no" to each question, the responses being designated 4, 2, and 0 points, respectively. The questionnaire had 25 items, so the total score ranged between 0 and 100.

VAS scores were obtained by asking the patient to rate the severity of their vertigo from 0 to 10.

3. Results

3.1. Demographic Data

A total of 67 patients participated in this study with a minimum follow up of one year. The mean age of patients was 52.53 ± 17.54 years. There were 33 (49.25%) females and 34 (50.75%) males, and 37 (55.22%) patients had a VN in the right ear.

The most prevalent comorbidities of patients were hypertension (39.7%), dyslipidemia (22.1%), type-2 diabetes mellitus (10.3%), and ischemic cardiopathy (5.9%).

The mean canal paresis was 55.37 ± 26.78 for the bithermal caloric test. Mean asymmetry was 70% ± 30% and 45.33% ± 30% for cervical and ocular VEMPs, respectively.

Mean values for horizontal, superior, and posterior canal of the vHIT were 0.45 ± 0.19, 0.29 ± 0.31, and 0.45 ± 0.17, respectively.

Based on the results of the vestibular tests, we could establish the affected branches of the vestibular nerve. In all, 42 (62.68%) and 4 (5.9%) patients had a single affection of the superior and inferior branch, respectively, while 5 (31.34%) patients had a total involvement of the vestibular nerve.

Mean values for canal paresis, cervical and ocular VEMPs asymmetry, and vHIT gain values depending on the affected branch are shown in Table 1.

Table 1. Mean values for canal paresis, cervical and ocular VEMPs asymmetry, and vHIT gain values, depending on the affected branch.

	Mean Canal Paresis
Bithermal caloric test	55.37 ± 26.78
	Asymmetry
cervical VEMPs	70% ± 30%
ocular VEMPs	45.33% ± 30%
	VOR values
vHIT horizontal canal	0.45 ± 0.19
vHIT superior canal	0.29 ± 0.31
vHIT posterior canal	0.45 ± 0.17

Overall, 51 out of 67 patients (86%) had an abnormal CDP assessment. Looking at different subtypes, we identified 35 (52.85%) patients who showed a vestibular pattern where conditions 5 and 6 were primarily affected. A combination of a vestibular and visual preference pattern was observed in 10 (14.95%) patients. "Severity pattern" was observed in seven (10.44%) patients.

We observed a significant correlation between the composite score and baseline vestibular function elicited either by caloric, VEMPs, or vHIT test ($p < 0.05$).

Mean values for baseline VAS and DHI are shown in Table 2. There was a significant correlation between baseline vestibular function and first visit questionnaire scores ($p < 0.05$) and also between baseline composite score and first visit questionnaire scores ($p < 0.05$).

Table 2. Mean baseline values for baseline VAS and DHI.

	Mean ± SD
DHI (Functional)	27.14 ± 8.39
DHI (Emotional)	17.46 ± 7.73
DHI (Physical)	21.30 ± 7.38
DHI (Total)	66.70 ± 18.70
	Mean ± SD
Visual Analogue Scale	7.59 ± 1.85

3.2. Gain and Saccades' Evolution

Mean values for horizontal, superior, and posterior canal at each follow up are presented in Table 3.

Table 3. Mean values for the horizontal, superior, and posterior canal at each follow up.

	Initial	**7 Days**	**1 Month**	**3 Months**	**6 Months**	**12 Months**
Horizontal canal	0.45 ± 0.19	0.54 ± 0.25	0.69 ± 0.25	0.76 ± 0.23	0.79 ± 0.27	0.83 ± 0.23
Superior canal	0.29 ± 0.31	0.52 ± 0.21	0.62 ± 0.24	0.7 ± 0.2	0.74 ± 0.24	0.75 ± 0.22
Posterior canal	0.45 ± 0.17	0.69 ± 0.2	0.81 ± 0.21	0.78 ± 0.21	0.82 ± 0.19	0.8 ± 0.18

When we compared every gain elicited in the different follow ups with the baseline, both horizontal and superior canal gains were significantly higher ($p < 0.001$) from one month until the last follow up.

The main gain recovery for the horizontal canal was 0.1 ± 0.04 for the first three months after the vestibular insult. After the 6-month follow up, the gain restoration significantly decreased to 0.01 ± 0.03 ($p < 0.001$). The HC gain bar graphic at every follow up is shown in Figure 1.

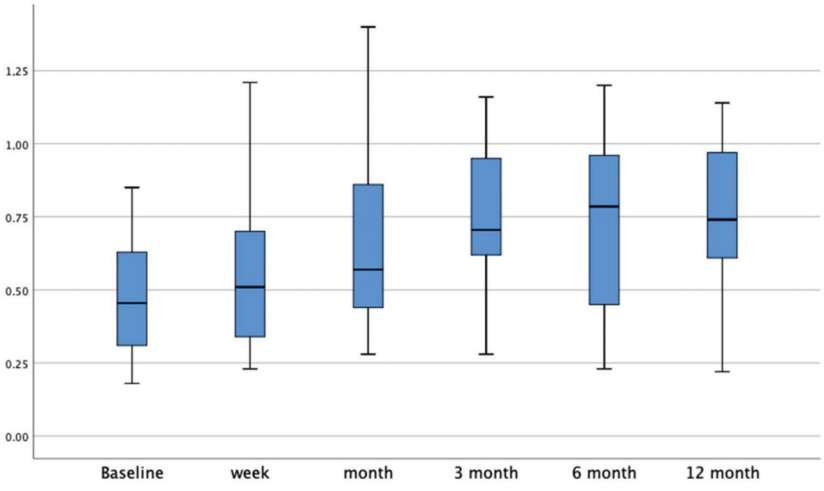

Figure 1. Bar graphic showing the HC gain values at every follow up.

The main gain recovery for the superior canal was 0.1 ± 0.03 for the first three months after the vestibular insult. After the 6-month follow up, the gain restoration significantly decreased to 0.01 ± 0.049 ($p < 0.01$).

When we analyzed the evolution of the posterior canal gain in the global population, we did not observe a significant gain restoration ($p > 0.05$). If we excluded those patients with selective superior vestibular neuritis, we also observed a main gain recovery of 0.1 ± 0.029 for the first three months after the vestibular insult, with a significant decrease of such restoration after the 3-month follow up.

Table 4 shows the mean data for presence, latency, amplitude, and PR for both covert and overt saccades during the different follow-up periods.

Table 4. Mean data for presence, latency, amplitude, and PR for both covert and overt saccades during the different follow-up periods.

COVERT Saccades	**Initial**	**7 Days**	**1 Month**	**3 Months**	**6 Months**	**12 Months**
Presence (%)	56.7%	68.8%	56.4%	50.0%	38.5%	40.8%
Latency (ms)	107.16 ± 30.32	107 ± 12.02	105 ± 19.57	104.11 ± 16.93	103.53 ± 9.64	100.2 ± 21.17
Amplitude (°/s)	177.03 ± 56.31	170.5 ± 68.32	167.5 ± 53.31	137.78 ± 72.56	175.53 ± 80	150.45 ± 72.91
PR	22.69 ± 27.91	18.4 ± 13.26	22.86 ± 18.25	27.47 ± 17.74	29.72 ± 23.91	32.12 ± 28.47
OVERT Saccades	**Inicial**	**7 Días**	**1 Mes**	**3 Meses**	**6 Meses**	**12 Meses**
Presence (%)	92.5%	90.6%	84.6%	69.4%	74.4%	65.3%
Latency (ms)	218.02 ± 52.84	219.14 ± 62.13	203.3 ± 59.8	213.52 ± 53.02	211.3 ± 49.09	201.72 ± 53.25
Amplitude (°/s)	217.8 ± 49.71	210.86 ± 57.21	178.09 ± 50.12	185.12 ± 50.47	187.69 ± 74.21	170.09 ± 66.39
PR	37.8 ± 12.2	25.7 ± 7.81	22.9 ± 6.93	18.1 ± 2.73	17.4 ± 2.91	13.4 ± 4.17

The presence of covert and overt saccades significantly decreased after the 3-month and 6-month follow up, respectively, compared to the baseline results. The latency and amplitude significantly decreased after the 6-month follow up when compared to the baseline results.

We observed a significant decrease in the overt saccades' PR score from 3 months after the vestibular insult until the one-year follow up compared with initial data (Figure 2).

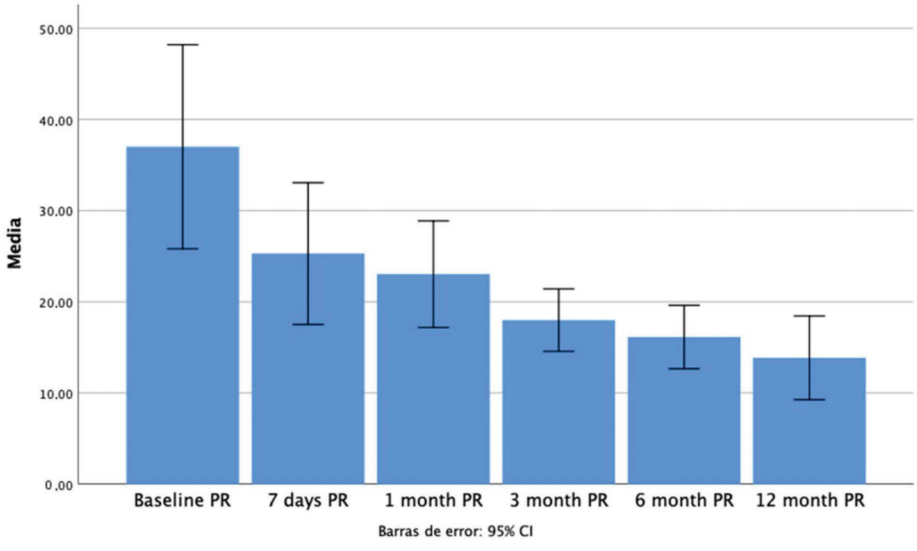

Figure 2. Bar chart for PR values at each follow up.

3.3. Postural Response Evolution

We observed a significant improvement in CDP's conditions 5 and 6 and the composite score in the 6-month evolution compared to baseline ($p < 0.001$). We also observed a significant improvement ($p = 0.01$) in the anterior limits of stability in the same period.

We did not observe any further significant posturographic improvement from the 6-month follow up until the end of the study.

As seen in Figure 3, those patients with a final HC gain below 0.7 had worse composite scores at every follow up, but those differences were not significant ($p > 0.05$).

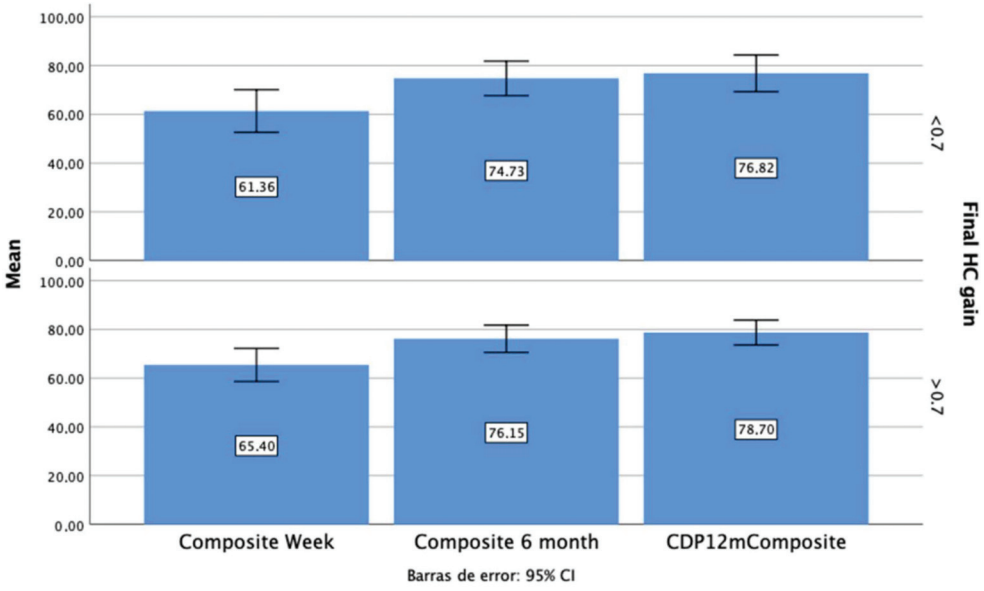

Figure 3. Composite score at every follow up, depending on the HC final gain.

3.4. Handicap Measurement Evolution

Regarding DHI and VAS measurement, we observed a significant decrease in both values from the first week until the last follow up, compared to the baseline measurement. When we compared each measurement with the previous one, we found a significant decrease in both values from the first-week visit until the 3-month follow-up measurement.

The variables DHI and VAS were found to be strongly positively correlated, r = 0.770, $p < 0.001$.

As shown in Figure 4, those patients who finally obtained an HC gain above 0.7 had lower scores in either DHI or VAS measurement at every follow up ($p < 0.05$).

3.5. Relations of the Initial Damage with Vestibular Restoration, Postural Response, and Perceived Handicap

Those patients with an initial HC gain below 0.5 had significantly worse HC gain values and higher DHI and VAS scores at every follow up.

Additionally, those patients with an initial HC gain below 0.5 had a worse composite score at every follow up, but those differences were not significant ($p > 0.05$).

Regarding VEMPs measurement, the initial affectation of this myogenic potential predicted a worse HC gain at the 7-day follow up, without any further significant differences at ulterior follow ups. The initial caloric dysfunction did not significantly correlate either with the initial HC gain or the rest of the measurements elicited by vHIT during the different follow ups.

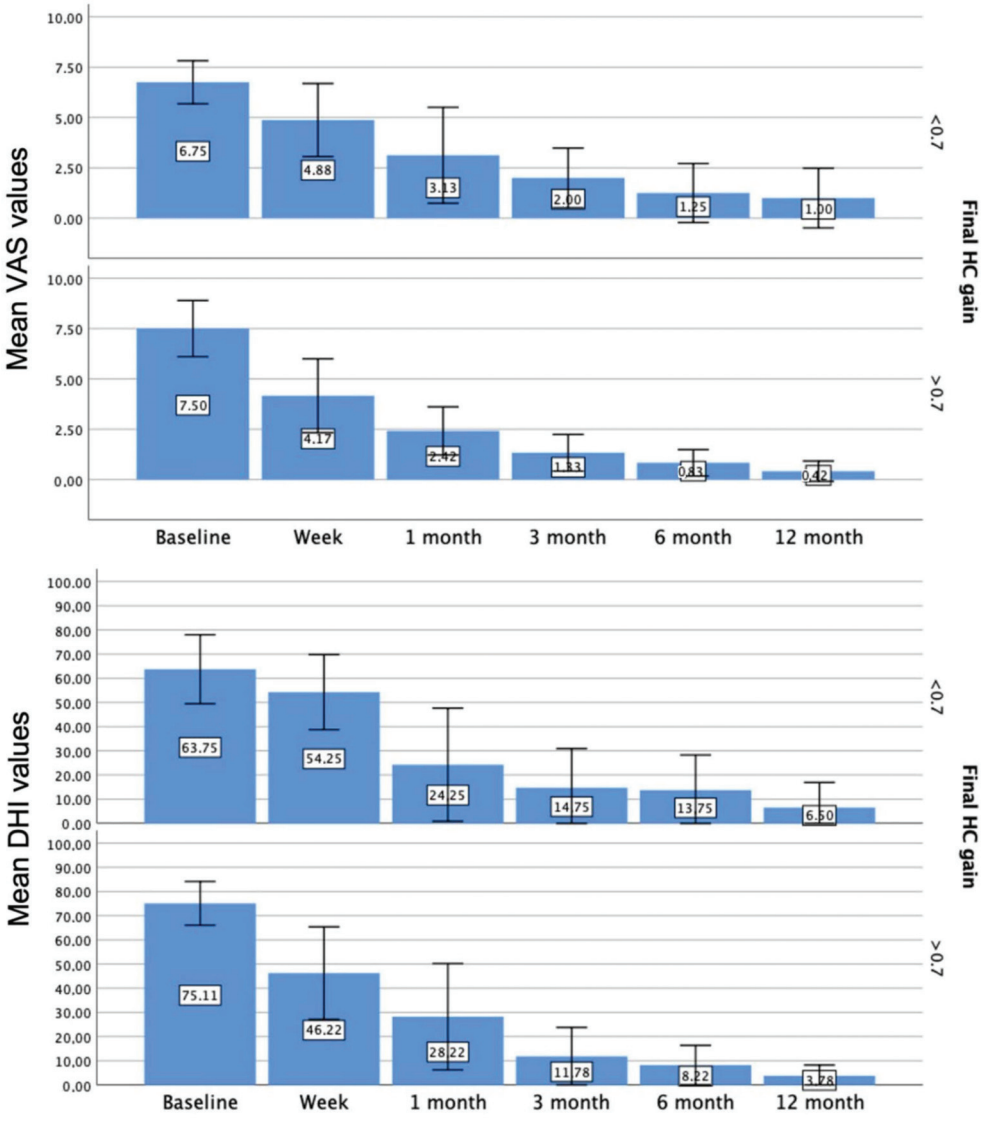

Figure 4. Bar chart for DHI and VAS score at every follow up, depending on the HC final gain.

4. Discussion

This article shows how different easily obtainable measurements could become an objective and complete measurement of the state of compensation. This would give us information about the patient's ability to abolish the residual symptoms after acute unilateral vestibulopathy and to recover postural control.

One of our findings was to show that ipsilateral-deficit VOR gains of the three semicircular canals constantly increased during the months following the onset of acute unilateral vestibular neuritis. Both the superior and the horizontal canals showed a decrease in the gain restoration after the 3-month follow up. In the case of vestibular neuritis, this gain improvement has two hypothesized components: central compensation and peripheral recovery.

The restoration resulting from the opposite vestibular nuclei is one of the key mechanisms of central compensation. This is achieved through biochemical events within the vestibular nuclei, and under specific conditions, strong synaptic plasticity may take place within the vestibular sensory organs. It is thought that this reactive plasticity can contribute to the repair of damaged contacts between hair cells and fibers of the vestibular nerve, thus gradually restoring peripheral sensory input [18].

As stated by other authors [19], the posterior canal's function is affected significantly less by vestibular neuritis. However, in 4% of our patients, the PC was affected with an average gain of 0.45 ± 0.17, similar to the deficit in either the horizontal or superior canal. We can assume that changes in velocity VOR gains over time are equally produced in the three semicircular canals.

A decrease in the number of saccades and their latency and amplitude was also observed. We previously described [14] in a retrospective study, how the overtaking of the covert saccade is a sign of compensation. Many authors have reached similar conclusions [20,21] especially in populations where the VOR can change, indicating some marker of recovery of peripheral sensory function.

We also observed a significant decrease in this value regarding the PR score from 1 month after the vestibular insult until the 1-year follow up. We agree with other authors [22] that this measure has the potential to serve as a criterion in the follow-up evaluation of the vestibular compensation process after a vestibular insult.

We observed an improvement in the postural response, measured by a computerized dynamic posturography, either in the composite score or in the stability limits. As observed with the gain restoration, we did not observe any significant improvement after the 6-month follow up, a similar time window, whereby we should concentrate our efforts to improve postural control of our patients after a vestibular insult.

Along with either vestibular restoration or increase of postural control, our population also showed an improvement in the perceived disability, measured either by DHI or VAS, which were strongly correlated.

In our population, the final HC gain elicited one year after the vestibular insult may have a determinative clinical role since those patients with a final HC gain below 0.7 developed higher perceived disability and worse composite score at every follow up. Other authors [23] observed that six months of daily incremental vestibulo-ocular reflex adaptation training, resulted in a significant increase in the retained VOR gain during both passive and active head-impulse testing, along with a reduction of perception of disability.

In the same way, the main clinical predictor for those patients with worse vestibular compensation was the initial vestibular damage. Those patients with lower initial gain elicited by vHIT also developed significantly worse vestibular restoration and higher perceived disability, compared to those patients with less vestibular insult.

Thus, we consider the gain as a predictor of recovery; an important clinical clue that could lead us to manage our patients individually according to certain clinical parameters such as the initial damage or characteristics of the refixation saccades.

5. Conclusions

Different easily obtainable measurements could become an objective and complete measurement of the state of compensation. This would give us information about the patient's postural control and disability at every follow up.

Our results provide us with a time window in which the vestibular restoration is still active and could give us clinical insights regarding the initial management of vestibular neuritis patients.

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Prevention of Severe Vestibular Hypofunction after Systemic Gentamicin

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Abstract: The importance of early evaluation by a neurotologist in patients with infective endocarditis treated with systemic gentamicin and its impact on the patients' quality of life was evaluated. This is a longitudinal retrospective cohort study of 29 patients who received intravenous gentamicin for the treatment of infective endocarditis. Patients were classified into two groups: group A, before a neurotologist was included in the treatment protocol, and group B, after the inclusion of a neurotologist. The frequency of the different symptoms in each group was measured, and the gain of the vestibulo-ocular reflex (VOR) and its relationship with the presence of oscillopsia. In total, 13 and 16 patients were assigned to groups A and B, respectively. The mean gain of the VOR measured using the video head impulse test in group A was 0.44 in the best side and 0.39 in the worst side. In group B, the mean gain was 0.71 (best side) and 0.64 (worst side) ($p < 0.0001$). The patients who complained about oscillopsia had a main gain of 0.41 in the best side and 0.35 in the worst side. Evaluation of vestibular function should be included in the infective endocarditis treatment protocol, including the adverse effects of systemic gentamicin.

Keywords: systemic gentamicin; infective endocarditis; vestibular hypofunction; oscillopsia; video head impulse test

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1. Introduction

Aminoglycosides are bactericidal antimicrobial agents that disrupt the integrity of the bacterial cell wall and impair bacterial protein synthesis [1]. These antibiotics are most frequently used to treat life-threatening infections and as synergistic agents together with other antibiotics for the treatment of infective endocarditis [2], especially gentamicin.

The use of aminoglycosides is limited by their side effects, including ototoxicity, which is manifested by the dysfunction of the auditory (hearing loss) or vestibular (balance deficit) system. Other remarkable side effects include nephrotoxicity and neuromuscular blockade [3].

Aminoglycoside-induced ototoxicity has been linked to genetic susceptibility. Some studies identified the A1555G mutation in the mitochondrial 12s rRNA gene as a primary genetic factor in cases of aminoglycoside-induced ototoxicity [4].

Some aminoglycosides affect hearing more, whereas others are more harmful to the vestibular system, including gentamicin [5]. Some authors suggest that gentamicin vestibulotoxicity is not related to elevated serum levels of the drug (it does not depend on the dosage), which means that it is idiosyncratic [6]. This antibiotic produces bilateral

vestibular loss without vertigo [7]. Although it is usually bilateral and symmetric, it can also be unilateral [8].

Otherwise, there are well-established factors that predispose individuals to vestibulotoxicity, for example, prolonged pharmacological therapy and some patient-related factors (e.g., renal insufficiency, increasing age, and concomitant use of other ototoxic drugs) [9,10].

The vestibulotoxic effect of gentamicin involves immediate inhibition of hair cell transmitter release by blocking mechanotransduction [11], and sustained exposure causes vestibular hair cell damage and death due to apoptosis. Type I hair cells are more susceptible to loss than type II hair cells because they show an increased uptake and retention of gentamicin [12].

The impairment of cellular activity due to aminoglycosides may be temporary or permanent [13]. Early recognition of impending vestibulotoxicity is very important to the prevention of permanent harm because bilateral vestibular loss profoundly affects an individual's quality of life [5].

Vestibulotoxicity is suspected if a patient complains of imbalance, which is worse while walking in the dark, and oscillopsia during head movements [14]. Vertigo is infrequent [15]. Oscillopsia is a disabling condition in patients with bilateral vestibular hypofunction (BVH). When the vestibulo-ocular reflex (VOR) is bilaterally impaired, its ability to compensate for rapid head movements must be supported by refixation saccades [16].

The video head impulse test (vHIT) is a rapid physiological test that can be used to quantify vestibular function. It identifies unilateral or bilateral vestibular weakness [17]. Currently, it is one of the most used diagnostic options, and its utility in the field of neurotology has been invaluable. It is a quick and easy to perform test to evaluate vestibular function.

In many cases, secondary symptoms (such as instability) that may present as a side effect of this drug are not taken into account due to the severity of the infective endocarditis. Patients treated with aminoglycosides are often critically ill and bedridden. Thus, there may be a considerable delay in diagnosing bilateral vestibulopathy in these cases without systematic evaluation. Knowing that gentamicin can cause a vestibular deficit and that a simple test can detect this deficit, it could be very useful to include a neurotologist in the treatment team for patients with infective endocarditis.

The aim of this study was to clarify the importance of an early evaluation by a neurotologist in patients with infective endocarditis treated with systemic gentamicin in the development of vestibular toxicity and its impact on the patients' quality of life.

2. Materials and Methods

This was a longitudinal retrospective cohort study of 29 patients who were hospitalized in the cardiology service of a tertiary referral hospital and received systemic gentamicin for the treatment of infective endocarditis. Patients were classified into two groups: group A comprised patients who received treatment before 2017, that is, before a neurotologist was included in the treatment and follow-up protocol for patients with infective endocarditis, and group B comprised patients who received treatment between January 2017 and December 2019.

In group A, patients received treatment without control or exhaustive monitoring by a neurotologist. These patients sought consult at the outpatient clinic referred by a cardiologist due to intense and permanent vestibular symptoms after the discontinuation of treatment. In group B, patients underwent exhaustive monitoring by a neurotologist at the symptom onset.

During the monitoring process, the patient was questioned every day about the appearance of vestibular symptoms, dizziness, or imbalance. When any of the patients, throughout the treatment, reported the appearance of any of these symptoms, they were evaluated by the neurotologist and gentamicin was withdrawn from the patient's treatment. In this evaluation, in addition to an exhaustive neurotological examination (including the clinical head impulse test), an audiometry and a video head impulse test were performed.

The patient was re-evaluated before discharge and one month after discharge.

The infective endocarditis protocol in this referral hospital (prior to confirmation of an adequate kidney function) is to start with an empirical treatment (cloxacillin 12 g/24 h IV + ampicillin 12 g/24 h IV + gentamicin 3 mg/kg/24 h IV). The neurotologist's role was to monitor patients who, during their hospital stay, began to experience balance-related symptoms, such as dizziness, instability, or oscillopsia. In the outpatient clinic, patients were interviewed and vHIT was performed. Subsequently, the cardiologist and neurotologist evaluated the risk/benefit of gentamicin discontinuation and opted for the second-line antimicrobial option to prevent further progression of vestibulotoxicity.

After a month, a second vHIT was performed in group B. Since patients in group A were not evaluated by the neurotologist during their hospital stay, only the vestibular function at the time of the neurotology outpatient clinic visit was evaluated, and it was not possible to assess their vestibular function at follow-up. Patients with previous vestibular disorders were not included in the study.

For the vHIT, we used the ICS Impulse® device, with software version 4.0 (Otometrics A/S, Taastrup, Denmark), consisting of lightweight tight-fitting goggles with an embedded accelerometer and a 250 Hz sampling rate video camera that captures the patient's right eye movements, as reflected on a half-silvered mirror aided by a low-level infrared light-emitting diode. The distance from the target to the pupil was 1 m, and calibration was performed before the vestibulo-ocular testing procedure was initiated. In total, 40 impulses were delivered (20 in each direction), randomizing the intervals and testing side. The minimum accepted peak speed was 150 deg/s. Vertical impulses were not considered in the present study.

To evaluate the results, the absolute mean VOR gain was considered. The gain of the VOR was obtained after each head impulse and calculated as the ratio of the eye velocity to the head velocity; the procedure in our system measures the area under the curve ratio of the head velocity and eye velocity. The mean of the different impulses in each direction is given but as gain referenced to the affected (mean VOR gain for ipsilesional) or non-affected (contralesional) side. Normal gain is defined as $\geq$0.80 and abnormal when <0.80. The relative gain value was calculated as the amount of gain asymmetry according to the formula: Gas = (1 − (lower gain/higher gain)) × 100 (%) [18].

BVH consists of a bilaterally reduced or absent angular VOR function (which is documented by a bilaterally pathological horizontal angular VOR gain of <0.6, as measured by the vHIT). It has been included in the diagnostic criteria for bilateral vestibulopathy in the consensus document of the Classification Committee of the Bárány Society [19].

The patients were specifically asked about their oscillopsia. These questions were presented as "yes or no" questions. For an affirmative answer, the patient had to mention permanent and non-fluctuating oscillopsia while walking through different environments in their daily life. During the anamnesis, the following questions about oscillopsia in daily life activities were used: Does the world around you seem to move or jump when you are sitting, standing, or walking? Do you feel this sensation when you are running or driving? Is this sensation worse when walking on sand or grass? Can you read a poster while walking? Can you look for contacts in your mobile device while walking? Oscillopsia was considered to be present when the answers for all these questions were "Yes" [16].

A complete anamnesis and clinical examination, including an ocular-motor examination, was performed in all patients (spontaneous nystagmus, position nystagmus, head shaking nystagmus, saccades, smooth pursuit, and test of skew), and vestibular loss was confirmed using vHIT (gain < 0.8).

Statistical analysis was performed using SPSS Statistics 23 program. The Mann–Whitney U test (Bonferroni correction) was performed to compare the number of days that passed from the start of the treatment to the onset of symptoms until the ENT evaluation, the distribution of gains in the vHIT tests of both groups, and the relationship between the gains and the presence of oscillopsia. The Pearson's chi-square test was performed to compare the frequencies of symptoms and oscillopsia in both groups.

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the institutional IRB (PI9810/2017A), and informed consent was obtained from each study participant.

3. Results

In the study, 29 patients were included, all of whom received intravenous treatment with gentamicin at a dose of 3 mg/kg/24 h. Between January 2010 and December 2016, 250 patients were treated in our hospital for infective endocarditis. Of them, 13 (5.2%) were referred to our outpatient clinic for dizziness or permanent instability. These 13 patients were included in group A. From January 2017 to December 2019, 79 patients were treated for infective endocarditis. Sixteen (20.2%) of these patients manifested with dizziness or imbalance after the initiation of treatment, and they were included in group B.

The ages were 58 ± 6 years (group A) and 54 ± 7 years (group B). Seven men and six women were included in group A, and nine men and seven women in group B. No differences were observed in terms of age and sex (Table 1).

Table 1. Main data of the sample.

	Group A	**Group B**	
Patients	13	16	
Age	58 ± 6	54 ± 7	
Sex	7 men/6 women	9 men/7 women	
Days from treatment to test	70	6	$p < 0.0001$
Days from symptoms to test	65	2	$p < 0.0001$
Days treatment to symptoms	5	4	
Imbalance	31%	69%	$p = 0.042$
Imbalance + dizziness	69%	31%	$p = 0.042$
Oscillopsia	62%	19%	$p = 0.027$
Worst side gain	0.39 ± 0.11	0.64 ± 0.11	$p < 0.0001$
Best side gain	0.44 ± 0.10	0.71 ± 0.12	$p < 0.0001$
Worst side gain after 1 month		0.72 ± 10	
Best side gain after 1 month		0.80 ± 10	
	Oscillopsia	No Oscillopsia	
Worst side gain	0.35 ± 0.07	0.63 ± 0.09	$p < 0.0001$
Best side gain	0.41 ± 0.07	0.70 ± 0.11	$p < 0.0001$

The aim of this study was to analyze the average time from treatment prescription to the neurotologist's examination. The mean number of days from the beginning of the systemic gentamicin treatment to the assessment by the neurotologist was 70 days in group A compared to 6 days in group B ($p < 0.0001$).

Another measurement parameter was the timeframe at which the vestibular tests were performed after the symptoms started. The mean number of days from the onset of the symptoms (dizziness, imbalance, or oscillopsia) until the vestibular tests were performed was 65 days in group A and 2 days in group B ($p < 0.0001$).

When calculating the mean time from the initial prescription of the treatment to the onset of vestibular symptoms (recorded in the clinical history), both groups showed similar data: the time difference between the day when treatment started and the day when symptoms started was 5 days in group A and 4 days in group B ($p = 0.076$).

Considering the severity of the symptoms, 31% of the patients in group A showed only an imbalance, and 69% showed an imbalance and dizziness. Conversely, 69% of the patients in group B showed only an imbalance, and 31% suffered from an imbalance and dizziness (Table 1).

Oscillopsia is one of the most disabling symptoms in patients with BVH. In group A, 62% (8/13) of the patients suffered from oscillopsia during the neurotologist visit while in group B, only 19% (3/16) manifested it ($p = 0.027$) (Table 1).

A reduced vestibular test response is expected in both ears in cases of BVH. For this reason, we stratified the results of the vHIT as the "best side" or "worst side".

The mean gain to the worst side was 0.39 ± 0.11 in group A and 0.64 ± 0.11 in group B ($p < 0.0001$). The mean gain to the best side was 0.44 ± 0.10 in group A and 0.71 ± 0.12 in group B ($p < 0.0001$) (Figure 1).

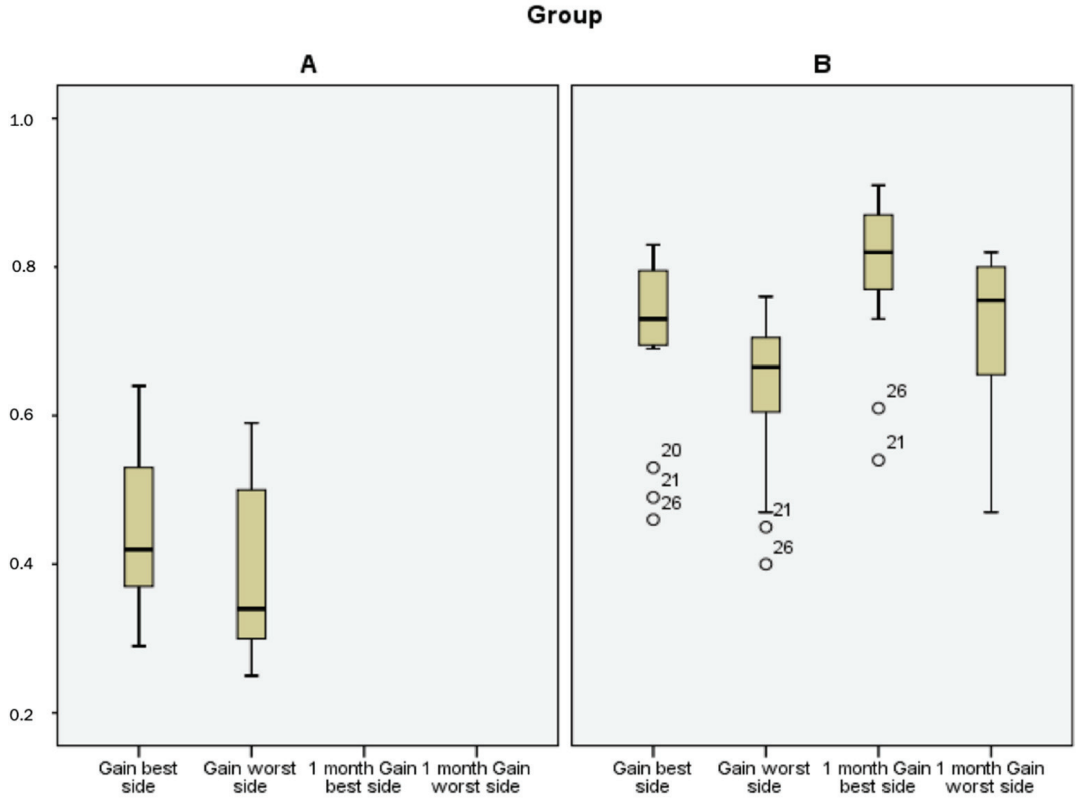

Figure 1. Box plot of the gains to the best or the worst side in each group of patients. (**A**): Group A at the first evaluation. (**B**): Group B at the first evaluation and after 1 month.

After 1 month, the mean gain measured with the vHIT in group B was 0.72 ± 0.10 and 0.80 ± 0.10, respectively (Figure 1). None of the patients complained of oscillopsia at theone-month follow-up.

Another parameter calculated was the gain on both sides in patients with oscillopsia. The mean gain in patients (both groups) who showed oscillopsia was 0.41 in the best side and 0.35 in the worst side. The mean gain in patients who did not present oscillopsia was 0.70 in the best and 0.63 in the worst side, respectively ($p < 0.0001$) (Figure 2).

If we compare the patients in group A with the worst patients (patients with the worst vestibular function) in group B (the worst 20% of the patients), it is observed that the mean gain in group A was 0.39 while in the worst patients in group B, it was 0.44. It is necessary to highlight that the worst patients of group B, during their follow-up, improved their gains up to a mean gain of 0.55.

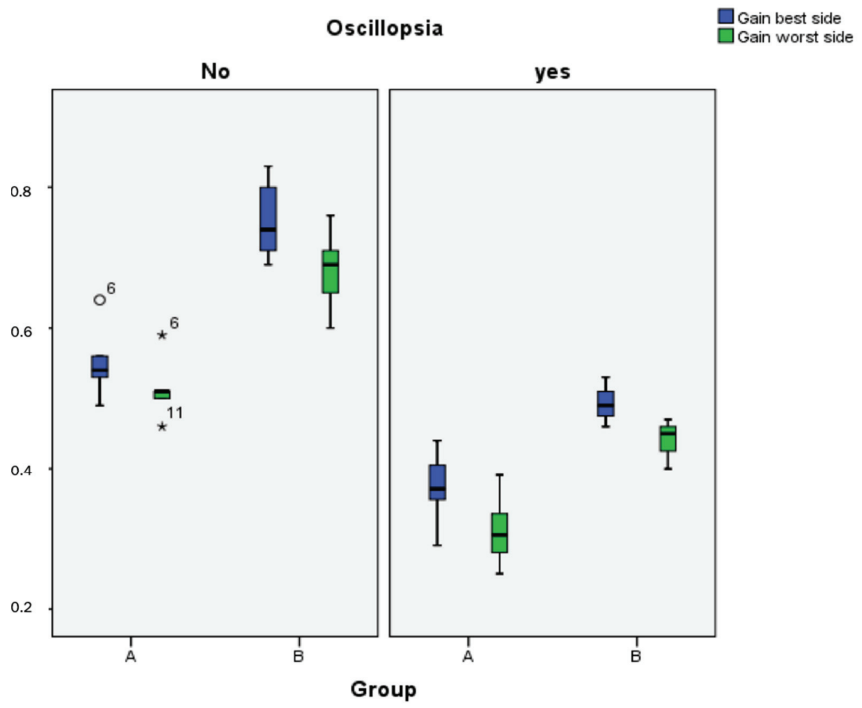

Figure 2. Patient gains and the presence of oscillopsia. Regardless of the group (A or B), the presence of oscillopsia is related to the low gain of the vestibulo-ocular reflex (* Atypcal values).

4. Discussion

It is necessary to begin this discussion by addressing the main limitation of the study. Two groups were compared in which the intervention was not identical. In the first one, there was no neurotological care during the admission of the patients, nor were they questioned about symptoms related to their balance until, due to their persistence, they were referred for evaluation in the neurotology unit. Conversely, the patients in the second group were monitored for their symptoms, and they were immediately treated by a neurotologist at the onset of symptoms. This may have resulted in a significant selection bias.

However, the intention of this study was to investigate the importance of monitoring these symptoms in patients who were treated with systemic gentamicin for infective endocarditis. The results showed that this intervention is crucial. In fact, the difference between the days to be evaluated for instability, dizziness, or oscillopsia in both groups was more than 2 months (65 days vs. 2 days). Not asking about a certain symptom does not mean that patients do not suffer from it. In our opinion, asking about dizziness, instability, or oscillopsia in patients receiving systemic gentamicin (especially in long treatment regimens) should be recommended [14].

Trying to be even more rigorous, we compared the patients in group A (we understand that this group includes the most severe patients and those with the greatest symptoms in that series) with those patients in group B with more severe bilateral vestibular hypofunction. Not only did the worse patients in group B show less impairment in their vestibular function, but they also improved during the one-month follow-up.

There are very few references in the literature about the importance of the participation and early intervention of a neurotologist in the progression of vestibulotoxicity produced by systemic gentamicin [8,14] and none related to the treatment of infective endocarditis.

Bilateral vestibular loss after severe vestibulotoxicity implies a significant decrease in the patient's quality of life [5]. Gentamicin can produce mild and early vestibulotoxicity (reversible and asymptomatic) in some patients [20]. Because of this, informing patients that the slightest symptom of imbalance should be reported and recommending routine vestibular testing are key to identifying vestibulotoxicity early and making a significant difference in the prognosis and development of permanent vestibular damage [8].

Vestibular symptoms are usually the initial adverse effect of systemic gentamicin therapy. Although physicians are well aware of this, these side effects are not readily recognized (especially vestibular symptoms), and these etiologies are under-reported [21]. In our study, groups A and B were compared, and there was a statistically significant difference between the mean number of days from the beginning of gentamicin therapy until the neurotologist's evaluation of the patient. In the same way, this difference can also be seen from the day the symptoms started to the day when the evaluation was performed.

In total, 20% of the patients in group B were evaluated. In group A, 5% were evaluated. It is assumed that in group A, only those patients who showed more severe symptoms were evaluated and that some patients with a mild (or moderate) vestibular deficit were not evaluated. Good monitoring of these patients makes it possible to detect vestibular deficits before they become severe, with a greater alteration in the quality of life.

There was no statistically significant difference between the groups in terms of the time period between the start of treatment and the onset of symptoms. Symptoms are usually mild at the beginning, which is why patients do not report them until they are severely affected; however, vestibulotoxicity occurs very quickly. A study reported that all affected patients (treated with gentamicin) were asymptomatic but presented vestibular abnormality within 3.5 h after administration of gentamicin [8].

Symptoms were more severe in group A because there was a higher percentage of imbalances, dizziness, and oscillopsia. This group was more clinically affected when compared to group B. BVH is related to the total amount of gentamicin received, which can cause great impairment in an affected individual [5], and permanent damage results in persistent oscillopsia and disequilibrium [22].

Notably, 20% of the treated patients in group B were evaluated by a neurotologist. This percentage may seem high compared to other studies [8], but some of them did not present altered vestibular function. They were studied, and therefore, were included in the study because they presented some symptoms, generally only instability. It should also be considered that our patients receiving gentamicin were evaluated after a mean use of gentamicin of four days while other studies have assessed vestibular damage in patients in whom the use of gentamicin is necessary for one or two days [8].

The vHIT gain of both sides in group A was considerably lower than that in group B, and the gain of the best side in group A was lower than that of the worst side in group B. In another study, patients with gentamicin vestibular toxicity (GVT) showed a continuous spectrum of VOR gain deficits from almost normal to total bilateral vestibular loss (BVL) but received gentamicin for 1.9 days. Most patients showed symmetric VOR gain deficits on both sides [7]. This is the reason why these patients do not have vertigo since vertigo will only manifest when the vestibular deficit is unilateral.

Most previous studies on GVT focused on patients with severe BVL that was measured through caloric and rotational tests [23]. When vHIT was used for the evaluation of vestibular function in BVL related to the use of aminoglycosides, the gains were close to our results for group A [24].

The vestibular damage in group A can be considered as "permanent" because it was registered two months after the treatment began and ended. However, the damage in group B can be considered as "temporary" because it was registered for less than a week after the treatment began and practically at the time when the symptoms started. For this reason, the vHIT was repeated one month later in group B (and after changing gentamicin), showing a significant improvement in the gain, and reaching the lower limit of normality on the best side. The physiology of the cell can be recovered once the aminoglycoside is

separated from the cell receptor, which is why the vestibular function returns to normal after acute intoxication in some patients [5,25].

This shows that after the early evaluation by the neurotologist and discontinuation of gentamicin and using a non-ototoxic drug (second choice for infective endocarditis protocol) as previously agreed between the cardiologist and the neurotologist, vestibular loss was reduced after one month.

Patients with loss of vestibular function are unable to stabilize vision during head motion toward the affected side, experiencing blurred vision, and they need to make "catch-up" saccades to refixate the gaze [26]. One of the most important symptoms of BVH is oscillopsia [16]. It is well known that vHIT gains in patients with BVH are low [27].

A statistically significant difference was found when comparing the gains in the vHIT of patients who had oscillopsia versus those who did not. Those who suffered from oscillopsia showed gains lower than 0.6 on both sides in the test, defining BVH according to previous studies [16].

Oscillopsia is a very disabling symptom that is directly related to the level of vestibular dysfunction. Therefore, it is very important to prevent patients from exceeding a certain limit in their loss of vestibular function.

5. Conclusions

The inclusion of vestibular function evaluation in an infective endocarditis treatment protocol should be recommended, considering the adverse effects of aminoglycosides.

The adverse effects of systemic gentamicin in the inner ear can be controlled by paying attention to the patient's symptoms as soon as they start and replacing this medication with a non-ototoxic drug.

Bilateral vestibular loss produces very disabling symptoms, such as oscillopsia, which have a significant impact on the patient's quality of life and therefore must be prevented.

We recommend questioning patients daily about vestibular symptoms and, if they appear, performing an early neurotological evaluation, in order to detect vestibular deficits, and withdrawing gentamicin. Patients must be re-evaluated before discharge and at least one month after completing the treatment.

Prospective randomized studies are needed to clarify the implications of early intervention, including the withdrawal of systemic gentamicin and its association with bilateral vestibular loss. Moreover, this study emphasizes the crucial importance of such studies.

Author Contributions: S.F.-C. and A.B.-C. contributed to the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. S.F.-C., A.B.-C. and R.M.-C. performed the data analysis and statistical analysis. S.F.-C., A.B.-C., R.M.-C., M.J.F.-N., R.V.-F., H.S.-G., S.S.C.-R. and M.S.-L. contributed in the literature search, clinical examinations and data collection. This has been including in the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: There are both ethical and legal restrictions on sharing the original study datasets. The electronic health records data cannot be shared publicly because it consists of personal information from which it is difficult to guarantee de-identification (Law 03/2018 from Spanish Government—BOE-A-2018-16673). There is a possibility of deductive disclosure of participants and therefore full data access through a public repository. The original datasets could only be made available under a new data sharing agreement with which includes: (1) commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate measures, and (3) a commitment to destroy or return the data after analyses are complete. For more information on data availability restrictions you can contact the ethics committee local IRB CEIm Area de Salud de Salamanca at comite.etico.husa@saludcastillayleon.es.

Requests can be made to the corresponding author, who will connect the request to designated IRB representatives, and eventually send the information.

Conflicts of Interest: The authors declare no conflict of interest.

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New Therapeutic Maneuver for Horizontal Semicircular Canal Cupulolithiasis: A Prospective Randomized Trial

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Abstract: Background: There are debates on whether mastoid oscillation has any benefit or harm in treating horizontal semicircular canal (HSCC) cupulolithiasis. The goal of this study was to investigate the therapeutic effects of the new maneuver using only inertia and gravity and compare it with the previously reported cupulolith repositioning maneuver using mastoid vibration (CuRM). Methods: We enrolled 57 patients diagnosed with HSCC cupulolithiasis. Patients were randomly allocated to the previously reported CuRM or the new maneuver (briefly, 30° head rotation to the affected side and thereafter bidirectional side-lying) using simply inertia and gravity, and their immediate and short-term effects were evaluated. Results: The immediate success rate did not differ significantly between the CuRM (8 of 22, 36.4%) and the new maneuver (10 of 35, 28.6%) groups (p = 0.538, Pearson's chi-square test). The late resolution rates at the first follow-up of the CuRM (75%, 9 of 12) and new maneuver groups (82.6%, 19 of 23) were very high, and there was no statistical difference between them (p = 0.670, Fisher's exact test). Conclusions: This study showed that the new maneuver was effective for treating HSCC cupulolithiasis with an immediate success rate of 28.6% (10 of 35). Although it did not show better results than the existing maneuver using vibration, there was no statistical difference. Considering the debate on the effectiveness of oscillation, we believe our new maneuver is a conservative alternative that uses only inertia and gravity, and it can be easily performed in clinics where oscillation equipment is not available.

Keywords: horizontal semicircular canal; benign paroxysmal positional vertigo; apogeotropic; cupulolithiasis; treatment outcome

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1. Introduction

Benign paroxysmal positional vertigo (BPPV) is the leading cause of vestibular disorders [1]. According to recent demographic studies, posterior canal-BPPV (PC-BPPV) was most common (45–49%), followed by horizontal semicircular canal (HSCC) canalolithiasis (15–22.8%) and HSCC cupulolithiasis (14.5–40%) [2,3]. Although several treatment maneuvers for PC-BPPV (e.g., modified Epley maneuver or Semont maneuver) or HSCC canalolithiasis (e.g., Barbeque roll maneuver, Gufoni maneuver, and Asprella maneuver . . .) are known to have a high treatment success rate (50–over 90%) [1], the immediate treatment of HSCC cupulolithiasis is often challenging (32%, according to a recent study) [3]. HSCC cupulolithiasis is characterized by positional vertigo and persistent direction-changing positional nystagmus (DCPN) beating to the uppermost (apogeotropic) ear induced by turning the head to the right or left in a supine position (supine head roll test), while in HSCC canalolithiasis of the posterior arm, DCPN beats to the lowermost (geotropic) ear during the supine head roll test [4]. Apogeotropic HSCC BPPV is believed to be caused by either otolith debris attached to the cupula (cupulolithiasis) or free-floating debris within the anterior arm of the HSCC (canalolithiasis) [4]. Generally, HSCC cupulolithiasis and canalolithiasis of the anterior arm of HSCC may be differentiated by their

nystagmus characteristics, such as duration, latency, and fatigability during the supine head roll test. Apogeotropic DCPN in cupulolithiasis is persistent and lacks latency or fatigability, whereas, in canalolithiasis, nystagmus is transient and shows latency or fatigue [5–8]. Considering these two variants of apogeotropic HSCC BPPV, clinicians can choose a treatment maneuver that is effective for both variants or effective for an individual variant.

In HSCC cupulolithiasis, it is also presumed that otolith debris can be attached to either the utricular or the canal side of the cupula. However, clinicians cannot differentiate between them during the diagnostic head roll test. Therefore, the ideal treatment maneuver should be designed considering the possibility of both cases. Until now, several treatment maneuvers have been proposed to treat the HSCC cupulolithiasis regardless of the location where the otolithic debris is attached to the cupula, including a head shaking maneuver in a supine position, a cupulolith repositioning maneuver by mastoid oscillation (CuRM) [9], head-tilt hopping exercises [10], and, recently, Zuma's maneuver [11]. However, the effectiveness of each treatment method has not been sufficiently verified in a large number of patients, and no standard maneuver has been established. In general, the repositioning maneuver for HSCC cupulolithiasis relies on mechanisms such as mastoid oscillation, gravity, and inertia (rapid acceleration or deceleration) to detach the otolith debris from the cupula and move it into the utricle. However, there may be a controversy that mastoid vibration can rather induce the unintentional detachment of the intact otoconia from the utricular macula [12–15], and hopping exercises may be difficult for elderly patients with limited physical activity or patients with severe symptoms.

Here, we introduce a new treatment maneuver for treating HSCC cupulolithiasis without using a vibrator or hopping exercise, based on a mechanism using only inertia and gravity, considering both the canal-side and the utricular-side debris. The aim of this study was to investigate the therapeutic effects of the new maneuver, and we compared the effects with the previously introduced maneuver using mastoid oscillation.

2. Patients and Methods

2.1. Patients

We enrolled 57 patients with HSCC cupulolithiasis who visited the emergency room or outpatient clinic of Konkuk University Medical Center, Seoul, Korea, between September 2020 and January 2022. The criteria for inclusion in this study were: (1) complaining of positional vertigo and (2) persistent direction-changing horizontal nystagmus toward the uppermost ear (apogeotropic nystagmus) in the supine head roll test. The exclusion criteria were: (1) otologic symptoms suggesting middle ear or other labyrinthine disorders; (2) recent history of labyrinthine disorders such as acute unilateral vestibulopathy, sudden sensorineural hearing loss, Meniere's disease, or central nervous system disorders; and (3) BPPV patients with multiple canal involvement or those with a transition to HSCC cupulolithiasis from other subtypes of BPPV during or after a positional nystagmus test or treatment maneuver.

All enrolled patients were evaluated for spontaneous and gaze-evoked nystagmus, saccades and smooth pursuit, limb ataxia, and balance function. There was no identifiable neurologic deficit in the participants in the initial evaluation and during the follow-up. The study design was explained to the patients, and written informed consent was obtained from each patient. The study protocol was approved by the Institutional Review Board (KUMC 2020-07-079-002).

2.2. Diagnosis of HSCC Cupulolithiasis and Lateralization

All patients underwent positioning maneuvers including bowing, lying down, supine head roll, Dix-Hallpike, and straight head hanging position. During the positioning maneuvers, nystagmus was observed without eyeball fixation using a video-Frenzel goggle device (SLMED, Seoul, Korea) [16]. A typical HSCC cupulolithiasis was diagnosed by the following nystagmus findings: (1) direction-changing horizontal nystagmus beating

towards the uppermost ear (apogeotropic nystagmus) in both right and left head turning in the supine position, (2) persistent apogeotropic nystagmus without latency in the supine head roll test to exclude canalolithiasis of the anterior arm of HSCC, and (3) no evidence of prominent vertical or torsional nystagmus component suggesting BPPV involving the anterior or posterior semicircular canal.

The affected side was determined with the following assumptions: (1) the intensity of the apogeotropic nystagmus is weaker when the head is turned to the affected side according to Ewald's second law [8,17,18]; (2) the lying-down nystagmus beats mostly towards the affected side, while the bowing nystagmus beats mostly towards the healthy side [8,17,19]; and (3) a null point, where the nystagmus is suppressed, is mostly observed on the affected side with a 15- to 30-degree head turn [16].

2.3. Treatment Procedures and Treatment Effects Evaluation

This study used a prospective randomized trial. We prospectively investigated the immediate and short-term treatment effects of the CuRM and the new maneuver. Patients were randomized into either the CuRM or new maneuver group by a computerized random number function in Microsoft Excel 2019 (Microsoft Crop.; Redmond, WA, USA).

The CuRM was performed as follows [9]: (1) at the beginning, the patient was placed in the supine position; (2) the head was turned 135° to the affected side (1st position, the body was moved from supine to lateral decubitus to the affected side), then oscillation was applied at the suprameatal triangle in the posterior superior area of the affected side auricle with a 60 Hz hand-held vibrator for 30 s to detach the otoliths from the cupula (canal-side debris may be detached); (3) the head was turned 45° to the healthy side (2nd position, lateral decubitus to the affected side); (4) the head was turned 90° to the healthy side (3rd position, supine position); (5) the head was turned 90° to the healthy side (4th position, lateral decubitus to the healthy side), then oscillation was applied if apogeotropic nystagmus was observed (utricular-side debris may be detached); (6) the head was turned 90° in the same direction (5th position, prone position), then the patient was slowly returned to a sitting position.

The new maneuver was performed as follows: (1) the patient was placed in the sitting position in the center of the examination table (Figure 1A); (2) the head was turned 30° to the affected side to align the affected side cupula axis to the sagittal plane (1st position, Figure 1B); (3) the patient was quickly brought down on the healthy side and held for two minutes in that position (2nd position, Figure 1C). Initial brisk healthy side downward acceleration of the affected side cupula may detach the canal-side debris from the cupula, and final brisk deceleration of the cupula may detach the utricular-side debris from the cupula. Two minutes of waiting at this step may help the utricular-side debris fall into the utricle by gravity. (4) The patient was slowly returned to the sitting position and kept in that position for 1 min (3rd position, Figure 1D); (5) the head was turned 30° to the affected side, then the patient was rapidly brought down on the affected side and held for two minutes (4th position, Figure 1E). Initial brisk affected side downward acceleration of the cupula may detach the utricular-side debris from the cupula, and final brisk deceleration of the cupula may detach the canal-side debris from the cupula. Two minutes of waiting at this step may help the canal-side debris fall into the canal by gravity. (6) The head was quickly turned 45° upward and kept in that position for 2 min to displace otolith debris of the anterior arm into the posterior arm of the HSCC (5th position, Figure 1F); (7) the patient was slowly returned to the sitting position (Figure 1G).

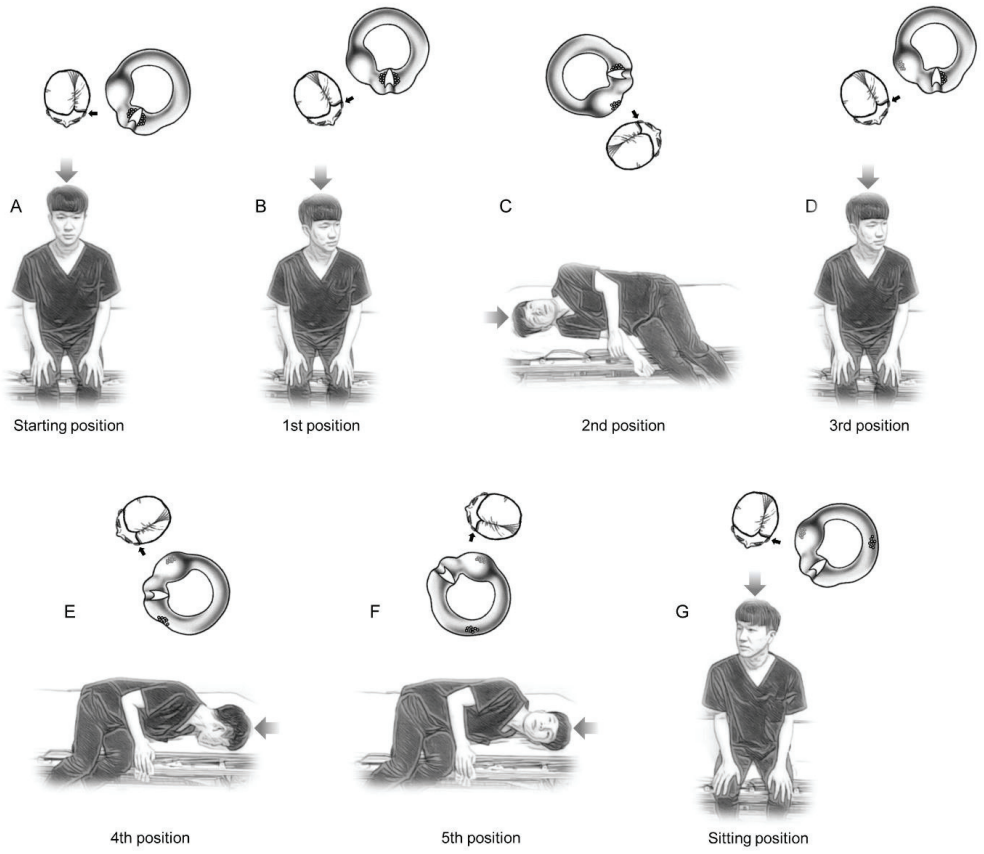

Figure 1. New repositioning maneuvers for treating left-sided horizontal semicircular canal (HSCC) cupulolithiasis. (**A**) The patient was seated in the center of the examination table. (**B**) The head was turned 30° to the affected side to align the affected side cupula axis to the sagittal plane (1st position). (**C**) The patient was rapidly brought down on the healthy side and held for two min in that position (2nd position). (**D**) The patient was slowly returned to the sitting position and kept in that position for 1 min (3rd position). (**E**) The head was turned 30° to the affected side, then the patient was quickly brought down on the affected side and held for two min (4th position). (**F**) The head was quickly turned 45° upward and kept in that position for 2 min (5th position). (**G**) The patient was slowly returned to the sitting position (Figure 1G). At the top of each posture, the left (small black arrow) HSCC (viewed from the top of the head, large gray arrow) are expressed, and the supposed movement and detachment of the otolithic debris from the cupula are also demonstrated.

The immediate treatment response was assessed by the supine head roll test 30 min after a single session of maneuver. The treatment was regarded as a success if the positional nystagmus was resolved or changed to a transient (lasts only a few seconds) geotropic form. If the first treatment was not successful, the patient received the same maneuver again. If the second trial was also unsuccessful, that was considered a treatment failure. Patients who did not respond to the treatment were scheduled for a follow-up visit one to four days later. At the first follow-up, the patients underwent a supine head roll test. The resolution of positional nystagmus or the change to transient geotropic nystagmus was considered a late resolution. The patients who still had apogeotropic nystagmus at the first follow-up again received the previously applied maneuver. In the same way, the maneuver was performed a maximum of twice, and the patients with treatment failure were scheduled for a second

follow-up visit one to four days later. We collected the follow-up intervals only for patients who did not succeed immediately, and we could not collect the data from the patients who did not participate in the follow-up. The mean period between the first treatment and the first follow-up (the first interval) and between the first follow-up and the second follow-up (the second interval) in the total sample were 4.3 and 5.6 days, respectively. The first intervals in the CuRM group and the new maneuver groups were 6.2 days and 3.4 days ($p = 0.036$, Mann–Whitney U test), respectively, while the second intervals were 4.3 days and 7.5 days ($p = 0.236$, Mann–Whitney U test), respectively. All patients received no post-treatment instructions such as forced prolonged position or Brandt–Daroff exercises. We did not re-evaluate the patients who had a successful response to the treatment.

2.4. Statistical Analysis

Mann–Whitney U test was used to assess the differences in nonparametric data (age, mean symptom duration from onset to evaluation, and mean follow-up intervals) between the CuRM and new maneuver groups. Pearson's chi-square test was used to assess the differences in categorical data (sex ratio, affected side ratio, and the immediate success rate) between the two groups. Fisher's exact test was used to assess the difference in the late resolution rate at the first follow-up visit and the proportion of patients with a prior BPPV history between the two groups. All statistical analyses of the data were performed using SPSS version 22.0 (IBM SPSS Corp.; Armonk, NY, USA), and values of p less than 0.05 were considered significant.

3. Results

3.1. Patient Characteristics

Fifty-seven patients with HSCC cupulolithiasis (13 males and 44 females; age range, 13–77 years) were randomly allocated to the CuRM ($n = 22$) or the new maneuver ($n = 35$) for treatment. There were five (22.7%) males and seventeen (77.3%) females (mean age, 50.8 ± 14.6) in the CuRM group and eight (22.9%) males and twenty-seven (77.1%) females (mean age, 50.7 ± 11.9) in the new maneuver group. The affected side was on the right in 11 (50.0%) of 22 patients in the CuRM group, and 12 (34.3%) of 35 patients in the new maneuver group. The mean symptom duration of vertigo until the initial assessment was 2.43 ± 6.73 days in the CuRM group, and 2.86 ± 6.74 days in the new maneuver group. There was no significant difference in the mean age, sex ratio, affected side ratio, and duration of vertigo between the two groups. (Table 1) There were eight (14.0%) of 57 patients who had a history of BPPV prior to their first visit (two of twenty-two, 9.1%, in the CuRM group, and six of thirty-five, 17.1%, in the new maneuver group), and there were no significant differences in the proportion of patients with a prior BPPV history between the two groups ($p = 0.466$, Fisher's Exact test).

Table 1. Subject characteristics ($n = 57$).

	CuRM ($n = 22$)	New Maneuver ($n = 35$)	p-Value
Age, mean ± SD	50.8 ± 14.6	50.7 ± 11.9	0.700 †
Sex, male:female	5:17	8:27	0.991 ‡
Affected side, right:left	11:11	12:23	0.239 ‡
Duration of vertigo, days	2.43 ± 6.73	2.86 ± 6.74	1.000 †

CuRM: cupulolith repositioning maneuver by mastoid oscillation. p-value < 0.05 was considered significant. † Mann–Whitney U-test. ‡ Pearson's chi-square test.

3.2. Immediate and Short-Term Treatment Effects

In twenty-two patients who were treated with the CuRM, the immediate success rate was 36.4% (eight of twenty-two). Among the remaining 14 patients with treatment failure, two patients did not show up for their first follow-up visit, and 12 patients were assessed for a positional nystagmus test at the first follow-up. Apogeotropic nystagmus was not observed in 75% (nine of twelve) patients during the supine head roll test, of whom

eight showed no nystagmus and one showed geotropic nystagmus. Three patients with apogeotropic nystagmus were treated with the CuRM at the first follow-up, which was not successful in any of the three patients. On the second follow-up visit, all three patients still showed apogeotropic nystagmus and were treated with the CuRM, which was not successful again in any of the three patients (Table 2 and Figure 2).

Table 2. Treatment results of the CuRM and the new maneuver.

	CuRM (n = 22)	New Maneuver (n = 35)	p Value
Initial visit (immediate response)			
Success	8 (of 22, 36.4%)	10 (of 35, 28.6%)	0.538 †
Apogeotropic nystagmus	14 (of 22, 63.6%)	25 (of 35, 71.4%)	
First follow-up			
Follow-up loss	2	2	
Spontaneous resolution	9 (of 12, 75.0%)	19 (of 23, 82.6%)	0.670 ‡
Success	0 (of 3, 0%)	1 (of 4, 25.0%)	
Apogeotropic nystagmus	3 (of 3, 100%)	3 (of 4, 75.0%)	
Second follow-up			
Follow-up loss	0	1	
Spontaneous resolution	0 (of 3, 0%)	2 (of 2, 100%)	
Success	0 (of 3, 0%)	N/A	
Apogeotropic nystagmus	3 (of 3, 100%)	N/A	

CuRM: cupulolith repositioning maneuver by mastoid oscillation, N/A: not applicable. † Pearson's chi-square test. ‡ Fisher's exact test.

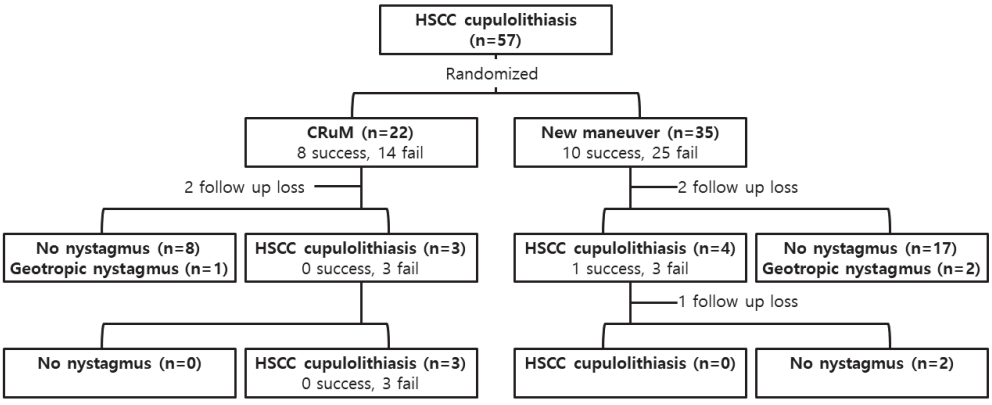

Figure 2. A summary of the treatment results through the follow-up. HSCC: horizontal semicircular canal, CuRM: cupulolith repositioning maneuver by mastoid oscillation.

In thirty-five patients who were treated with the new maneuver, the immediate success rate was 28.6% (10 of 35). Among the remaining 25 patients with treatment failure, two patients did not show up for the first follow-up, and 23 patients were evaluated for a positional nystagmus test at the first follow-up. Apogeotropic nystagmus was not observed in 82.6% (19 of 23) patients during the supine head roll test, of whom 17 showed no nystagmus and two showed geotropic nystagmus. Four patients with apogeotropic nystagmus received the new maneuver at the first follow-up, which was successful in one patient. The remaining three patients with treatment failure were scheduled for a second follow-up. On the second follow-up visit, one patient did not show up, and two patients were assessed for a positional nystagmus test, and both showed no nystagmus (Table 2 and Figure 2).

There was no significant difference in the immediate success rate between the CuRM (eight of twenty-two, 36.4%) and the new maneuver (10 of 35, 28.6%) groups (p = 0.538,

Pearson's chi-square test). There was no significant difference in the late resolution rate at the first follow-up between the CuRM (9 of 12, 75%) and new maneuver (19 of 23, 82.6%) groups ($p = 0.670$, Fisher's exact test).

4. Discussion

Although numerous maneuvers have been proposed to treat HSCC cupulolithiasis, the reported efficacies have been varied and a standard protocol has not been established yet. Most of the existing methods used inertia and gravity, or oscillation. However, the effect of vibration is a controversial topic. In the previous studies, mastoid oscillation was applied during the repositioning maneuver for BPPV, with the hypothesis that it might help detach the otoliths from the cupula or help the otoliths move into the utricle without adhering to the cupula or canal wall [9,20], but there are many reports that the application of vibration does not bring any therapeutic benefit [4,21–24]. In addition, it is reported that BPPV itself can occur after head and neck trauma or surgeries (such as nasal osteotomy or dental surgery) that cause impact or vibration [13,15,25–27].

Considering these controversies and the potential adverse effect of vibration on labyrinthine health, in this study, we designed a new maneuver conservatively using only inertia and gravity (by body repositioning and head rotation) to treat HSCC cupulolithiasis and compared its effect with the previously proposed maneuver using mastoid vibration. As our new maneuver does not use vibration, it can be performed in clinics that do not have oscillation equipment. Some early maneuvers for HSCC cupulolithiasis were limited in covering all possible locations of the otolithic debris in positional relation with the cupula (canal-side or utricular-side debris). For example, considering the current anatomical point of view, the Gufoni maneuver seems to be more effective for the utricular-side debris than the canal-side debris [1,16,28,29]. The Appiani maneuver, on the other hand, seems to be more effective for the canal-side debris than the utricular-side debris [1,30]. Our new maneuver for HSCC cupulolithiasis was designed focusing on the following considerations: (1) using only inertia and gravity and maximizing the effect, and (2) it should be effective for both the utricular-side and the canal-side debris. Currently, it is thought that the axis of the HSCC cupula is directed slightly lateral from the sagittal plane [19,20], and therefore a null point in the HSCC cupulolithiasis is usually observed with the head turned 20° to 30° to the affected side in the supine position [5]. Before rapid lying-down on the healthy or affected side, in the first and third position of our new maneuver, we tried to maximize the effect of inertia and gravity on the dislodged otoconia by turning the head to the affected side by 30° to ensure that the axis of the affected side cupula was parallel to the sagittal plane. In order to achieve the second consideration that it should be effective for the utricular-side and the canal-side debris, in our maneuver, we applied a rapid side-lying motion bidirectionally. These two considerations (30° head rotation to the affected side and thereafter bidirectional side-lying) are the main differences from the existing maneuvers such as the Gufoni maneuver, the Appiani maneuver, and Zuma's maneuver. So, we think we can simply call our new maneuver a "bidirectional side-lying maneuver".

In this study, the immediate success rates of CuRM and the new maneuver were 36.4% (8 of 22) and 28.6% (10 of 35), respectively ($p = 0.538$, Pearson's chi-square test). This result appeared to be lower than that reported previously. However, when comparing the results, caution should be taken as each report differs in the way in which treatment success is defined. Kim et al. [9] reported that HSCC cupulolithiasis was resolved in 97.4% (76 of 78) of patients after an average of 2.1 repetitions of the maneuver, but this high remission rate was the result of up to a maximum of six treatments during a very long follow-up period (29.8 months, range 10–54 months). In Kim et al.'s report [9], the rate of remission after a single treatment was 61.5% (48 of 78). However, since they performed a head roll test at a follow-up two days after the first treatment and ended the treatment when no nystagmus or vertigo appeared, their successful cases might include patients with spontaneous remission during the follow-up. In addition to the definition of treatment success, diagnostic protocols,

follow-up protocols, and additional instructions such as forced prolonged position or Brandt–Daroff exercises may affect the outcomes. Kim et al. [9] performed the head roll test three times during the diagnostic process, and after the maneuver, the patients were instructed to sleep in the lateral decubitus position on the healthy side. Repeated supine head roll tests may induce the detachment of otolith debris from the cupula [28,31], and a forced prolonged position itself may resolve the HSCC cupulolithiasis [32]. In this study, to confirm the effect of the maneuver itself, we performed the head roll test to a minimum during the diagnostic process, assessed the patients 30 min after the treatment, and did not give additional instructions to the patient after the treatment.

Another notable finding was that the late resolution rates at the first follow-up of the CuRM (75%, nine of twelve) and the new maneuver (82.6%, 19 of 23) were very high (Table 2). Several previous studies found that untreated HSCC cupulolithiasis had a short natural course. Shim et al. found that symptom remission took 3.7 days and the disappearance of positional nystagmus took 4.4 days [33], while Imai et al. found that symptom remission took 13 days in untreated HSCC cupulolithiasis [34]. It is thought that the head motions in daily life may induce the natural detachment of otoliths from the cupula, and the spontaneous dissolution of otoconia may also contribute to the short spontaneous remission [33]. In addition, it can be assumed that the time-dependent spontaneous dissolution of otoliths may affect the response to the repositioning maneuver, so the duration from the onset of BPPV to the treatment maneuver may affect the treatment response rate.

Our new treatment maneuver included fast side-lying on both the healthy side and the affected side. Before the side-lying, the head was turned 30° to the affected side to align the affected side cupula axis with the sagittal plane. Rapid deceleration and gravity help to detach the otolith debris from the cupula, specifically utricular-side debris when lying on the healthy side, and canal-side debris when lying on the affected side. Theoretically, a rapid acceleration in the initial stage of the side-lying may help detach the contralateral side otolith (canal-side debris when lying on the healthy side, and utricular-side debris when lying on the affected side), just as the rapid acceleration during upward head-turning helps to move the otolith to the opposite side of the acceleration. However, the effect of the acceleration that occurs during the rapid side-lying may not be very helpful, because it may be difficult to lay down as fast as the speed of turning the head. If our new repositioning maneuver does not work, it may be because the acceleration or deceleration was not fast enough. However, a recent study has shown that a faster execution of the Gufoni maneuver provides little benefit than a slower execution in treating apogeotropic HSCC BPPV [35], so this speculation remains debatable.

The location of the otolith in HSCC cupulolithiasis is a topic of interest. Kim et al. have noted the advantage of their repositioning maneuver, which provides an estimated location of the otolith [9]. Similarly, in our new maneuver, the immediate resolution of nystagmus after the maneuver may suggest utricular-side debris, and the transformation from apogeotropic nystagmus to geotropic form may suggest canal-side debris. However, the absence of response to the maneuver does not provide information on the location of the otolith. Therefore, we did not analyze the estimated location of the otoliths in this study.

The new maneuver we designed may have potential limitations. In order for the treatment maneuver to be widely used, it is advantageous for the maneuver to be simple. Although we have tried to keep the procedures as simple as possible, clinicians may need to become familiar with this new maneuver through repeated training before using it. Additionally, even if our new maneuver does not involve radical movements such as hopping, it may still be difficult for patients with limited physical activity to lie down or rotate their heads quickly. Lastly, in patients with HSCC cupulolithiasis, rapid side-lying on the healthy side may provoke more vertiginous symptoms than side-lying on the affected side only.

5. Conclusions

Our results showed that the new maneuver is an effective maneuver for treating HSCC cupulolithiasis with an immediate success rate of 28.6% (10 of 35). Although it did not show better results than the existing treatment method using vibration, there was no statistical difference in the immediate response rates between the two maneuvers. Considering the debate about the effectiveness of oscillation, we believe our new maneuver is another effective maneuver that uses only inertia and gravity, and it can be easily performed in clinics where oscillation equipment is not available.

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Effect of Dexamethasone Combination with Gentamicin in Chemical Labyrinthectomy on Hearing Preservation and Vertigo Control in Patients with Unilateral Meniere's Disease: A Randomized Controlled Clinical Trial

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Abstract: Chemical labyrinthectomy using gentamicin is a popular method for treating intractable vertigo attacks in Meniere's disease. However, the risk of hearing loss remains a major concern for clinicians. We investigated the effect of simultaneous dexamethasone and gentamicin application on hearing preservation and vertigo control in patients with intractable unilateral Meniere's disease. A single-institutional, prospective, single-blinded, randomized clinical trial was conducted. Gentamicin-soaked Gelfoam® was directly applied on the oval window following middle ear exploration. On the round window, dexamethasone-soaked Gelfoam® was applied in the gentamicin with dexamethasone group (GD group, n = 18), and saline-soaked Gelfoam® was applied in the gentamicin with sham reagent group (GO group, n = 19). The hearing change 8 weeks after the procedure and vertigo control 2–12 months after the procedure were investigated. The high-frequency hearing threshold was significantly increased in the GO group (p = 0.005 and 0.012 for 4 and 8 kHz, respectively), but not in the GD group. The short-term (2–6 months) vertigo control was more successful in the GD group (57.89% vs. 94.44%, p = 0.019), but long-term control (6–12 months) was insignificant. In conclusion, the combined application of gentamicin and dexamethasone in chemical labyrinthectomy is an effective method for protecting high-frequency hearing and vertigo control.

Keywords: Meniere's disease; chemical labyrinthectomy; dexamethasone; gentamicin

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1. Introduction

Meniere's disease (MD) is an inner ear disorder characterized by episodic vertigo, fluctuating sensorineural hearing loss combined with aural fullness, and/or tinnitus [1]. The most annoying and concerning symptom of this disease is unpredictable, acute, and recurrent vertigo attacks. Therefore, most of the medical and surgical treatments are focused on controlling vertigo attacks rather than hearing symptoms [2,3]. The first-line treatment is medication and lifestyle modification. Although there is insufficient scientific evidence to support this first-line treatment, patients are generally prescribed medications such as betahistidine and/or diuretics and recommendations for lifestyle modification, such as a low-salt diet and avoidance of excessive stress, alcohol, smoking, and caffeine. The most commonly used second-line treatment for non-responders is intratympanic corticosteroid (ITC) injection. However, patients who suffer from intractable vertigo even after second-line treatment require tertiary treatment [2]. There are several invasive treatment options for these patients, such as endolymphatic sac surgery, chemical labyrinthectomy (intratympanic gentamicin (ITG) injection), labyrinthectomy,

and vestibular neurectomy, based on the patients' residual hearing level. Chemical labyrinthectomy is a procedure that involves the ablation of vestibular type I hair cells using aminoglycosides. Since the introduction of chemical labyrinthectomy using streptomycin by Fowler in 1948, the procedures and drugs for chemical labyrinthectomy have been consecutively investigated [4]. Currently, gentamicin via intratympanic injection or direct middle ear application is the most frequently used treatment because previous studies have shown better treatment outcomes with minimal morbidity [5]. Although this procedure is convenient and has minimal morbidity, the risk of hearing loss from chemical labyrinthectomy using gentamicin remains a major concern for clinicians because gentamicin is toxic not only to vestibular hair cells but also to cochlear hair cells [6]. In humans, half of all patients who received repeated systemic high-dose aminoglycoside therapy showed high-frequency hearing loss [7]. The hearing level after chemical labyrinthectomy using gentamicin can be aggravated up to 31.08% depending on the administration and titration method [8,9]. Further, the short-term repeated gentamicin application showed a cumulative effect increasing the chance of hearing loss [10,11].

The drug administered to the middle ear passes through the round and oval window membranes into the inner ear. The round window is closer to the cochlea, but the oval window is close to both the cochlea and the vestibule. We hypothesized that concomitant application of dexamethasone and gentamicin on the round window and the oval window, respectively, can reduce hearing loss by acting mainly through the cochlea due to its proximity to the compartment. This hypothesis was based on research that reported that dexamethasone prevented gentamicin-induced hearing loss in animal models [12,13]. Furthermore, there can be a synergistic effect of gentamicin and dexamethasone in controlling vertigo attacks because the two drugs have different mechanisms of controlling vertigo [14]. Thus, the purpose of this randomized clinical trial is to investigate the effectiveness of concomitant intratympanic application of dexamethasone and gentamicin following middle ear exploration.

2. Materials and Methods

2.1. Patient Enrollment

This was a single-institutional, prospective, single-blinded, randomized clinical trial conducted between 11 November 2015 and 16 October 2021. This study was approved by the institutional review board of Severance hospital (Seoul, Korea) before patient enrollment (Project number 4-2016-0096). All participants provided written informed consent. Patients were eligible if they were: (1) 19 years or older; (2) diagnosed with definite MD according to the diagnostic criteria suggested by the Barany Society (2015); and (3) scheduled to undergo chemical labyrinthectomy for intractable vertigo attacks [1]. Patients with intractable vertigo were prescribed betahistidine and diuretics, along with lifestyle modifications for more than three months; additional treatment with intratympanic dexamethasone injection did not reduce the number of vertigo spells during following three months. A vertigo attack was defined as more than 20 min of spontaneous true-vertigo-type dizziness regardless of ear symptoms. Participants were excluded if they had a history of: (1) central vertigo; (2) head trauma; (3) other otologic disease (such as tympanic membrane perforation, otitis media, benign paroxysmal positional vertigo, and unilateral vestibulopathy of the other ear); and (4) suspected bilateral MD. One or two weeks prior to chemical labyrinthectomy, all participants underwent pure-tone audiometry and bithermal caloric test.

2.2. Patient Grouping, Randomization, and Power Analysis

The patients were randomized into two groups: gentamicin with normal saline (GO group) and gentamicin with dexamethasone (GD group). Randomization was performed using an online random number generator, with stratified block randomization performed by the research coordinator. The treatment allocation was concealed from the patient to mitigate bias. To calculate the sample size, G * Power software (Dusseldorf, Germany) was

used. The expected mean difference of hearing threshold between the two groups was set at 10 dB and the standard deviation (SD) at 8 dB because a difference of less than 10 dB is possible in intra-subject variability of pure-tone audiometry [15]. The power analysis indicated that a sample size of at least 11 per group was required for an alpha level of 0.05 and a statistical power of 80%. Assuming a 20% failure rate, the target sample size was 13 in each group.

2.3. Surgical Procedure and Follow-Up

After administering local anesthesia to the external auditory canal, a tympanomeatal flap was elevated. Middle ear exploration was performed to identify the round and oval windows under a surgical microscope. If the surgical view was poor, a surgical endoscope was used. Pieces of gelatin sponge (Gelfoam®, Pfizer, Brooklyn, NY, USA) were soaked in gentamicin, dexamethasone, or normal saline. In the GO group, gentamicin-soaked Gelfoam® pieces were applied to the oval window, and saline-soaked Gelfoam® pieces were applied to the round window. In the GD group, gentamicin-soaked Gelfoam® pieces were applied to the oval window, and dexamethasone-soaked Gelfoam® pieces were applied to the round window.

The patients were scheduled to visit the outpatient clinic at 2, 4, and 8 weeks after the procedure. If the patient's tympanic membrane was well healed at four weeks after the procedure, a pure-tone audiogram was performed at the next visit (eight weeks after the procedure). Thereafter, the patients regularly visited the clinic every 2–3 months and were asked whether they had any vertigo attacks until 12 months after the procedure. The vertigo attacks were defined as aforementioned.

2.4. Outcome Measurement

The parameter for primary outcome was the difference in the hearing preservation between the two groups. PTA_4 (average threshold shift of 0.5, 1, 2, and 3 kHz frequencies) and PTA_{high} (average threshold shift of 4 and 8 kHz frequencies) were evaluated before and after the procedure. The PTA_{high} was separately evaluated because gentamicin ototoxicity may primarily affect the high-frequency region of the cochlea. In addition, the effect of gentamicin ototoxicity should be separated from the hearing fluctuation of MD, which is mainly in the low- to mid-frequencies. The secondary outcomes were (1) changes in the results of bithermal caloric test, (2) changes in the frequency of vertigo attacks (2–6 and 6–12 months after the procedure), and (3) the need for secondary treatment due to failure to control vertigo attacks.

2.5. Statistical Analysis

All continuous data were described as mean (SD). If the data passed the normality test (Shapiro–Wilk test), the Student's t-test was used to compare the two groups; if not, the Mann–Whitney U test was used. The Wilcoxon matched-pairs signed rank test was used to compare the groups before and after the procedure. Fisher's exact test (two-tailed) based on a contingency table was used to compare the proportion between the two groups. All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). The significance level was set at $p < 0.05$ for all statistical analyses.

3. Results

3.1. Information of Participants

The enrollment of the participants began on 11 November 2015 and ended on 15 July 2020. A total of 37 participants were analyzed: 19 in the GO group and 18 in the GD group (Figure 1). Five participants (three in the GO group and two in the GD group) were lost during follow-up. According to inclusion/exclusion criteria, patients who are suspicious of vestibular migraine, autoimmune hearing loss, and familial history of MD were not included. None of the enrolled patients had surgical complications, including tympanic membrane perforation, post-operative infection, and taste change, at eight weeks after the

surgical procedure. There was no statistically significant difference in age, sex, hearing level at each frequency, canal paresis value, or frequency of vertigo attacks between the two groups (Table 1). As expected, both groups showed moderate-to-severe hearing loss (51.38 dB and 49.17 dB in the GO and GD groups, respectively) and canal paresis (44.15% and 39.57% in the GO and GD groups, respectively).

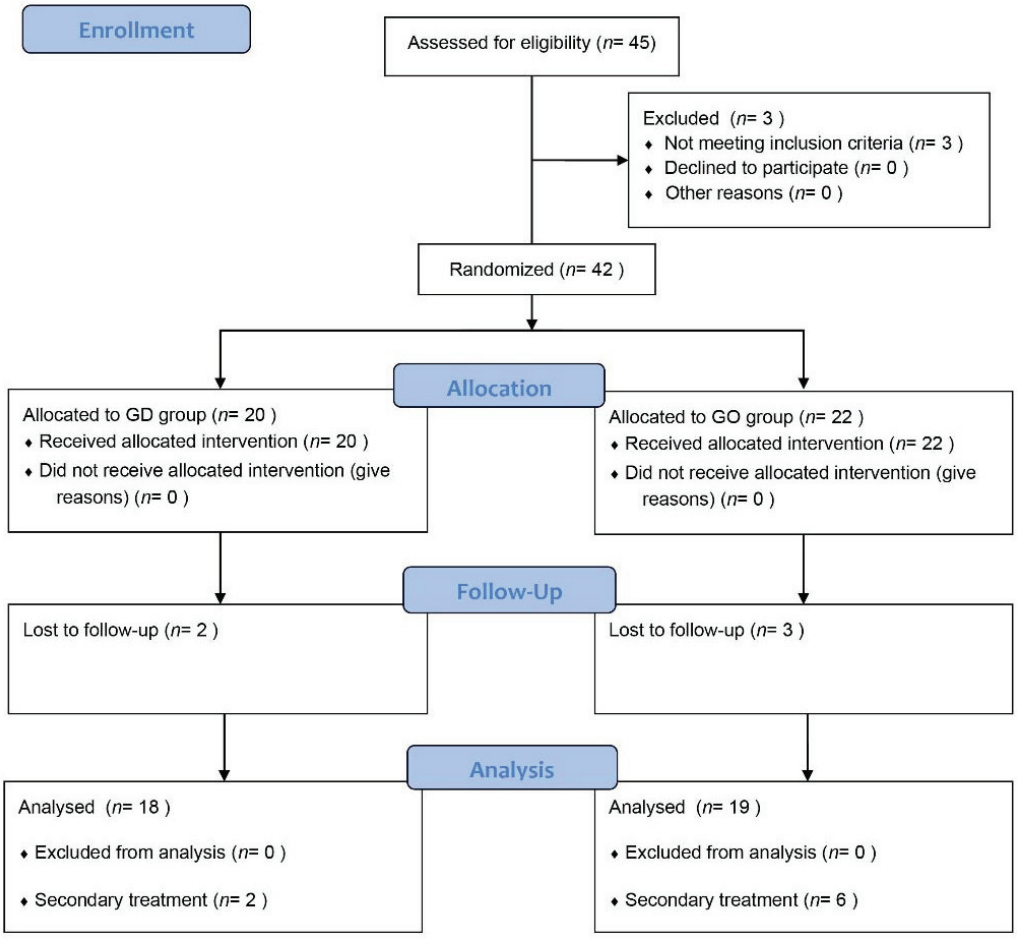

Figure 1. Flow diagram of study participants.

Table 1. Baseline characteristics of study participants.

Characteristic	GO Group (n = 19)	GD Group (n = 18)	* p-Value
Age, mean (SD), years	55.05 (16.06)	54.78 (15.13)	0.958 [a]
Sex, male (%)	7 (36.8)	8 (44.4)	0.743
PTA_4, mean (SD), dB	51.38 (18.39)	49.17 (16.56)	0.703 [a]
0.5 kHz	53.42 (21.48)	51.67 (17.90)	0.789 [a]
1 kHz	53.16 (20.63)	50.83 (18.81)	0.723 [a]
2 kHz	47.89 (18.66)	45.83 (16.56)	0.725 [a]
3 kHz	51.05 (17.92)	48.33 (17.41)	0.643 [a]
PTA_{high}	59.34 (21.55)	67.36 (19.26)	0.223 [b]
4 kHz	52.89 (20.02)	56.94 (18.56)	0.580 [b]
8 kHz	65.79 (24.28)	77.78 (22.18)	0.126 [a]
CP value in caloric test before surgery, mean (SD), %	44.15 (27.19)	39.57 (24.22)	0.593 [a]
Frequency of vertigo attacks, mean (SD), per month	1.70 (1.27)	1.97 (1.46)	0.512 [b]
Disease duration to surgery (SD), days	1723 (1524)	1908 (1619)	0.663 [b]

[a] Student's t-test, [b] Mann–Whitney U test, * $p < 0.05$. GO: gentamicin combined with normal saline; GD: gentamicin combined with dexamethasone; SD: standard deviation; PTA_4: average threshold shift of 0.5, 1, 2, and 3 kHz frequencies; PTA_{high}: average threshold shift of 4 and 8 kHz frequencies; Frequency of vertigo attacks: average number of vertigo attacks per month during recent 6 months before chemical labyrinthectomy.

3.2. Hearing Preservation

The paired analysis of hearing threshold before and after the procedure revealed that the procedure induced significant hearing loss at 4 and 8 kHz (p = 0.005 and 0.012, respectively) only in the GO group (Figure 2). There were no significant changes in the thresholds of all frequencies in the GD group. The change in thresholds after the procedure was significantly higher in PTA_{high} in the GO group (p = 0.037) but not in PTA_4 (Figure 3). In particular, the threshold change was significantly higher at the 4 kHz frequency in the GO group (p = 0.049) (Table 2).

Table 2. Changes in the results of pure-tone audiometry and caloric test after chemical labyrinthectomy.

Characteristic	GO Group (n = 19)	GD Group (n = 18)	* p-Value
PTA_4, mean (SD), ΔdB	3.95 (13.22)	4.17 (12.51)	0.959 [a]
0.5 kHz	2.63 (18.44)	3.61 (15.79)	0.864 [a]
1 kHz	3.68 (16.15)	4.72 (15.38)	0.843 [a]
2 kHz	4.21 (11.82)	5.28 (12.77)	0.817 [b]
3 kHz	5.26 (13.49)	3.06 (12.85)	0.963 [b]
PTA_{high}, mean (SD), ΔdB	8.82 (12.81)	−0.42 (12.52)	0.037 [b]*
4 kHz	8.42 (14.25)	−1.39 (13.91)	0.049 [b]*
8 kHz	9.21 (15.12)	0.56 (13.49)	0.174 [b]
Change of CP value in caloric test, mean (SD), Δ%	6.24 (31.95)	21.05 (23.30)	0.118 [a]

ΔdB: difference in the hearing threshold between the values before and after chemical labyrinthectomy; Δ%: difference in the canal paresis value in caloric test before and after chemical labyrinthectomy; CP: canal paresis; [a] Student's t-test; [b] Mann–Whitney U test. * $p < 0.05$.

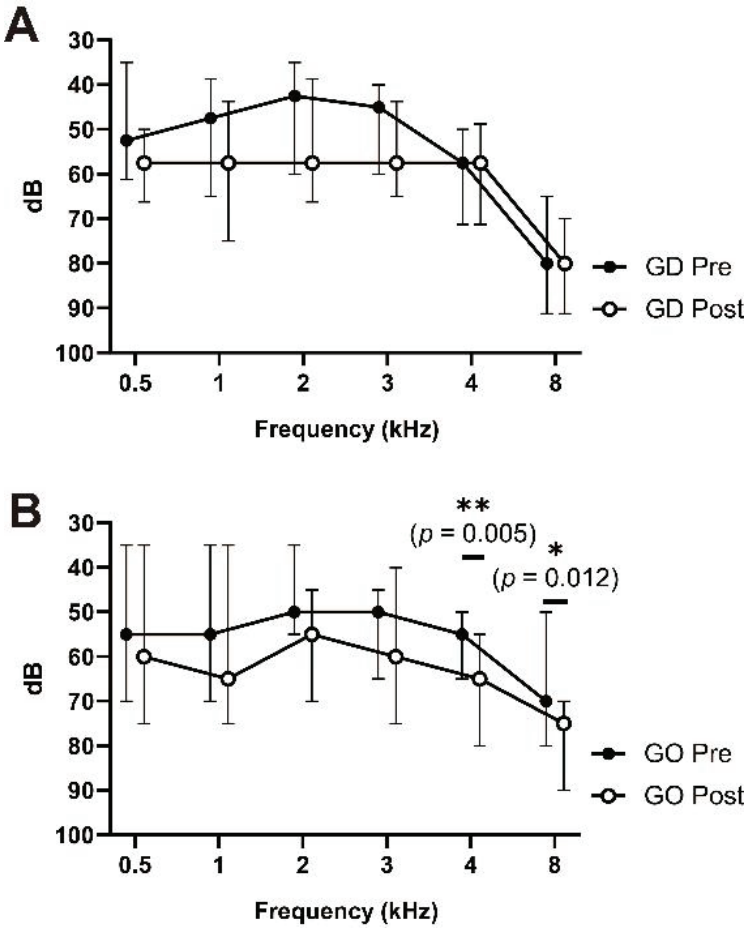

Figure 2. Hearing functions before and after chemical labyrinthectomy: (**A**) pure-tone audiogram of the GD group. (**B**) Pure-tone audiogram of the GO group. The high-frequency hearing thresholds (4 and 8 kHz) significantly worsened eight weeks after chemical labyrinthectomy only in the GO group. The black/hollow circles indicate median values. The error bars indicate the interquartile range. Wilcoxon matched-pairs signed rank test was used for analysis. GD: gentamicin combined with dexamethasone; GO: gentamicin combined with normal saline; Pre: before surgery; Post: 8 weeks after surgery. * $p < 0.05$, ** $p < 0.01$.

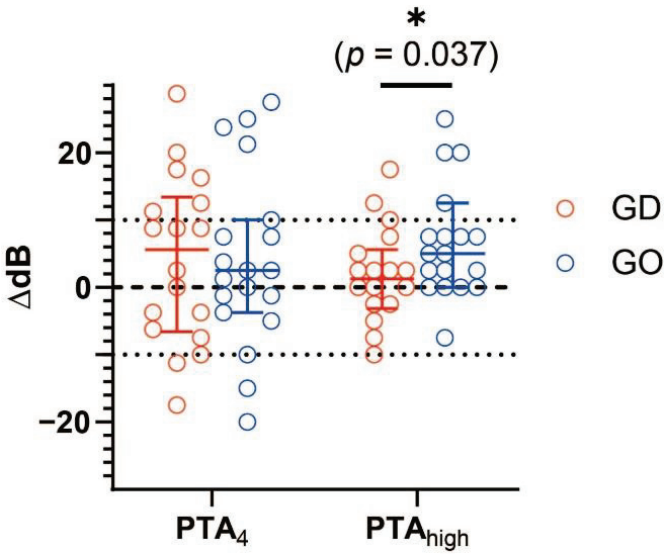

Figure 3. Change in hearing threshold in low- to mid-frequencies (PTA_4) and high frequencies (PTA_{high}). The average threshold shift after surgery was significantly larger in the GO group compared to the GD group. The circles indicate individual results of threshold shift. The large bar indicates the median value, and the error bars indicate the interquartile range. Mann–Whitney U test was used for analysis. Two individual results in PTA_{high} were outside the y-axis limits and not shown in the graph. GD: gentamicin combined with dexamethasone; GO: gentamicin combined with normal saline; PTA_4: average threshold shift of 0.5, 1, 2, and 3 kHz frequencies; PTA_{high}: average threshold shift of 4 and 8 kHz frequencies. * $p < 0.05$.

3.3. Secondary Outcomes

The average canal paresis in the bithermal caloric test was increased in both groups. The GD group showed a tendency to a larger increase in canal paresis (change by 6.24% vs. 21.05%), but the difference was not significant. Secondary treatment, including ITC and revision chemical labyrinthectomy, was required to treat vertigo in eight participants until the last follow-up (Table 3): two were in the GD group and six were in the GO group. The proportion of patients who needed secondary treatment was higher in the GO group, but the difference between the two groups was not statistically significant. We defined "treatment success" as the frequency of vertigo attacks being less than 40% compared to before chemical labyrinthectomy without secondary treatment (similar to classes A and B in the classification suggested by the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines) [16,17]. "Complete control" was defined as the absence of vertigo symptoms during the period (similar to class A in the classification suggested by the 1995 AAO-HNS guidelines). The GD group showed a significantly larger proportion of "treatment success" patients 2–6 months after the procedure ($p = 0.019$) and "Complete control" patients 2–12 months after the procedure ($p = 0.038$). However, the effects of both treatments diminished over time. Taken together, the GD group tended to show better dizziness control until 1 year after the treatment.

Table 3. Vertigo control results after chemical labyrinthectomy.

Characteristic	GO Group (n = 19)	GD Group (n = 18)	* p-Value
Secondary treatment required (%)			
2–6 months	4 (21.05)	1 (5.56)	0.340
2–12 months	6 (31.58)	2 (11.11)	0.232
Complete control (%) [a]			
2–6 months	8 (42.11)	11 (61.11)	0.330
2–12 months	3 (15.79)	9 (50.00)	0.038 *
Treatment success (%) [b]			
2–6 months	11 (57.89)	17 (94.44)	0.019 *
2–12 months	10 (52.63)	15 (83.33)	0.079

[a] Absence of vertigo during the period. [b] Less than 40% of the frequency of vertigo compared to baseline during the period. * $p < 0.05$.

4. Discussion

In this prospective single-blinded randomized trial, chemical labyrinthectomy using gentamicin combined with dexamethasone showed a protective effect on high-frequency hearing level compared to the conventional method that uses gentamicin with normal saline. Furthermore, the combination method could more efficiently control the frequency of vertigo attacks until six months after the procedure. Given the results of this study, dexamethasone not only seems to have a protective effect on the ototoxicity of gentamicin, but also a synergistic effect with gentamicin to control vertigo.

Dexamethasone and gentamicin rapidly reach the perilymph fluid via passive diffusion through the round and oval windows after direct drug administration to the middle ear cavity [10,18,19]. Because both windows are in the basal turn of the cochlea, the drug concentration would have a gradient from basal to apical in which tonotopically high to low frequency of sound stimulation is detected. Thus, high-frequency hearing may be more sensitively affected by drug administration [11,20]. Gentamicin applied locally on the oval window, as in this study, diffuses to the vestibule more easily because it is close to the oval window. In contrast, the diffusion of dexamethasone (near the round window) to the vestibular organ is relatively difficult because there is no communication to the vestibular organ in scala tympani, but it easily diffuses to the cochlea due to the anatomical proximity. Therefore, local application of gentamicin and dexamethasone on the oval and round windows may be an ideal approach to control vertigo and preserve hearing.

MD is well known to have characteristic fluctuating hearing loss in low- to mid-frequencies [1]. Our results also showed a larger SD of threshold shifts after the procedure at 0.5 and 1 kHz frequencies in both groups. This may be attributed to the fluctuating hearing of the enrolled patients with MD in low- to mid-frequencies. In addition, MD may have a large intra-subject variation in hearing and vestibular function based on the status of the disease phase. For instance, a patient in the ictal phase would have aggravated low- to mid-frequency hearing and canal paresis compared to a patient in the stable state. This can bias the analysis of PTA_4 and canal paresis between the two groups. Thus, we additionally analyzed PTA_{high} to mitigate possible biases in the evaluation of the different effects of the two methods. This might also be useful in the evaluation of the hearing protection effect of dexamethasone against possible ototoxic effect of gentamicin because gentamicin is known to mainly affect high-frequency hearing levels [21].

The protective effect of dexamethasone on ototoxicity has been reported previously. In numerous animal studies, dexamethasone has shown a protective effect on ototoxicity induced by cisplatin and aminoglycoside [12,13,22]. Although the exact mechanism of gentamicin ototoxicity is unclear, the cell apoptosis pathway via reactive oxygen species (ROS) formation is thought to be mainly involved [23,24]. Dexamethasone is believed to decrease cell apoptosis via the nuclear factor kappa B pathway, as well as ROS formation [25,26]. This may be a critical mechanism that explains our results on high-frequency hearing

preservation. Dexamethasone is presumed to reduce endolymphatic hydrops by increasing aquaporin; Na^+ absorption from the endolymphatic space to the perilymphatic space by regulating epithelial Na^+ channels; and Na, K-ATPase expression, which may contribute to vertigo control [27–29]. A previous systematic review reported that the ITC group had significant vertigo control compared to the placebo group [30]. Based on our result, the different mechanisms of dexamethasone and gentamicin may have a synergistic effect.

Previous studies on chemical labyrinthectomy using gentamicin to treat MD showed heterogeneous methods in the application of gentamicin, resulting in vertigo control and hearing preservation [9]. The administration methods of gentamicin are mainly categorized as intratympanic injection in aqueous form or use of sustained-release vehicles. Although sustained-release vehicles such as Gelfoam® seem to provide precise and constant delivery of the drug, both methods were reported to show a similar effect on vertigo control (complete control rate of 70–80%) [9,31]. To date, studies comparing the treatment outcomes between intratympanic injection and sustained-release vehicles are sparse. The results of ITG and sustained-release vehicles should be analyzed with a consistent protocol in future studies. When comparing the results about the vertigo control to those of other studies described above, our results for the GO group are moderately satisfactory, with a success rate (less than 40% of the frequency of vertigo compared to the baseline during 2–12 months) of 52.6%. Although the exact reason for the relatively low vertigo control rate compared to other studies is not known, several factors can be considered. First, the application of gentamicin only in the oval window did not release a sufficient amount of gentamicin into the scala vestibule. Conventional intratympanic application of gentamicin can reach the vestibular organ via both the oval and round window, which may provide higher concentration compared to our method. The GD group might show a higher success rate for vertigo control due to the additional effect of dexamethasone to the effect of gentamicin. Second, dexamethasone diffused to scala tympani might impede the diffusion of gentamicin from scala vestibuli to scala tympani by increasing osmolality of scala tympani, which consequently causes higher gentamicin concentration in the scala vestibule. This might result in more vestibular ablation in the GD group than in the GO group. Although the change in canal paresis value was not statistically significant, the GD group showed relatively larger mean canal paresis value change than that in the GO group. Third, the number of patients enrolled in this study was not sufficient. For instance, canal paresis value changes showed relatively large standard deviation. Although several meaningful results were obtained from the study population, the study should be extended to a larger population to obtain more convincing results. However, the additional effect of concomitant application of dexamethasone with gentamicin on vertigo control and hearing protection seems promising; therefore, dexamethasone can be used with other gentamicin administration methods. In the future, the outcomes of serial administration of ITC following ITG could be investigated in further studies.

The limitation of this study was the short follow-up period, which was up to 12 months after the procedure. Therefore, vestibular results could not be concluded in this study. Considering that MD spontaneously regresses over time, the treatment outcome of this study might be underestimated when compared to studies that have reported a longer follow-up period [32]. Especially for ITC, some studies reported the short-term effect six months after the injection; our result also reflected this short-term advantage of ITC [33]. We thought that short-term effect evaluation of intratympanic dexamethasone in vertigo control and hearing preservation is more appropriate because the concentration of dexamethasone has a half-life of several hours of in the cochlea, as reported in an animal experiment [34]. Although the effect of dexamethasone is expected to last only a short time, a long-term follow-up result of more than two years should also be investigated in future studies.

In conclusion, the direct middle ear administration of gentamicin combined with dexamethasone protects high-frequency hearing and shows better short-term vertigo control compared to gentamicin combined with normal saline.

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The Non-Concordance of Self-Reported and Performance-Based Measures of Vestibular Dysfunction in Military and Civilian Populations Following TBI

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Abstract: As a predominately young, physically active, and generally healthy population, service members (SMs) with vestibular dysfunction (VD) following a TBI may not be accurately represented by the current civilian reference ranges on assessments of VD. This study enrolled SMs who were referred for vestibular rehabilitation following a mild/moderate TBI. The participants self-reported VD using the Activities-specific Balance Confidence (ABC) scale and the Dizziness Handicap Inventory (DHI) followed by evaluation of vestibular performance using computerized dynamic posturography sensory organizational test (CDP–SOT). Retrospective analysis of these outcomes comparing the study sample of SMs to the reported civilian samples revealed SMs self-reported lower VD with significantly higher balance confidence (ABC: 77.11 ± 14.61, $p < 0.05$) and lower dizziness (DHI: 37.75 ± 11.74, $p < 0.05$) than civilians. However, the SMs underperformed in performance-based evaluations compared to civilians with significantly lower CDP–SOT composite and ratio scores (COMP: 68.46 ± 13.46, $p < 0.05$; VIS: 81.36 ± 14.03, $p < 0.01$; VEST: 55.63 ± 22.28, $p < 0.05$; SOM: 90.46 ± 10.17, $p < 0.05$). Correlational analyses identified significant relationships between the ABC and CDP–SOT composite ($r = 0.380$, $p < 0.01$) and ratio scores (VIS: $r = 0.266$, $p < 0.05$; VEST: $r = 0.352$, $p < 0.01$). These results highlight the importance of recognizing and understanding nuances in assessing VD in SMs to ensure they have access to adequate care and rehabilitation prior to returning to duty.

Keywords: vestibular dysfunction; traumatic brain injury; TBI; military service members; activities-specific balance confidence; dizziness handicap inventory; CDP–SOT

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1. Introduction

Traumatic brain injuries (TBI) have increasingly become a major public health concern in both civilian and military populations, where a high prevalence among military service members (SMs) is attributed to combat operations or training-related tasks [1,2]. More than 400,000 SMs experienced TBIs during the Global War on Terrorism, with the majority classified as mild TBIs (mTBI) [3]. Although many symptoms of mTBIs often subside, there are frequent reports of persistent sequelae following a TBI such as dizziness, imbalance, and vertigo due to deficits in the vestibular system, which integrates multisensory information and is vulnerable to TBIs. These symptoms can result in acute and/or chronic functional limitations that can affect return to duty and unit readiness [4–7].

Short- and long-term consequences following a TBI that result in vestibular dysfunction were previously studied using various performance-based measures for balance and self-reported symptom severity and functional limitations [7,8]. Performance-based balance

measures have been developed to objectively capture symptom burden for TBIs; however, balance measurement tools such as Functional Gait Assessment and Computerized Dynamic Posturography may lack the sensitivity to capture instability in high-functioning populations such as military SMs or collegiate athletes [9–11]. These balance assessments commonly used in clinical practice have demonstrated mixed reports with SMs at times underperforming civilians, while others demonstrate a ceiling effect where researchers have notably distinguished that SMs with a TBI exhibited scores that fell within the normal range or outperformed the civilian reference ranges [9–11]. The prevalence of TBIs in SMs and the substantial portion of TBI patients reporting vestibular-related impairments [7,12,13] make it necessary to identify performance-based assessments that are sensitive to subtle vestibular deficits in high-performing populations.

Although performance-based outcomes are critical for quantitatively identifying deficits and tracking recovery, self-reported factors are important for developing treatment plans, qualifying complaints, and enhancing patient compliance [14–16]. Subjective self-report measures often include the Dizziness Handicap Inventory (DHI), the Rivermead Post-Concussion Questionnaire (RPQ), the Sport Concussion Assessment Tool (SCAT3), and the Post-Concussion Symptom Scale (PCSS), which have been shown to support complaints of imbalance [17–21]. However, inconsistent findings have been reported regarding the relationships between the patients' perceived ability and actual performance on vestibular-related functional tasks [21–23]. These inconsistencies have been found in both civilian and military populations. Both Inness [21] as well as Moore et al. [24] reported a dissociation between subjective and objective balance measures in civilians, whereas Herbert [7] demonstrated significant relationships between subjective self-reported dizziness using the Dizziness Handicap Index (DHI) and objective balance measured by the computerized dynamic posturography sensory organization test (CDP–SOT) in Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF) veterans.

Discerning which measures are appropriate in military populations for detecting effects of TBIs on vestibular performance and symptom presentation can support the clinicians' ability to better assess, diagnose, treat, and inform return-to-duty decisions for SMs. This study intends to evaluate the relationships between self-reported and performance-based assessments of vestibular function in a sample of SMs seeking treatment for vestibular impairment following a TBI and compare these measures between SM and comparable civilian-reported outcomes.

2. Materials and Methods

2.1. Design and Participants

This study utilized a single-site randomized enrollment of active-duty SMs between 18 and 49 years of age who were referred for vestibular rehabilitation with a history of mild or moderate TBI. Study-trained providers identified and referred interested patients to research staff who verified eligibility and enrolled participants. All the enrolled participants reported a mild or moderate TBI in accordance with the ACRM criteria [25] and confirmed by the Ohio State University TBI Identification (OSU TBI ID) tool [26] that occurred between 4 weeks to 5 years prior to study enrollment. Only individuals who self-reported dizziness symptoms as indicated with a score between 16 and 64 on the Dizziness Handicap Inventory (DHI) were included in the study. The participants had pre-intervention (baseline) and post-intervention assessments before and after vestibular rehabilitation treatment, in which intervention outcomes were previously assessed and compared by Loftin [27] and Vander Vegt [28]. Only baseline assessments of the same sample were used in our analysis. Of the 62 individuals enrolled into this study, six participants were excluded from analyses for incomplete baseline data or outcome measures that exceeded three standard deviations. The participant demographics for the final sample that was included in our analyses are found below. The Institutional Review Board of the Regional Health Command—Atlantic approved the protocol for this study. All the participants provided signed informed consent prior to their participation and after all the procedures were explained.

2.2. Procedures

Pre-intervention evaluation consisted of the collection of basic demographics, medical history information, confirmation of a mild or moderate TBI using the OSU TBI ID, and completion of an assessment battery that included a variety of self-reported and performance-based metrics to capture the spectrum of the vestibular symptom burden associated with TBIs. Self-reported measures included the Dizziness Handicap Inventory (DHI) and the Activities-specific Balance Confidence scale (ABC); the primary performance-based measure used was the computerized dynamic posturography sensory organization test (CDP–SOT), which provides a composite (COMP) score and visual (VIS), vestibular (VEST), and somatosensory (SOM) ratio scores. Additional performance-based measures assessed as part of the larger study included the head shake SOT, the dynamic visual acuity test, and the neuro-otologic test system (NOTC). However, results from these assessments were not included in the current analysis due to limited availability of comparison studies in civilian populations.

A total of 14 comparative peer-reviewed studies in civilians (Table 1) were identified for statistical comparison with our active-duty military sample. These studies were identified by searching the following keywords: "vestibular therapy," "TBI/mTBI," "concussion," "military TBI," etc. We selected studies with similar metrics and varying civilian patient populations that reported summary data for the DHI, the ABC, or the CDP–SOT.

2.3. Activities-Specific Balance Confidence Scale (ABC)

The ABC scale is used to assess confidence while performing various balance-dependent tasks. This 16-item measure has the respondents rank their ability to perform common daily activities (e.g., walking, reaching, using an escalator, and bending) from 0% (no confidence) to 100% (complete confidence). This survey produces one overall confidence number computing an average confidence rating over all the items. The ABC scale is valid, has been recognized to have high internal consistency, and has demonstrated the sensitivity to discriminate between individuals with and without falls in patients with vestibular impairments (alpha = 0.91) [29].

2.4. Dizziness Handicap Inventory (DHI)

The DHI is a 25-item self-reported questionnaire to quantify the perceived impact of dizziness-related deficits. The items are answered using three response levels: "no" is scored as 0 points, "sometimes" is scored as 2 points, and "yes" is scored as 4 points, with the maximum score of 100. A higher score indicates that the respondent perceives a higher impairment. The DHI is valid and has demonstrated high internal consistency for quantifying self-perceived vestibular handicap (alpha = 0.89) [14].

2.5. Computerized Dynamic Posturography Sensory Organization Test (CDP–SOT)

The CDP–SOT was assessed using the NeuroCom® Balance Manager SMART EquiTest® clinical research system (CRS) (Natus Medical Inc., Pleasanton, CA, USA), which consists of a fixed visual surround as the participants stand with standardized foot placement on a moveable dual force plate. The patients are harnessed as they perform three trials, each of six conditions: (1) eyes open, no sway; (2) eyes closed, no sway; (3) eyes open, visual/surround sway; (4) eyes open, support surface sway; (5) eyes closed, support surface sway; and (6) eyes open, support surface and visual/surround sway. Comparisons between these six conditions yield four center-of-pressure postural control scores. The CDP–SOT equilibrium composite score represents overall balance with a higher number indicating better balance; it is the weighted average of all the six conditions. A score of 0 means the patient fell and a value of 100 indicates perfect stability. The visual ratio represents the input of the visual system for maintaining balance and stability; it is computed by dividing the average performance in condition 4 by the average in condition 1. The somatosensory ratio represents a sensation produced by mechanical forces (e.g., proprioception, pressure, and touch), determined by dividing the average performance in condition 2 by the average

performance in condition 1. The vestibular ratio represents the stability when visual and somatosensory inputs are removed; it is determined by dividing the average performance in condition 5 by the average performance in condition 1. Ratio scores are reported as whole numbers. The CDP–SOT shows a moderate level of reliability [30].

2.6. Statistical Analysis

For comparative studies that reported the means, standard deviations, and sample size, we used two-tailed independent-samples *t*-tests, and for comparisons to studies with only published means and sample sizes, we used one-sample *t*-tests for group comparison to our sample. Cohen's d for effect size of independent-samples *t*-tests were calculated with pooled variance, while Cohen's d for effect size of one-sample *t*-tests used the standard deviation of the military sample. To examine the relationships between the self-reported measures (DHI and ABC) and the performance-based metrics (CDP–SOT composite and ratio scores), we computed Pearson's correlation coefficients. All data analyses were performed using SPSS version 27.0 (SPSS Inc., Chicago, IL, USA) using two-tailed tests with an α value set at 0.05.

3. Results

3.1. Demographic Characteristics

Our military sample included 56 active-duty SMs with an average age of 32.52 years (SD = 8.17), who were predominately male (83.83%) and identified as White (62.5%). The sample had an average of 4.19 lifetime TBIs (SD = 3.7), with 46 SMs (82.14%) sustaining a blunt-force TBI as their most recent mechanism of injury (MOI, 17.85% blast-force TBI) and an average time since injury (TSI) of 13.63 months (SD = 16.17) since their most recent TBI (Table 1). In contrast, seven comparable civilian studies had a mean age significantly higher than that of our military cohort (civilian studies: a–d, j, $p < 0.01$, h, n, $p < 0.05$), and five studies' samples were significantly younger (e, g, k–m, $p < 0.01$, Table 1). Additionally, all the civilian studies that reported gender included a higher percentage of women (a, b, d, f, h–k, m; the percentage of men ranged from 33.33% to 69.44%, Table 1), and the TSI was significantly different between our military sample and most comparable civilian studies that reported TSI (g, h, j–m, $p < 0.01$, Table 1). Full demographic and clinical characteristics, including sample means, standard deviations, and ranges for all subjective and objective measures for our military sample and comparable civilian studies of adults with post-concussion vestibular symptoms are summarized in Table 1.

3.2. Service Members Self-Report Fewer Vestibular Deficits Following TBIs

We compared the total ABC score in our military sample to five civilian studies (e–g, i, j) that also utilized the ABC scale. In our military sample, we observed an average total ABC score of 77.11 (SD = 14.61). In contrast, three civilian studies that collectively spanned adolescents (e), age- and TSI-matched (f), and late adulthood (j) reported scores that were significantly lower compared to the self-reported perceived balance ability in our military sample (civilian studies: e, $p < 0.05$, d = 0.47; f, $p < 0.05$, d = 0.35; j, $p < 0.01$, d = 0.86; Table 2), while one study reported significantly higher scores (civilian study: g, $p < 0.01$, d = 1.51; Table 2). We then compared the perceived impact of dizziness-related deficits in our military sample to nine civilian studies that included the DHI (a–i). Our military sample reported an average DHI score of 37.75 (SD = 11.74), while five civilian studies reported significantly different total DHI scores ($p < 0.05$). Specifically, our military sample self-reported a significantly lower dizziness-related impairment compared to four civilian studies (c, $p < 0.01$, d = 2.12; e, $p < 0.05$, d = 0.38; f, $p < 0.01$, d = 1.29; i, $p < 0.05$, d = 1.52; Table 2). However, one civilian study (g) did report a significantly lower patient dizziness-related impairment compared to our military sample (civilian study: g, $p < 0.01$, d = 1.99; Table 2).

Table 1. Demographic characteristics of the study participants and comparable civilian studies.

	Military Sample (*n* = 56)	**a (*n* = 214)**	**b (*n* = 92)**	**c (*n* = 44)**	**d (*n* = 10)**	**e ABC (*n* = 58) DHI (*n* = 59)**	**f (*n* = 8)**	**g ABC (*n* = 129) DHI (*n* = 127)**	**h (*n* = 10)**	**i (*n* = 6)**	**j (*n* = 100)**	**k (*n* = 108)**	**l (*n* = 62)**	**m (*n* = 12)**	**n (*n* = 48)**
Authors. Reference	–	Vereeck et al., 2007 [22]	Tamber et al., 2009 [31]	Findling et al., 2011 [32]	Basford et al., 2003 [33]	Alsalaheen et al., 2016 [34]	Moore et al., 2016 [24]	Dunlap et al., 2020 [35]	Kaufman et al., 2006 [17]	Adams & Moore, 2017 [36]	Whitney et al., 2006 [37]	Register-Mihalik et al., 2008 [38]	Sosnoff et al., 2011 [39]	McDevitt et al., 2016 [40]	Row et al., 2019 [41]
Age- (years), mean SD	32.52 ±8.17	**53.9** ** ±13.5	**47.2** ** ±11.46	**38.4** ** –	**40.9** ** ±11.3	**15** ** ±1.8	31 –	**20** ** ±7	**41** * ±11	39.33 ±13.7	**59** ** ±17	**18.83** ** ±1.27	**20.04** ** ±1.47	**20.5** ** ±1.8	**47.49** * ±16.12
Gender- Males, n (%)	47 (83.93%)	110 (51.4%)	28 (30.43%)	–	6 (60%)	20 (33.89%)	4 (50%)	–	6 (60%)	2 (33.33%)	38 (38%)	75 (69.44%)	–	7 (58.3%)	–
Race- White, n (%)	35 (62.5%)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
# of TBI- mean SD	4.19 ±3.7	–	–	–	–	–	–	–	–	**1.67** ** ±1.21	–	–	**1.24** ** ±0.61	2.6 ±2.9	–
MOI- Blunt, n (%)	46 (82.14%)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TSI- (months), mean SD	13.63 ±16.17	–	–	–	–	–	10.68 –	**7.07** ** ±7.92	**33.60** ** –	19.84 ±10.66	**36** ** ±60	**0.05** ** ±0.03	**44.3** ** –	**0.92** ** –	12.52 ±13.70

ABC = Activities-specific Balance Confidence scale, DHI = Dizziness Handicap Inventory, MOI = mechanism of injury, SD = standard deviation, TBI = traumatic brain injury, TSI = time since injury, * $p < 0.05$, ** $p < 0.01$; bold values represent significant findings.

Table 2. Comparison of the self-reported vestibular symptom burden following a TBI.

	Military Sample (n = 56)	**a (n = 214)**	**b (n = 92)**	**c (n = 44)**	**d (n = 10)**	**e ABC (n = 58) DHI (n = 59)**	**f (n = 8)**	**g ABC (n = 129) DHI (n = 127)**	**h (n = 10)**	**i (n = 6)**	**j (n = 100)**
ABC-mean	77.11	–	–	–	–	**67** *	**72** *	**96** **	–	76.8	**60** *
SD	±14.61	–	–	–	–	±27	–	10	–	±13.2	±24
DHI-mean	37.75	35.1	39.91	**62.7** **	32.2	**44** *	**53** **	**12** **	32	**64.1** *	–
SD	±11.74	±25	±18.95	–	±23	±20	–	±14	±23	±21.5	–
Range	[16–62]	[0–96]	[4–86]	[28–94]	[4–68]	–	[30–96]	–	[4–68]	[30–96]	–

ABC = Activities-specific Balance Confidence scale, DHI = Dizziness Handicap Inventory, SD = standard deviation, * $p < 0.05$, ** $p < 0.01$; bold values represent significant findings.

3.3. Service Members Experience More Performance-Based Vestibular Impairment Following a TBI

We next compared vestibular impairment indexed by the CDP–SOT performance, including composite and visual, vestibular, and somatosensory ratio scores, between our military sample and comparative civilian studies, which were limited to three studies of collegiate athletes (k–m) and one study in the general population (n). We observed an average CDP–SOT composite score of 68.46 (SD = 13.46) in our military sample, while two athletic studies reported significantly higher total composite scores compared to our military sample (l, $p < 0.01$, d = 2.42; m, $p < 0.05$, d = 0.68; Table 3). However, when we examined the CDP–SOT scores by visual, vestibular, and somatosensory ratio scores of our military sample and the four comparable civilian studies (k–n), we observed significant differences in at least two of the three ratios in all the four studies (Table 3). Though our military sample reported lower visual ratio scores (81.36, SD = 14.03) than all the four comparable civilian studies (k–n), visual ratio scores were only significantly different than in one athletic study (l, $p < 0.01$, d = 1.57) and civilian study n ($p < 0.01$, d = 0.56; Table 3). In contrast, our military sample showed significantly lower vestibular ratio scores (55.63, SD = 22.28) than all the three civilian athletic studies (k, $p < 0.05$, d = 0.33; l, $p < 0.01$, d = 2.19; m, $p < 0.01$, d = 0.85; Table 3) and lower somatosensory ratio scores (90.46, SD = 10.17) than all the four civilian studies, athletic or otherwise (k, $p < 0.01$, d = 0.66; l, $p < 0.01$, d = 1.08; m, $p < 0.05$, d = 0.56; n, $p < 0.05$, d = 0.42; Table 3).

Table 3. Comparison of the performance-based vestibular function by the CDP–SOT following a TBI.

	Military Sample (*n* = 56)	**k (*n* = 108)**	**l (*n* = 62)**	**m (*n* = 12)**	**n (*n* = 48)**
CDP–SOT					
COMP-mean	68.46	72.67	**91.6** **	**76.1** *	72
SD	±13.46	±14.23	±1.5	±8.5	±12
VIS-mean	81.36	83	**97** **	84	**88** **
SD	±14.03	±18	±1.4	±10	±9
VEST-mean	55.63	**63** *	**90.7** **	**69** **	54
SD	±22.28	±23	±3.8	±1	±26
SOM-mean	90.46	**95** **	**98.3** **	**95** *	**94** *
SD	±10.17	±6	±1.1	±5	±6

CDP–SOT = computerized dynamic posturography sensory organization test, COMP = composite, SD = standard deviation, SOM = somatosensory subscore, VIS = visual subscore, VEST = vestibular subscore,* $p < 0.05$, ** $p < 0.01$; bold values represent significant findings.

3.4. Interrelationship of Self-Reported and Performance-Based Vestibular Measures in Military Service Members

Finally, Pearson's correlations were calculated to examine relationships between self-reported and objective performance-based measures in our military cohort. Within our military sample, we identified significant positive relationships between the patients' perceived balance ability and their balance performance scores (Table 4). Specifically, significant positive associations were identified between the ABC and the CDP–SOT total composite scores ($p < 0.01$), visual ratio scores ($p < 0.05$), and vestibular ratio scores ($p < 0.01$, Table 4). We did not observe any significant associations between the DHI and any of the CDP–SOT measures.

Table 4. Pearson's correlation coefficients of self-reported and performance-based measures.

	ABC		DHI	
	r	*p*	*r*	*p*
COMP	**0.380**	**0.004**	−0.239	0.076
VIS	**0.266**	**0.048**	−0.05	0.713
VEST	**0.352**	**0.008**	−0.23	0.089
SOM	0.220	0.103	−0.232	0.086

ABC = Activities-specific Balance Confidence scale, CDP–SOT = computerized dynamic posturography sensory organization test, COMP = composite, DHI = Dizziness Handicap Inventory, SD = standard deviation, SOM = somatosensory subscore, VIS = visual subscore, VEST = vestibular subscore; bold values represent significant findings.

4. Discussion

The strict requirements for military service results in an SM population that is predominately young, healthy, physically active, and may not be accurately represented by the general population. Here, we evaluated vestibular-related impairment measures in an active-duty military sample with a history of TBI and then compared the baseline evaluations of self-reported and vestibular performance-based measures to previous studies with civilian samples. The goals of this retrospective analysis were twofold: (i) to determine the relationship between active-duty SMs with mild to moderate TBIs and the broader civilian population with similar injuries and (ii) to assess the correlation between the self-reported and performance-based measures of symptom burden in the military TBI cohort.

Although TBIs are of higher prevalence in young adolescent and geriatric general populations [42], the paucity of research towards 24–65-years-old individuals predominately excludes SMs who face an increased occupational risk of TBIs. Similarly, TBI-related vestibular studies in civilians have largely centered around either adolescents/young adults with athletic injuries or older adults with age-related vestibular impairments and can have a wide range of the TSI. We observed a similar trend among the 14 comparable civilian studies in our analysis wherein the average age of civilian participants was significantly younger or older than in our military sample and sample sizes were limited in the two age-matched studies (f and j).

Comparing the ABC scores, our military sample showed a notable difference from comparable civilian populations in four of the five studies (e, f, g, j) that used the measure. The military population generally showed greater confidence in self-reported measures of balance than civilian studies in the general population with significant age differences. This is potentially due to the demographic nature of the military population as young and generally healthy individuals. Between the military sample and an age-matched civilian study (i), there was no detectable difference in confidence, while a young adult study (g) reported much higher confidence levels. Proprioception performance has been shown to be age-related, with peak acuity in young adults followed closely by middle-aged individuals [43,44]; it may explain an increased confidence level in the military sample.

The self-reported symptom burden varied with comparison to civilian studies with our military sample reporting similar DHI scores as half of the civilian samples, and notably lower than the other half of civilian studies. With the exception of one civilian study (g) reporting a significantly lower DHI score, most reports of the DHI, both military and civilian, fell into the moderate disability range, with two civilian studies (c and i) breaching severe scores [14]. Duration of symptoms, more so than age, has been associated with increased DHI scores [45], and not having the TSI for all the comparison studies limits interpretation of these data. Additionally, the report of lower symptom burden may also be a result of military culture as self-reporting injuries has inconsistent reliability in studies of SM populations [46,47].

When we compared vestibular performance-based CDP–SOT composite and respective ratio scores, poorer performance was found in our military sample in nearly every study comparison. These comparisons included both comparable physically active collegiate athletes as well as an older general civilian population. Collectively, this suggests that

the SMs experienced greater performance-based vestibular-related deficits following a mild or moderate TBI, though they self-reported fewer deficits than civilians. It is possible that SMs, while more objectively impacted by their injury, report a lesser degree of subjective symptom burden as a result of military culture. These findings reinforce the importance of a comprehensive approach to TBI diagnosis, treatment, and rehabilitation in this population.

The second objective of this investigation assessed relationships between self-reported and performance-based measures of symptom burden within the military population. The outcome data suggest that the ABC is a more useful indicator of objective symptom burden among active-duty SMs. The data suggested limited ability for the DHI to predict or approximate the vestibular performance impairment in our military TBI population. This result could be a byproduct of the nature of the DHI and ABC surveys as the ABC has great specificity with regard to the specific balance tasks measured in the CDP–SOT. While the DHI includes some specific balance and mobility questions, it also encompasses broader symptom domains, including psychosocial factors. Although the ABC appears to better approximate the vestibular performance in military patients with a TBI, and eliminating the DHI may streamline the standard of care, clinicians may choose to retain the DHI to address the many facets of brain injury and ensure active-duty SMs receive adequate care.

Although the current study adds to the shortfall of research in individuals aged 24–65 years with a history of TBI and addresses specific gaps related to military health, this study is not without limitations. This study was limited in scope due to its nature as a retrospective analysis of data collected for a clinical trial that measured pre-/post-intervention differences on a battery of additional objective metrics. Our sample size consisted of the data available from the initial pre-intervention assessment, and the aims of this analysis may have been better served with a more robust sample size.

Demographically, limited comparable studies were found, consisting of similarly aged civilians with head injuries that employed the same self-reported and performance-based measures. These findings should be replicated with a comparable group to account for age-, TSI-, and sex-related differences following a TBI. Additionally, unique to SMs, Roberts et al. [48] suggested within-group variability on occupational characteristics, such as differences in occupational specialties and training experiences, may cause variability in the objective performance.

Other limitations in the current study are related to confines of which types of measures were examined in the civilian TBI/vestibular literature and the measures themselves. There is a paucity of work that includes both self-reported (ABC, DHI) and performance-based (SOT) measures collectively. Of our 14 comparable civilian studies, none examined both self-reported and performance-based measures, and only four studies looked at both the ABC and the DHI (e–g, i). Comparisons of our military cohort to literature where both subjective and objective measures were conducted in the same civilian population would be ideal but not possible given the body of previous studies. However, as to not severely limit our analyses, we chose to include a wide range of civilian studies that included either self-reported or performance-based measures. Furthermore, the current study only made statistical comparisons to two self-reported measures (ABC, DHI) and one performance-based measure (CDP–SOT). Although additional objective measures, particularly related to the vestibular ocular reflex, would provide a greater insight into TBI-induced vestibular-related decreased performance, the measures conducted in this study, the ABC, the DHI, and the CDP–SOT are validated and routinely used instruments that have clinical utility. We believe that the results of our study using these outcomes are meaningful and can inform clinicians about differences between military and civilian patients.

Lastly, this study did not have an ability to stratify individuals based on the number of TBIs sustained nor mechanism of injury, which may provide valuable insights. Future examinations focused on comparisons between military and civilian populations should strongly consider the mechanism of TBI. Unlike most of the civilian population, SMs are particularly susceptible to low-level primary blasts and have high rates of vestibular deficits following blast TBIs [49].

5. Conclusions

TBIs have been and will remain a significant problem for active-duty SM. While there are existing studies that examine civilian and military populations with TBIs, there are few studies that directly compare self-reported and performance-based measures of vestibular impairment within and between these two populations. Overall, this study found differences between a military sample and typical civilian TBI patients, both demographically and in terms of symptom burden and overall performance on vestibular activities. This paper intended to highlight the importance of recognizing and understanding these differences to ensure SMs have access to adequate care and rehabilitation prior to returning to duty. Future studies are necessary to elucidate the best assessment and treatment options for SMs suffering from vestibular deficits following a TBI based on population-specific factors and an understanding of military medicine and culture.

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