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Intratympanic and surgical treatment for menière's disease

Edited by
Maoli Duan, Kimitaka Kaga, Jun Yang, Pedro Marques and Bryan Kevin Ward

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Intratympanic and surgical treatment for menière's disease

Topic editors

Maoli Duan — Department of Clinical Neuroscience, Karolinska Institutet (KI), Sweden

Kimitaka Kaga — Tokyo National Hospital (NHO), Japan

Jun Yang — Shanghai Jiaotong University School of Medicine, China

Pedro Marques — Faculty of Medicine, University of Porto, Portugal

Bryan Kevin Ward — Johns Hopkins University, United States

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EDITED AND REVIEWED BY
Michael Strupp,
Ludwig Maximilian University of Munich, Germany

*CORRESPONDENCE
Maoli Duan
maoli.duan@ki.se
Jun Yang
yangjun@xinhuamed.com.cn

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Editorial: Intratympanic and surgical treatment for Meniere's disease

Jun Yang[1,2,3]*, Yupeng Liu[1,2,3] and Maoli Duan[4,5]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Ear Institute, Shanghai Jiaotong University School of Medicine, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose diseases, Shanghai, China, [4]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [5]Division of Ear, Nose, and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

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Editorial on the Research Topic
Intratympanic and surgical treatment for Meniere's disease

Introduction

The treatment of Meniere's disease (MD) remains controversial and challenging. The issue of how to control vertigo while preserving auditory-vestibular function and improving quality of life is a practical dilemma for both doctors and patients. Intratympanic and surgical treatments are both recommended by the latest Clinical Practice Guideline: Ménière's disease (1) when conservative treatment is ineffective. Intratympanic steroid (ITS) injection and intratympanic gentamicin (ITG) injection are effective treatments for vertigo control in MD patients. ITS has the advantage of protecting hearing, while ITG is more effective for controlling vertigo. ITS is suitable for bilateral disease. The value of endolymphatic sac surgery is that vertigo control and hearing preservation can be achieved concurrently. Furthermore, the risk of endolymphatic sac surgery is low, and serious postoperative complications are rare. Triple semicircular canal occlusion (TSCO) is an alternative procedure for treating MD and is widely accepted by Chinese otolaryngologists. However, the 2020 American guideline (1) and the 2017 European consensus (2) did not recommend TSCO as a selective surgical intervention. Further evidence-based studies and the mechanism of TSCO are needed to achieve global acceptance. The Research Topic "*Intratympanic and Surgical Treatment for Meniere's disease*" consists of seven original articles and two reviews. We put the spotlight on these nine published studies in this Research Topic, as well as the following categories: Pathogenesis Research; Diagnostic Tool; and Intratympanic Treatment and Surgical Treatment.

Pathogenesis research

The pathogenesis of MD remains unclear. Numerous studies have confirmed that the endolymphatic sac (ES) can be stimulated by antigens and generate an immune response. Immune-related diseases, such as allergies and autoimmune diseases, play an important role in the pathogenesis of MD. The pathogenesis of MD is related to various cytokines and inflammatory mediators of allergies and autoimmune diseases. Huang et al. were the first to successfully directly identify cytokines in the human luminal fluid of the ES when they detected the upregulated expression of TNF-a, IL-6, and IFN-g in the luminal fluid of the ES in MD patients. This modified method provided solid evidence of immune activities in the ES of MD patients. Rizk et al. (3) summarized the published literature on the pathogenesis and etiology of MD from 1917 to 2021 in their latest review. They concluded that there has been a surge in immunologic research on the pathogenesis of MD over the last 20 years (3).

MD patients have a history of abnormal mood, mental anxiety, and overwork before the onset of symptoms. Autonomic nerve dysfunction can increase sympathetic nerve excitability, induce small blood vessel spasms, and raise vascular osmotic pressure. As a result, the microcirculation disturbance of the endolymph leads to the manifestations of MD. Kitahara et al. reported that long-term high levels of vasopressin may adversely affect inner ear microcirculation and endolymph metabolism, leading to the development of MD symptoms. After effective treatment of MD, patients' vasopressin levels can be maintained at low levels. However, there has been little research investigating vasopressin in MD in recent years; therefore, the mechanism of the effect of vasopressin on the inner ear still needs to be clarified.

Diagnostic tool

Wideband tympanometry (WBT) can sense the lesions of different structures of the middle ear using the probe tone in the frequency range of 0.25–8 kHz, which is better at detecting middle ear function than traditional acoustic immittance. Additionally WBT can indirectly detect inner ear pressure. Therefore, it can be applied to the diagnosis of inner ear diseases. In this Research Topic, an overall summary of the role of WBT in the diagnosis of MD was provided by Meng et al. They found differences between MD patients and normal individuals in terms of resonance frequency, absorbance, integral area of absorbance, and G-Width. The application of WBT in MD is based on the hypothesis that pressure changes caused by endolymphatic hydrops (EH) alter the tension of the annular ligament and the "third window" of the inner ear, and in the case of an intact ossicular chain, decreased mobility of the stapedial footplate results in the reduction of tympanic membrane compliance. At present, a broad range of clinical applications of WBT is not possible due to the small sample sizes in studies, a lack of follow-up results, and a lack of data in different age populations and ethnic groups. WBT can be altered as part of a test battery if further evidence-based studies in the field are improved.

Intratympanic gentamycin

Aminoglycosides are ototoxic to both vestibular and cochlear hair cells. Gentamicin is the first preference for intratympanic injection due to its greater vestibular toxicity compared with cochlear toxicity. ITG is well tolerated, controls vertigo attacks, and has a low incidence of severe hearing loss. The 2020 Clinical Practice Guideline (1) recommended administering ITG to patients with unilaterally active MD who are refractory to conservative non-destructive treatments. Caution must be exercised in patients with bilateral MD because ITG carries the risk of significant bilateral vestibular hypofunction and hearing loss. Wegmann-Vicuña et al. evaluated the effect of ITG and concluded that 59.6% of the patients in their sample group achieved complete vertigo control after one single dose of ITG with a follow-up period of up to 6 years. Patients receiving a single ITG injection showed less frequent chronic disequilibrium and demand of vestibular rehabilitation. They also suggested that the endpoint of treatment was a vestibulo-ocular reflex (VOR) gain reduction of >17.8%. The generally accepted treatment endpoint of ITG is when the patient does not have a vertigo attack over a 12-month period or a vestibular loss in objective tests in the affected ear (4). Guan et al. completed a retrospective study on the effectiveness of ITG treatment and the value of the Halmagyi head thrust test (HTT) for predicting treatment durability. It is noteworthy that the authors used traditional HTT instead of a video Head Impulse Test (vHIT) to identify the impact of vestibular function. The HTT can be performed without specialized equipment and is a facile test that can be performed anywhere. Clinicians should never forget to use it when resources are limited.

Surgical treatment

Non-ablative surgery is a dispensable component of surgical treatment for MD patients with usable hearing and residual vestibular function when conservative treatment is ineffective. Histopathological change of EH has inspired surgeons to manipulate the membranous labyrinth for the purpose of relieving vertigo and preserving hearing. Kersbergen and Ward reviewed the history of manipulation of the membranous

labyrinth. Femenic shunt, Fick sacculotomy, tack operation, cochleosacculotomy, otic-perotic shunt, and semicircular canal plugging were respectively introduced. The aim of these operations, with the exception of canal plugging, is to relieve vertigo and improve hearing by draining excess endolymph. The authors summarized the published literature on the outcomes of vertigo control and hearing function. Vertigo control was satisfactory in most cases, but hearing function was not well preserved. Although these procedures have been abandoned by clinicians, they remain as great innovations in the history of otologic surgery. Jiang et al. investigated the surgical outcomes of TSCO and vestibular nerve resection. Vertigo control rate was satisfactory in both groups; however, a lower rate of postoperative paroxysmal dizziness and unsteadiness was observed in the TSCO group. The limitation of TSCO is the small number of large studies associated with it, which were carried out by Chinese clinicians (5, 6). Further research on the mechanism of TSCO and evidence-based studies are required.

Endolymphatic sac surgery was not recommended by the 2020 American guideline due to uncertainty about its benefits and its discordant underlying mechanisms. Zhang et al. reported a series of cases of patients who underwent resection of the lateral wall of the endolymphatic sac. Complete vertigo control was achieved in 61.6% of the patients. The authors speculated that the procedure's mechanism involved the reduction of endolymphatic fluid secretions and the elimination of the immune response of the endolymphatic sac. Zheng et al. compared the surgical effect of local endolymphatic sac decompression, endolymphatic mastoid shunt, and wide endolymphatic sac decompression. The authors concluded that wide endolymphatic sac decompression has a higher vertigo control rate (88.6%), better improvement of QOL, and relatively higher hearing stability. Paparella first proposed wide endolymphatic sac decompression and speculated that this procedure could enhance the blood supply of the sac and improve its absorption function (7). It is interesting that the two seemingly discordant surgical approaches achieved similar outcomes. The role of the endolymphatic sac in EH and MD remains a mystery.

Conclusions

In summary, the nine articles presented in the Research Topic "Intratympanic and Surgical Treatment for Meniere's disease" may provide more information about the field. Challenges in diagnosing and treating MD patients still remain. First, MD is often accompanied by other diseases. Patients with long-term recurrent attacks are likely to have psychological disorders or mental illness. Second, owing to the long-term nature and repetitiveness of MD, the economic costs of diagnosis, treatment, and rehabilitation are notable. Third, the factors that affect the treatment outcomes of MD are complex, and therefore, further studies are needed.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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

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ORIGINAL RESEARCH
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Endolymphatic Sac Drainage Surgery and Plasma Stress Hormone Vasopressin Levels in Meniere's Disease

Tadashi Kitahara, Tadao Okayasu, Taeko Ito, Hiroto Fujita and Keita Ueda*

Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, Nara, Japan

Meniere's disease is a common inner ear disorder accompanied by vertigo attacks and fluctuating hearing loss that some believe is due to a stressful lifestyle. To elucidate the scientific relationship in neuro-endocrinology between Meniere's disease and stress, we examined the surgical results of endolymphatic sac drainage surgery and changes in stress-induced plasma arginine-vasopressin levels. We enrolled 100 intractable Meniere's patients and examined surgical results and plasma vasopressin levels. Fifty-four chronic otitis media patients who underwent tympano-mastoidectomy formed a control group. We assessed surgical results during a 2-year follow-up period, including vertigo and hearing loss. We examined plasma vasopressin levels just before surgery and 1 week, 1 year, and 2 years after surgery. In patients with intractable Meniere's disease, plasma vasopressin levels were significantly reduced 1 week after surgery compared to the decrease observed in chronic otitis media patients after tympano-mastoidectomy. In intractable Meniere's disease, long-lasting low plasma vasopressin levels after surgery were associated with significantly good surgical results. In recurrent Meniere's disease, a gradual plasma vasopressin level elevation was observed after surgery, followed by recurrent vertigo attacks and sensorineural hearing loss. It is suggested that long-lasting high levels of plasma vasopressin could have adverse effects on inner ear water metabolism and the subsequent Meniere's disease symptoms. Effective treatments for Meniere's disease might be best based on the maintenance of low plasma vasopressin levels.

Keywords: Meniere's disease, endolymphatic hydrops, endolymphatic sac drainage, steroids, stress hormone, vasopressin

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Kimitaka Kaga,
Tokyo National Hospital (NHO), Japan

Reviewed by:
Yasuo Mishiro,
Osaka City General Hospital, Japan
Jeremy Hornibrook,
University of Canterbury, New Zealand
Hong Ju Park,
University of Ulsan, South Korea

****Correspondence:***
Tadashi Kitahara
tkitahara@naramed-u.ac.jp

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INTRODUCTION

Over time, animals with receptors that detect only environmental vibrations have evolved into higher animals that have increased mobility and can respond to sound and vibration. Based on the need for better auditory and equilibrium perception, the semicircular canals and lagena, and then the cochlea, developed from the primitive otolith. Fish are already equipped with semicircular canal-like structures, but not with a cochlea. In mammals, the utricular and oval macula, ampullar crista, and inner and outer hair cells in the organ of Corti are specialized pressure receptors. These receptors in the inner ear have evolved so that different types of pressures, such as linear and angular

acceleration and sound, can be detected (1). Throughout the process of biological evolution, these receptors inside the inner ear have been housed in an aquatic environment, although additional structures, such as the middle ear and Eustachian tube, are formed around the inner ear to work these receptors more effectively according to environmental changes.

Even in human inner ear receptors that have evolved to effectively respond to the environment, disruption of the water metabolism of the inner ear can sometimes cause dysfunction. This kind of dysfunction sometimes leads to repeated episodes of vertigo and fluctuating hearing loss and tinnitus, that is, Meniere's disease. This syndromic triad has been described since the Hippocratic era, and audio-vestibular diseases that result from excessive water in the whole body have also been described throughout China's 2000-year history of Kampo medicine. Surprisingly, relationships between the inner ear function and local water metabolism were clarified much later in the 17th−18th century, when Cotuguno and Scarpa found the membranous labyrinth filled with endolymphatic fluids. Thereafter, in the 20th century, Yamakawa in Osaka (2) and Hallpike and Cairns in London (3) revealed inner ear endolymphatic hydrops as the oto-pathology in Meniere's disease.

Fluid homeostasis in the inner ear is dependent upon the production, transport, and absorption of water, similar to the kidneys. Thus, localized arginine-vasopressin (AVP), AVP-related molecules such as vasopressin receptors, and water channels or aquaporins (AQPs) are present in the inner ear (4, 5). AVP is produced in the hypothalamus-pituitary axis and taken to the target organs by blood flow. AVP acts on vasopressin receptor V1a (V1a-R) in the vascular epithelium and activates phospholipase C, resulting in the regulation of calcium ions and the vaso-diameter. AVP acts on vasopressin receptor V2 (V2-R) in the basolateral side of the vascular epithelium and activates adenylate cyclase (AC), resulting in the regulation of water absorption through cyclic AMP (cAMP) elevation with protein kinase A (PKA) activation (**Figure 1**).

V1a-R is localized not only in the stria vascularis but also in the endolymphatic sac. However, the role of V1a in the inner ear remains unclear. V2-R plays a pivotal role in water metabolism in the inner ear, as well as in the kidney through the AVP-V2R-AC-cAMP system mentioned above. In the renal tissues plasma AVP (pAVP) elevation and subsequent V2R-cAMP-PKA activation in the renal tubule might lead to the intracellular translocation of AQP2 from the basolateral side to the luminal side of the tubule, resulting in the reabsorption of urine (**Figure 1A**). In the endolymphatic sac tissues, pAVP elevation and subsequent V2R-cAMP-PKA activation in the endolymphatic sac might lead to intracellular translocation of AQP2 from the luminal side to the basolateral side of the endolymphatic sac with endosomal trapping, resulting in the pathogenesis of inner ear endolymphatic hydrops (**Figure 1B**). In injuries with massive bleeding, the water resorption system may be promoted in the renal tubules to keep adequate systemic blood flow and inhibited in the inner ear to prevent endolymphatic collapse. AVP application to the inner ear tissues could activate V2-R and AC with cAMP elevation and AQP2 translocation (6, 7), resulting in the inner ear endolymphatic hydrops (8, 9). Despite no histopathological findings in the inner ear using V2-R knock-out mice, there is no doubt that V2-R could play a pivotal role in water permeability in the inner ear, including the endolymphatic sac.

Temporal bone studies conducted in 1938 revealed that the pathological feature of Meniere's disease is endolymphatic hydrops (2, 3). Meniere's disease is a common disorder with an incidence of 15–50 per 100,000 persons. It is suggested that it occurs particularly in civilized people living a stressful lifestyle, one author has termed "Menierization is civilization" (10). AVP is one of the stress-related hormones, and therefore, it is associated with both stress and the development of inner ear endolymphatic hydrops. High levels of pAVP in patients with Meniere's disease have been reported since the 1990s (6, 11, 12), although this topic has been controversial with contrary findings (13).

Given the role of AVP in the renal tubules, it is logical that continuously high levels of pAVP could result in adverse effects on the inner ear fluid homeostasis, resulting in cochlear and vestibular dysfunction. However, the reports are limited to the notion that AVP, as one of the stress-related hormones secreted from the hypothalamus-pituitary axis, is associated only with physical stress. Therefore, the suggestion that high levels of plasma stress hormone AVP in patients with Meniere's disease could cause vertigo attacks or stressful vertigo attacks has remained controversial. This study aimed to investigate the scientific relationship in neuro-endocrinology between Meniere's disease and stress and whether elevated pAVP levels in Meniere's disease are a cause or a consequence of vertigo attacks.

MATERIALS AND METHODS

The present study was approved by the Ethics Committee of Osaka University Hospital (certificate number: 0421) and registered with ClinicalTrials.gov of the U.S. Food and Drug Administration (certificate number: NCT00500474).

Patients and Controls

One hundred patients (male/female = 42/58; age = 51.5 ± 15.1 years) with intractable Meniere's disease—diagnosed according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria (14)—were enrolled in the present study between 1997 and 2006. These cases received endolymphatic sac drainage surgery with intra-endolymphatic sac local steroids (endolymphatic sac drainage surgery group: R44/L56), as previously described (15, 16). Another 54 cases with chronic otitis media without any direct inner ear damage acted as a control group (male/female = 21/33; age = 54.2 ± 18.8 years) and received tympano-mastoidectomy (tympano-mastoidectomy group: R24/L30). There were no significant differences in patient background between the two groups.

The 100 patients with intractable Meniere's disease (unilateral: 77; bilateral: 23) received 100 endolymphatic sac drainage surgeries, and their surgical results regarding vertigo and hearing

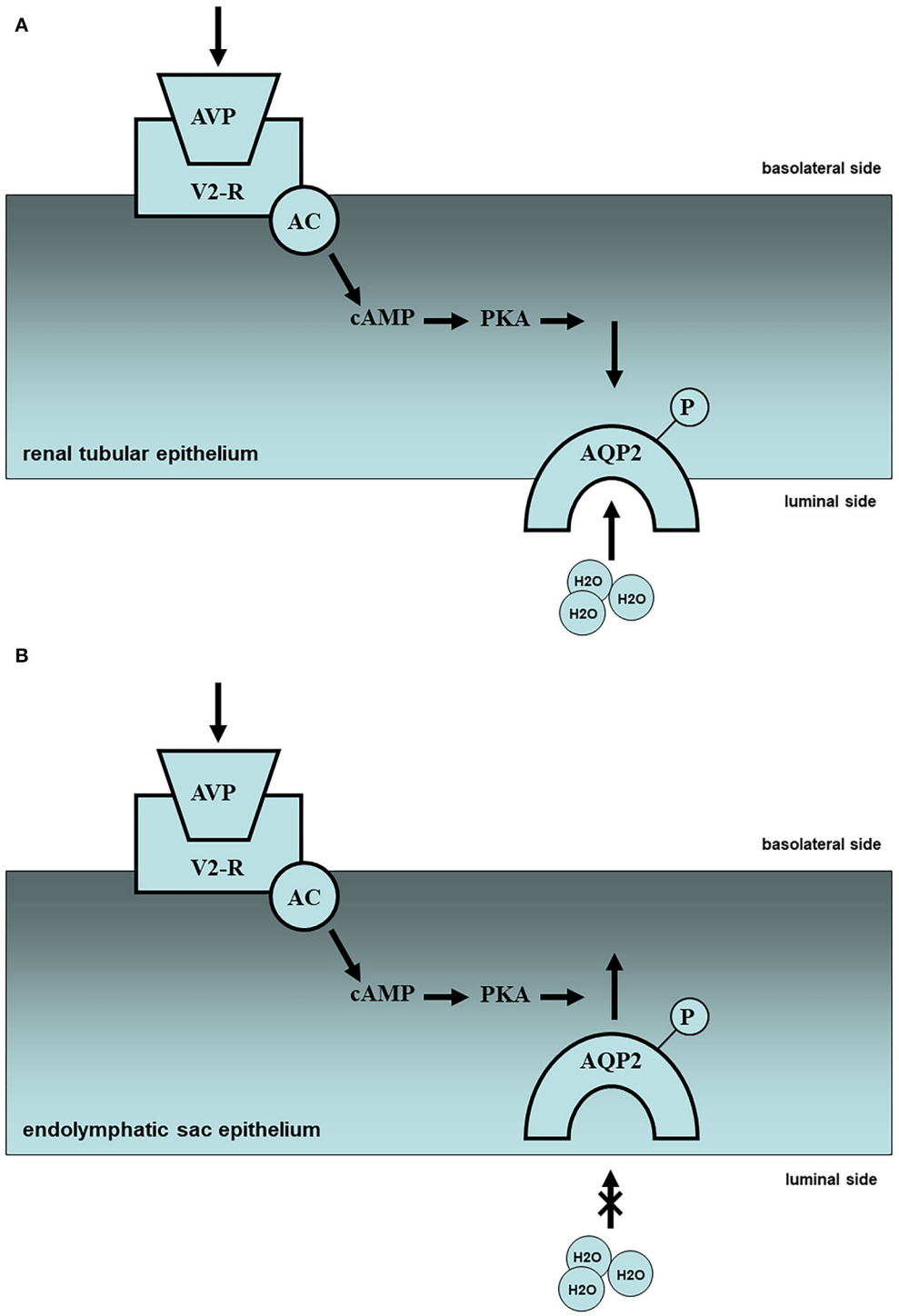

FIGURE 1 | Molecular mechanism of water metabolism in the kidney and endolymphatic sac (partial hypothesis). **(A)** In the renal tissues, plasma vasopressin (AVP) elevation and subsequent V2 receptor (V2R)-cyclic AMP (cAMP)-protein kinase A (PKA) activation in the renal tubule might lead the intracellular translocation of aquaporin-2 (AQP2) from basolateral side to luminal side, resulting in the reabsorption of urine, i.e., oliguria. Upward side: basolateral side; downward side: luminal side. **(B)** In the endolymphatic sac tissues, plasma vasopressin (AVP) elevation, and subsequent V2 receptor (V2R)-cyclic AMP (cAMP)-protein kinase A (PKA) activation in the endolymphatic sac might lead the intracellular translocation of aquaporin-2 (AQP2) from luminal side to basolateral side with endosomal trapping, resulting in the pathogenesis of inner ear endolymphatic hydrops, i.e., Meniere's disease. Upward side: basolateral side; downward side: luminal side.

were evaluated according to the 1995 AAO-HNS criteria (14). These patients were divided into a complete group (n = 48: zero vertigo and more than 10 dB improvement in hearing) and a non-complete group (n = 52: other). Short-term (15) and long-term results of this surgery (16) were described previously. In detail, the non-complete group was composed of those with zero vertigo/no change in hearing (n = 40), those with recurrent vertigo/no change in hearing (n = 5), and those with recurrent vertigo/more than 10 dB deterioration in hearing (n = 7).

Laboratory Examinations

Before collecting blood samples, all patients provided informed consent. Blood samples were collected from both groups at 8:00 a.m.−10:00 a.m. on the day of surgery and at 1 week, 1 year, and 2 years after surgery. Blood for the pAVP assay was transferred to an ethylenediaminetetracetic acid tube and centrifuged at 4°C, and the separated plasma was stored at −80°C. The pAVP level was determined by radioimmunoassay (arginine vasopressin radioimmunoassay kit: Mitsubishi, Tokyo, Japan) (6, 12).

Statistical Analysis

Statistical differences in the patient background (sex and age) between patients with Meniere's disease and controls were examined using a Mann–Whitney U-test. Statistical differences between the two groups in terms of outcomes were determined using an unpaired t-test, one-way analysis of variance (ANOVA), or two-way repeated ANOVA. All reported p-values were two-sided and those under 0.05 were considered significant. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Before the surgery, pAVP levels were significantly higher in patients with intractable Meniere's disease than in patients with chronic otitis media (t-test: p = 0.042). pAVP levels were significantly reduced immediately after endolymphatic sac drainage surgery (one-way ANOVA: p = 0.0040), and this reduction was much greater than that in patients with chronic otitis media after tympano-mastoidectomy (two-way repeated ANOVA: p = 0.014). Significantly lower pAVP levels remained for at least 2 years after endolymphatic sac drainage surgery

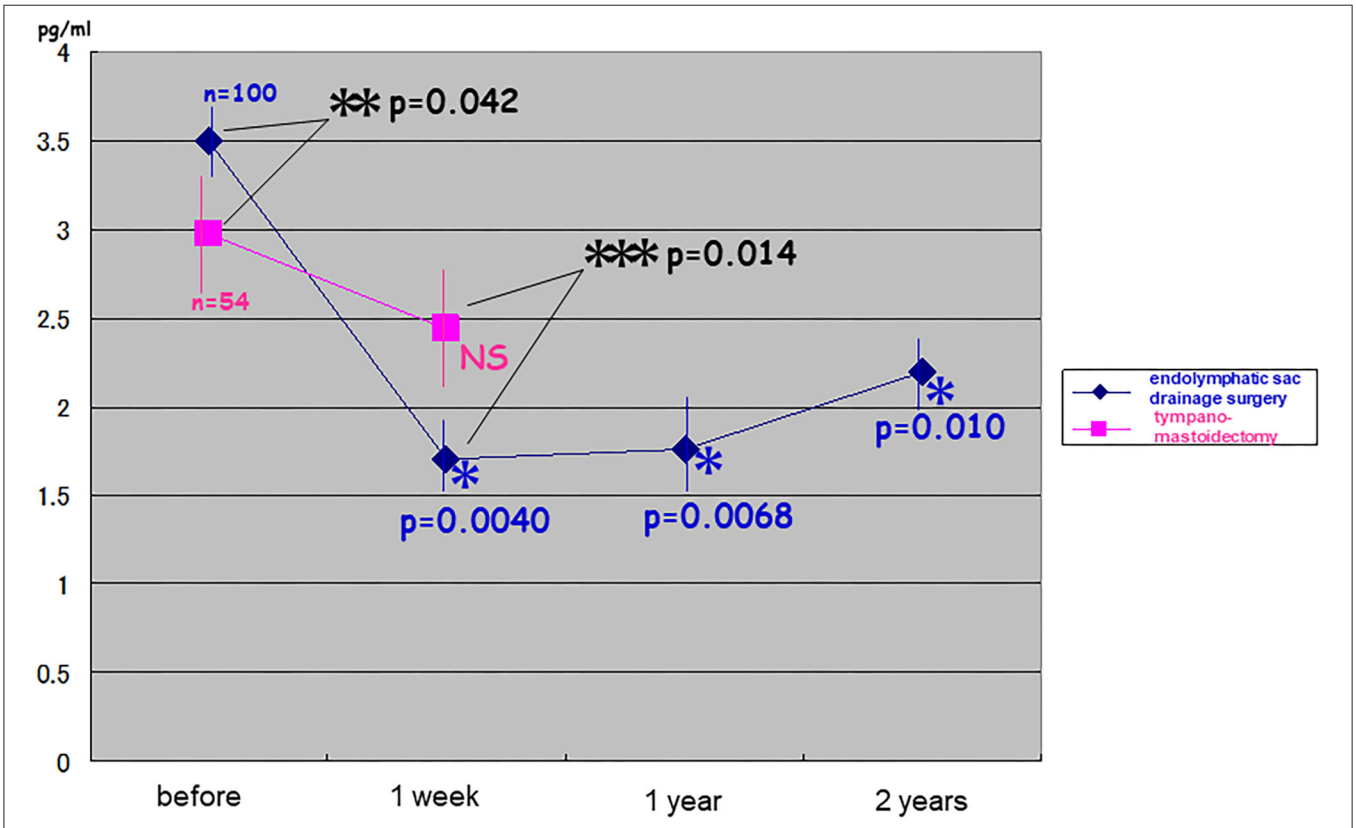

FIGURE 2 | Changes in plasma stress hormone vasopressin after endolymphatic sac drainage surgery vs. tympano-mastoidectomy. Plasma vasopressin (pAVP) in intractable Meniere's disease was significantly higher than that in chronic otitis media before surgery (t-test: $p = 0.042 < 0.05$). It was reduced immediately after endolymphatic sac drainage surgery (one-way ANOVA: $p = 0.0040 < 0.005$) and as was much greater than that in chronic otitis media after tympano-mastoidectomy (two-way repeated ANOVA: $p = 0.014 < 0.05$). The significantly lower levels of pAVP lasted at least for 2 years after endolymphatic sac drainage surgery (one-way ANOVA: $p = 0.0068 < 0.01$; $p = 0.010 < 0.05$).

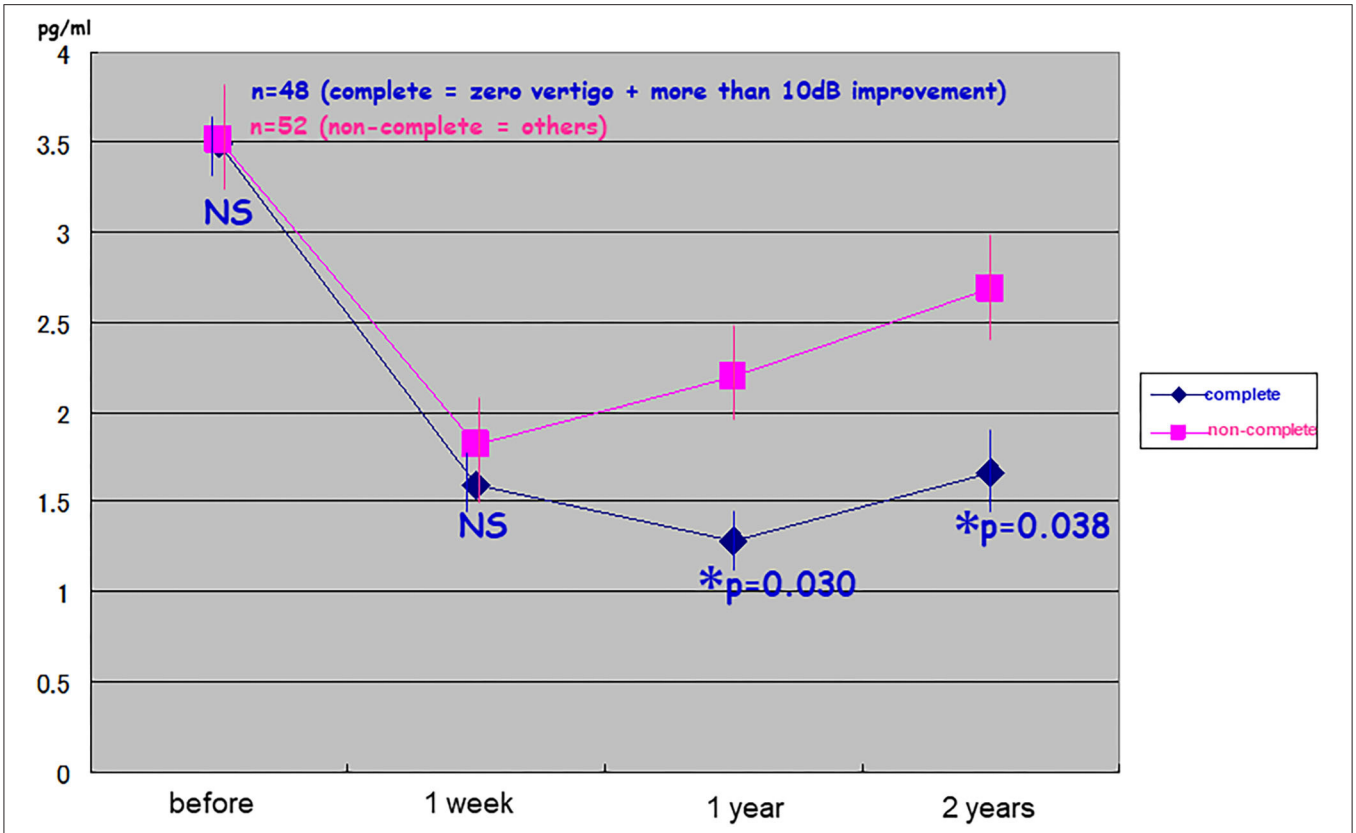

FIGURE 3 | Relationship between long-lasting suppression of plasma stress hormone vasopressin and good results in endolymphatic sac drainage surgery. One hundred patients with intractable Meniere's disease received endolymphatic sac drainage surgery were divided into the complete group ($n = 48$: zero vertigo and more than 10 dB improvement) and non-complete group ($n = 52$: others). The cases with good surgical results in vertigo and hearing at the 2nd post-operative year showed significantly lower levels of plasma vasopressin (pAVP) at least for 2 years predictively. *Significant ($p < 0.05$); NS, not significant.

[one-way ANOVA: $p = 0.0068$ (compared to immediately after surgery) and $p = 0.010$ (compared to patients with chronic otitis media after tympano-mastoidectomy)] (**Figure 2**).

Patients with good surgical results in terms of vertigo and hearing at the second post-operative year showed significantly low levels of pAVP at least for 2 years post-operatively (the complete pAVP: 1.67 ± 0.26; the non-complete pAVP: 2.71 ± 0.30; **Figure 3**). In detail, the non-complete group was divided into three, resulting in the averaged pAVP: 2.55 ± 0.48 of zero vertigo/no change in hearing, the averaged pAVP: 4.50 ± 1.43 of recurrent vertigo/no change in hearing, and the averaged pAVP: 4.78 ± 1.88 of recurrent vertigo/more than 10 dB deterioration in hearing (no statistical significance among three).

In one of the typical patients with intractable Meniere's disease, pAVP levels were reduced immediately after the first endolymphatic sac drainage surgery in 1999 and then vertigo and hearing gradually improved. After a while, pAVP re-elevation was observed during the first post-operative year and then followed by a recurrent vertigo attack and sensorineural hearing loss during the sixth post-operative year. Finally, this patient with recurrent Meniere's disease underwent a second endolymphatic sac drainage procedure in 2005, resulting in reduced pAVP levels and gradual improvement in vertigo and hearing again (**Figure 4**).

DISCUSSION

Plasma Vasopressin Elevation: Cause or Consequence of Meniere's Attacks?

Takeda et al. (11) first paid attention to high levels of pAVP in patients with Meniere's disease in the 1990s, although this topic has been controversial with contrary findings (13). In detail, patients with a vestibular type of Meniere's disease showed low levels of pAVP because of a combination with non-endolymphatic hydrops, and those with long-term profound sensorineural hearing loss demonstrated high levels of pAVP because they were candidates for delayed endolymphatic hydrops, suggesting relationships between continuous high levels of pAVP and endolymphatic hydrops genesis.

Takeda et al. also demonstrated that guinea pigs with chronic intraperitoneal application of AVP presented with cochlear endolymphatic hydrops with auditory brainstem response deterioration (8, 9). Moreover, Maekawa et al. (7) revealed that human endolymphatic sac tissues cultured with AVP application

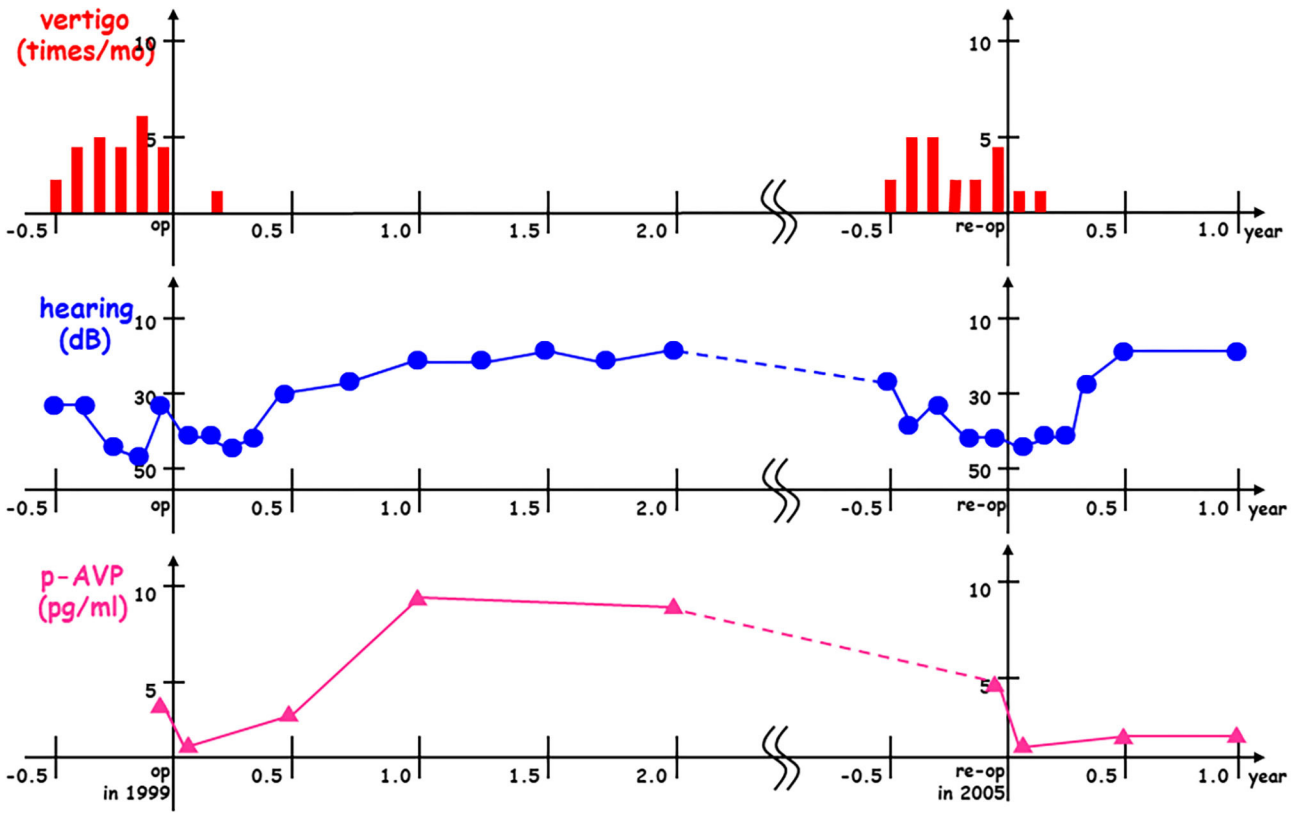

FIGURE 4 | Plasma stress hormone vasopressin re-elevation and subsequent Meniere's recurrence after endolymphatic sac drainage surgery. In this case with interactable Meniere's disease, plasma vasopressin (pAVP) was reduced immediately after the 1st endolymphatic sac drainage surgery in 1999 (op in 1999) and then vertigo (times/mo) and hearing (dB) were gradually improved. After a while, pAVP re-elevation was observed at the 1st post-operative year and then followed by recurrent vertigo attack and sensorineural hearing loss at the 6th post-operative year. Finally, this case with recurrent Meniere's disease received the 2nd endolymphatic sac drainage surgery in 2005 (re-op in 2005) to get pAVP dropped down with gradual improvement vertigo and hearing again.

resulted in cAMP activation and AQP2 translocation from the luminal side to the basolateral side of the endolymphatic sac to reduce endolymphatic absorption. These findings suggest that elevated AVP levels possibly cause endolymphatic hydrops and subsequent inner ear dysfunction.

In the present study, in intractable cases of Meniere's disease, long-lasting low pAVP levels after surgery were associated with significantly better surgical results. In recurrent cases with Meniere's disease, as seen in **Figure 4**, gradual pAVP elevation was initially observed after surgery, and this was followed by a recurrent vertigo attack and sensorineural hearing loss. Furthermore, in our recent inner ear magnetic resonance imaging (MRI) study, endolymphatic volume decreased after the surgery, resulting in significantly better surgical results (17). These findings suggest that long-lasting high levels of pAVP could have adverse effects on the inner ear water metabolism and possibly cause subsequent Meniere's symptoms.

On the contrary, in clinical studies, patients with a syndrome of inappropriate secretion of antidiuretic hormone and high levels of pAVP do not always have endolymphatic hydrops or Meniere's disease symptoms. There are some cases with low pAVP levels who are diagnosed with Meniere's disease. In basic studies there are no reports of endolymphatic hydrops or collapses in the inner ear of AVP- or V2R-deficient mice. These findings suggest that inner ear fluid homeostasis may work under complicated intracellular signal transduction cascades, including AVP-V2R.

Stress Hormone Management: A Possible Treatment Strategy for Meniere's Disease

Persistent high levels of pAVP could have adverse effects on the endolymph as a cause of endolymphatic hydrops and the onset of Meniere's symptoms. Consequently, efforts should be made to maintain low levels of pAVP to prevent disease development.

Takahashi et al. (18) reported the results of their questionnaire study, demonstrating that patients with Meniere's disease have characteristics associated with a type A personality, including operating at a more urgent pace, demonstrating higher levels of impatience, having a more competitive nature, getting upset easily, and associating self-worth with achievement. Although this study did not measure pAVP, it suggests that psychological counseling aimed at promoting self-awareness may result in some level of symptomatic control. Naganuma et al. (19) suggested increased water intake to decrease pAVP levels,

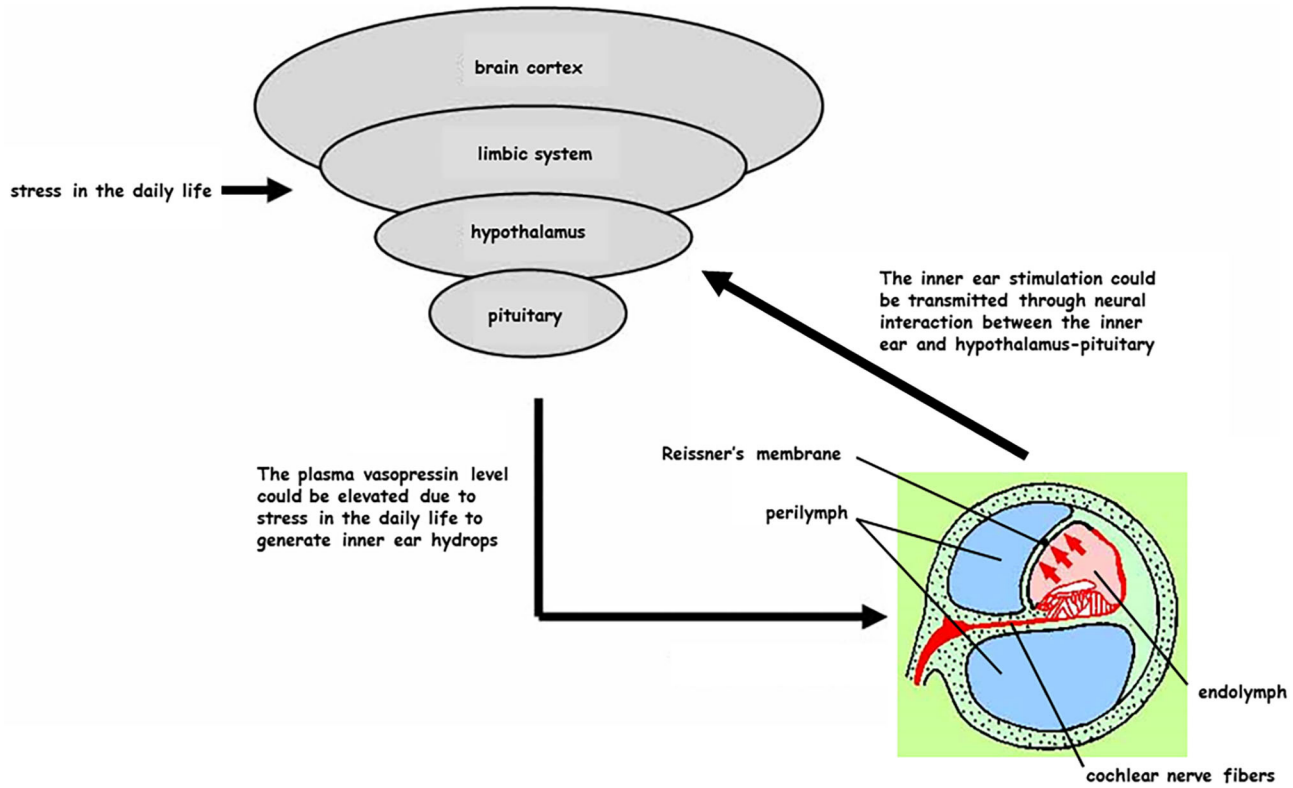

FIGURE 5 | Reciprocal interaction between the inner ear and hypothalamus-pituitary system (partial hypothesis). Civilized people are frequently exposed to stress in their daily life and plasma vasopressin (pAVP) could become elevated at any time to generate the inner ear endolymphatic hydrops. On the other hand, some treatments for the inner ear could be transmitted as a stimulation through the neural interaction from the inner ear to hypothalamus-pituitary.

reporting better therapeutic results compared with the usual medications. To investigate easier strategies for maintaining low pAVP levels, we conducted a randomized controlled trial that assessed the outcomes of new therapeutic interventions, namely the management of vasopressin secretion for the treatment of Meniere's disease. In this previous study, interventions such as abundant water intake, tympanic ventilation tubes, and sleeping in the darkness could be feasible to decrease vasopressin secretion (20). These findings suggest that there may be alternative effective treatments for Meniere's disease to maintain low pAVP levels.

In today's society it is difficult to lead a stress-free life, particularly in terms of finding a non-stressful job, having enough time to relax, and getting enough quality sleep. In intractable Meniere's disease cases, we recommend surgical treatment as a secondary strategy. Since surgical procedures place physical and mental stress on patients, pAVP levels generally increase and urine volume decreases during surgery. On the contrary, surgical procedures involving the middle ear and inner ear may result in a reduction in pAVP levels and an increase in urine volume during surgery (21). In the present study, endolymphatic sac drainage surgery involved the following processes: drilling the mastoidectomy, exposing the posterior fossa dura, opening the endolymphatic sac, and placing a high concentration of steroids around the opened endolymphatic sac (15, 16). In our study, pAVP levels were reduced immediately after endolymphatic sac drainage surgery, and this reduction was much greater than that seen in patients with chronic otitis media after tympano-mastoidectomy. These findings suggest that procedures associated with endolymphatic sac drainage surgery, from posterior fossa dura exposure to intra-endolymphatic sac treatment, may result in a reduction of pAVP levels, although there is no evidence these procedures actually reduce pAVP levels. However, direct connections between the inner ear endorgans and the hypothalamus-pituitary system have been demonstrated, not only physiologically (22) but also morphologically (23). These findings suggest that inner ear stimulation could transmit to the hypothalamus-pituitary axis to modulate AVP production and/or secretion (**Figure 5**).

Since Yamakawa (2) and Hallpike and Cairns (3) discovered endolymphatic hydrops in Meniere's disease the development of inner ear gadolinium-enhanced MRI has been a useful advance in inner ear imaging (24, 25). However, neither oto-pathologic observation nor MRI findings can prove that endolymphatic hydrops causes Meniere's symptoms. The causal mechanisms of endolymphatic hydrops and the onset of Meniere's symptoms

remain unclear, so symptomatic treatments might be preferable to medications and to surgery in particular.

In the present paper, we propose that pAVP-V2R activation in the inner ear could be one of the causes of endolymphatic hydrops and subsequent Meniere's attacks. In the modern era, it is difficult to avoid stress and maintain low levels of pAVP. Before considering molecular targeted therapy for AVP-V2R, we should implement simpler strategies for maintaining low levels of pAVP as outlined in basic studies of the molecular mechanisms of inner ear fluid homeostasis.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

TK and TO designed the research. TI, HF, and KU performed the research. TK analyzed the data and wrote the paper. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

ORIGINAL RESEARCH
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Efficacy and Durability of Intratympanic Gentamicin Treatment for Meniere's Disease

Yafeng Guan[1], *Divya A. Chari*[2,3,4,5], *Yu-Hsi Liu*[6] *and Steven D. Rauch*[2,5]*

[1] Department of Otolaryngology, The Hong Kong University-Shenzhen Hospital, Shenzhen, China, [2] Department of Otolaryngology – Head and Neck Surgery, Massachusetts Eye and Ear, Boston, MA, United States, [3] Department of Otolaryngology, UMass Memorial Medical Center, Worcester, MA, United States, [4] Department of Otolaryngology, University of Massachusetts Medical School, Worcester, MA, United States, [5] Department of Otolaryngology – Head & Neck Surgery, Harvard Medical School, Boston, MA, United States, [6] Department of Otolaryngology – Head and Neck Surgery, Kaohsiung Vetereans General Hospital, Kaohsiung City, Taiwan

Objective: To study the success of intratympanic gentamicin (ITG) treatment in reducing vertigo attacks in Meniere's disease (MD) and the value of the Halmagyi head thrust test (HTT) in predicting treatment durability.

Study Design: Retrospective cohort study.

Setting: Tertiary care vestibular clinic.

Patients: Unilateral MD patients treated with ITG from 2006–2019 with ≥6 months follow-up.

Main Outcome Measures: Demographics, audiometric data, subjective symptomatology, and HTT results were collected. Treatment success was defined as sufficient symptom relief. Treatment failure indicated vertigo control of less than 6 months duration. Treatment relapse indicated vertigo recurrence after 6 months.

Results: Of 255 patients, treatment success, failure, and relapse occurred in 226 (88.6%), 29 (11.4%), and 121 (47.1%) patients, respectively. 48 (18.8%) patients who failed to respond or relapsed underwent labyrinthectomy. Mean follow-up time was 3.7 yrs (range 0.5–12.8). After ITG treatment, 25% patients reported worse hearing; mean pure tone average (PTA) increased by 18.6 ± 11.3 dB and mean word recognition score (WRS) decreased by 33 ± 21%. Of the 148 patients with negative pre-treatment HHT, 103 (69.6%) converted to positive after ITG treatment. Mean time-to-relapse in the converted and non-converted HTT cohorts was significantly different (49.7 vs. 27.0 months, $p = 0.009$) even after adjusting for gender, age, laterality, duration of symptoms, and number of ITG treatments. There were no significant differences between the two groups in hearing outcomes or subjective symptoms (e.g. lingering disequilibrium).

Conclusions: ITG treatment effectively reduces the number of vertigo attacks in MD. HTT is valuable in predicting durability of treatment benefit.

Keywords: gentamicin, Meniere's disease, intratympanic (IT) injection, intratympanic treatment, head thrust test

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Bryan Kevin Ward,
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Nils Guinand,
Geneva University Hospitals (HUG), Switzerland
Habib Georges Rizk,
Medical University of South Carolina,
United States

***Correspondence:**
Steven D. Rauch
steven_rauch@meei.harvard.edu

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INTRODUCTION

Meniere's disease (MD) causes fluctuating and progressive sensorineural hearing loss (SNHL) and episodic vertigo and can be clinically challenging to manage. For the vast majority of patients with active MD symptoms, it is the episodic vertigo that is most disabling and has the most profound impact on quality of life. Fortunately, treatment of MD is most effective in the control of these acute vertigo attacks, while auditory symptoms such as aural fullness, tinnitus, and hearing loss tend to be less responsive to treatment interventions (1).

In our center, we adopt a conservative approach to diagnostic testing and treatment intervention, and embrace a patient-centered outcome philosophy (2). Our initial treatment intervention for MD patients with intractable vertigo is to provide guidance about trigger management. The three pillars of trigger management are (i) adoption of a regular daily schedule to get the body in a rhythm day-to-day, (ii) redress of any other medical or psychological health issues, and (iii) dietary recommendations to help maintain a constant fluid and electrolyte status to avoid overtaxing the homeostatic systems of their fragile MD ear (3, 4). Patients who continue to suffer vertigo attacks despite undergoing these conservative lifestyle modifications are prescribed a diuretic (5). In our experience, the combination of trigger management and diuretic leads to adequate control of symptoms in the majority of patients. Worldwide, betahistine is widely used as maintenance therapy to reduce or prevent MD attacks. However, it is not approved for use by the U.S Food and Drug Administration because of the quality of evidence for its efficacy in MD is poor (1). Thus, it is problematic for us to prescribe it and for our patients to obtain it. We do not use it. In this remaining cohort who fail to control vertigo with diet/lifestyle interventions and diuretic, intratympanic gentamicin (ITG) is our treatment of choice. Intratympanic corticosteroid (ITC) injection may be offered as a preliminary strategy prior to ITG to patients in whom the MD affects their only hearing ear or patients with serviceable hearing in the affected ear (6). There have been numerous reports in the literature of the efficacy of ITG (7). In the small percentage of MD patients who fail to respond to ITG, surgical interventions such as transmastoid labyrinthectomy, endolymphatic sac decompression, and vestibular neurectomy may be offered (8–10).

If treatment intervention is undertaken and the patient returns for follow-up reporting that the symptom control is adequate, we consider this a treatment success. If the patient reports inadequate symptom control and requests additional therapy, we consider this a treatment failure and offer alternative interventions. Although all MD patients new to our clinic are encouraged to have a baseline comprehensive vestibular test battery, which serves as a reference point should they fail to respond to treatment, (3) many patients decline to undergo these diagnostic procedures because of availability, cost, time considerations, or discomfort. We strongly recommend, and most patients accept, some vestibular function testing (in particular, cervical vestibular evoked myogenic potential [cVEMP]) prior to invasive treatment such as ITG or surgery (4, 5). This pre-treatment testing seeks to specifically address two questions: (i) How "sick" is the affected ear, and (ii) is there any indication of occult dysfunction in the unaffected ear. We have shown previously that 25–30% of asymptomatic ears in unilateral MD patients have abnormal cVEMP (11) and have subsequently shown that these asymptomatic ears with abnormal cVEMP have a significantly greater risk of eventual development of active MD (12).

MD follows a fluctuating course and thus it can be challenging to determine whether a reduction in vertigo attacks arises from drug administration or whether it is simply a consequence of the natural history of the disease. We monitor ITG patients for two indicators of drug effect, a subjective indicator of new onset disequilibrium and an objective indicator of new onset of refixation saccades with a Halmagyi head thrust test. Following administration of ITG, patients often notice a "tipsy disequilibrium" that begins approximately 3–5 days after treatment. Specifically, this is new onset of a generalized disequilibrium that is intensified by movement. The sensation is distinctly different from a full-blown Meniere vertigo attack but very similar or identical to the sensation patients experience following a Meniere attack, when they are no longer having vertigo but are still suffering labyrinthine upset that leads to disturbance of their vestibulo-ocular reflexes and general balance. It is presumably due to onset and progression of post-injection deafferentation. The sensation intensifies to peak around 10–14 days and then gradually fades over an additional four weeks. Post-treatment vestibular function testing may be used to determine the drug effect, but this process can be costly and time-consuming and vestibular function testing is not available in all clinics. As an alternative, the Halmagyi head thrust test (HTT) may be used in the pre- and post-treatment office assessment to determine whether the patient's vestibular function has been impacted by the gentamicin. ITG is typically administered with the goal of hastening reduction of vestibular function within the inner ear. Somewhat analogous to the Fast Forward button on a video player, ITG accomplishes in a matter of weeks the "burn out" that would normally take many years. Conversion of a negative (normal) pre-treatment HTT to a positive (abnormal) post-treatment result indicates some definite degree of peripheral vestibular hypofunction induced by the drug. The HTT is a facile test that can be performed in the clinical setting without specialized equipment.

Herein, we retrospectively review the short- and long-term audiologic and vestibular outcomes following ITG treatment in individuals with unilateral MD and investigate the value of the HTT in predicting durability of ITG treatment benefit.

METHODS

Study Design

A retrospective chart review was conducted for all MD patients treated with ITG from 2006–2019. Inclusion criteria included patients with unilateral MD as defined by previously published practice guidelines (1) with at least 6 months follow-up after administration of ITG. Pre- and post-treatment audiometric

data, subjective vestibular symptomatology such as vertigo, dizziness, and/ or disequilibrium within one month of treatment, and HTT results were recorded along with demographic information. Pre-treatment audiograms were obtained within 1–2 weeks prior to ITG administration. Subjects who complained of subjective hearing loss underwent a post-treatment audiogram, typically around four weeks after treatment. The protocol was deemed exempt by the Massachusetts General Brigham Institutional Review Board (protocol number 2019P003735).

Intratympanic Gentamicin (ITG) Administration

Patients were positioned supine with the head turned slightly toward the contralateral side. The tympanic membrane was anesthetized at two positions (anterior and posterior) with topical phenol. A ventilation opening is created at the anterior site and 1 mL of room temperature 40 mg/mL gentamicin sulfate was instilled into the posterior site with a 25-gauge spinal needle. The entire 1 mL was instilled, which served to flush air bubbles out

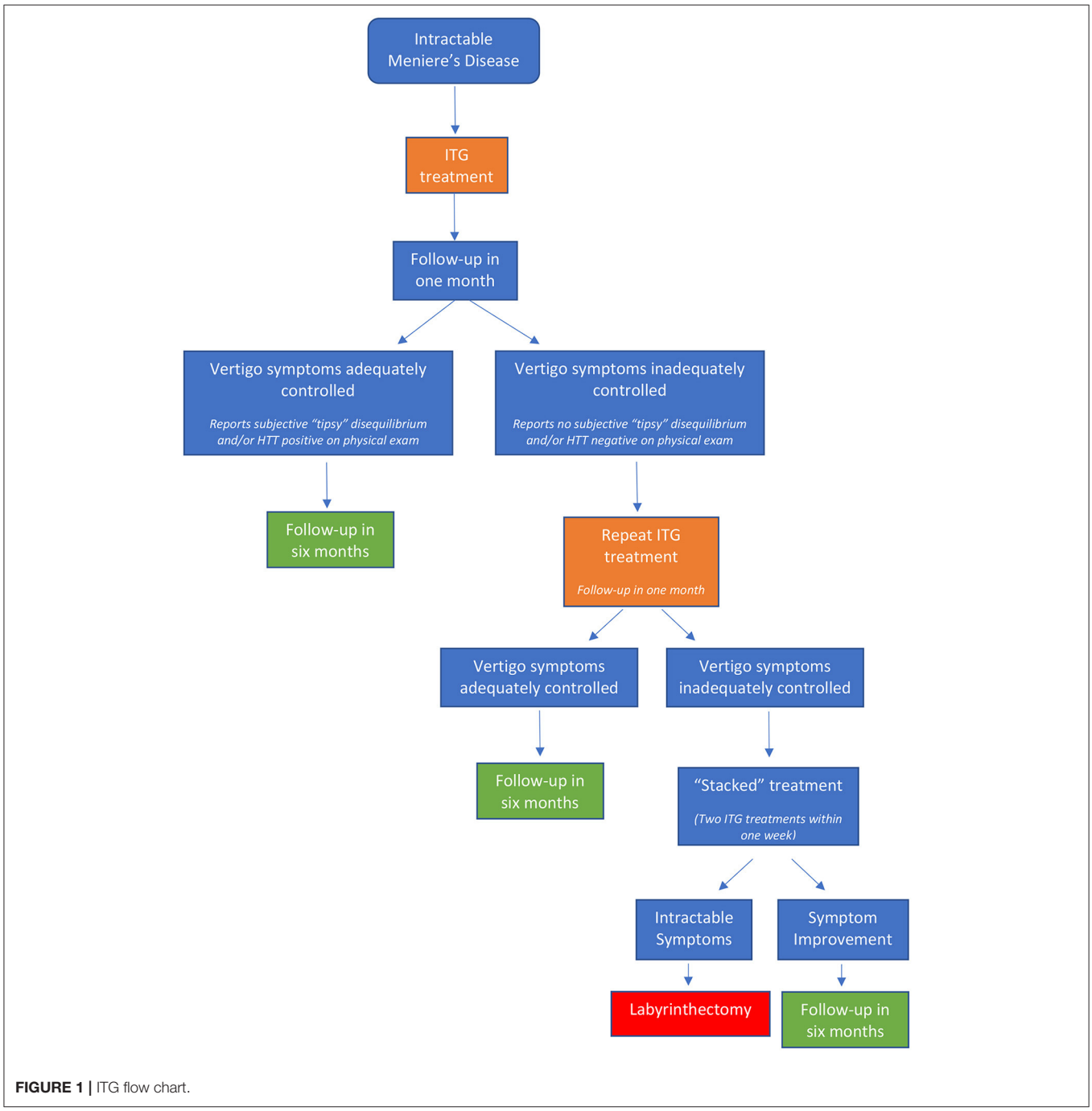

FIGURE 1 | ITG flow chart.

through the anterior ventilation opening and fill the middle ear with drug. Excess gentamicin solution that exceeded the volume of the middle ear filled the external auditory canal. Patients remained supine with the treated ear slightly up for one hour and were discharged with instructions to keep the ear dry.

Definitions of Treatment Effect

Following ITG administration, patients were categorized into three treatment groups: *success*, *failure*, and *relapse*. Treatment success included patients who reported adequate abatement of vertigo attacks for at least 6 months and requested no additional treatment or intervention. Treatment failure included patients with vertigo control of less than 6 months duration who required further intervention. Treatment relapse included patients with vertigo recurrence following a quiescent period of more than 6 months after initial treatment (**Figure 1**).

Halmagyi Head Thrust Test (HTT)

At the one-month follow-up visit after ITG treatment, an HTT was performed. After confirming that the patient had no significant neck problems and demonstrated normal ocular motility and side-to-side gaze tracking while sitting upright, the patient was asked to fixate their gaze on the examiner's nose. The patient's head was then rotated suddenly and unpredictably in a short, but high velocity horizontal motion to each side. Presence of a refixation saccade was scored as a positive (abnormal) test result. Patients who had a documented pre-treatment negative HTT that subsequently converted to positive post-treatment were categorized into the "converted HTT" group. Patients who had a documented pre-treatment negative HTT that remained negative post-treatment were categorized into the "non-converted HTT" group. In addition to this objective assessment of treatment effect, patients were queried for presence and time course of subjective symptoms of imbalance that were new since the treatment.

Statistical Analysis

Standard descriptive statistics were used to describe the study population. Statistical analysis was completed using Statistics Package for Social Science (IBM SPSS version 23; SPSS Inc., Chicago, IL) and GraphPad Prism 8 (San Diego, CA). Statistical significance was set at $p < 0.05$. χ^2 tests were used for comparative analysis of qualitative variables among groups. A Mann Whitney Wilcoxon test and independent two-sample *t*-test were used to compare differences between the converted and non-converted HTT groups. After adjusting for baseline data, including gender, age, laterality, duration of symptoms, and number of ITG treatments, a logistic regression analysis was used to compare the two groups. Comparison of time-to-relapse of the two groups was performed with a Cox proportional hazards regression model.

RESULTS

Demographics

A total of 255 unilateral MD subjects met inclusion criteria, all of whom had been treated with ITG. The mean age was 57 yrs (range: 15–83) and there were 135 (52.9%) male subjects. Demographics are shown in **Table 1**. The mean follow-up period was 3.7 yrs (range: 0.5–12.8 yrs). There were 125 (49.0%) affected right ears. The mean duration of symptoms as calculated from the onset of symptoms was 7.1 yrs (range: 0.3–45 yrs). The number of ITG administrations varied in the cohort; 85 (33.3%) subjects received one injection, 83 (32.6%) subjects

TABLE 1 | Demographics of patients treated with ITG.

Variable	Category	Number (%)	Total
Gender	Male	135 (52.9%)	255
	Female	120 (47.1%)	
Age (yrs)	Min	15	255
	Max	83	
	Mean±SD	57.4 ± 11.0	
Laterality	Left	130 (51.0%)	255
	Right	125 (49.0%)	
Length of time with MD (yrs)	Min	0.3	244
	Max	45.0	
	Mean±SD	7.1 ± 7.3	
Number of treatments	Once	85 (33.3%)	255
	Twice	83 (32.6%)	
	≥Three times	87 (34.1%)	
Drop attack before ITG	Yes	81 (31.8%)	255
	No	174 (68.2%)	
Head thrust test before ITG	Negative	172 (81.5%)	211
	Positive	39 (18.5%)	
Interval until reaction	No reaction	22 (9.8%)	224
	Days	113 (50.4%)	
	Weeks	89 (39.7%)	
Hearing loss level before ITG	None	3 (1.2%)	244
	Mild	26 (10.7%)	
	Moderate	109 (44.7%)	
	Severe	103 (42.2%)	
	Profound	3 (1.2%)	
Hearing loss level after ITG	No	5 (3.5%)	144
	Mild	11 (7.6%)	
	Moderate	62 (43.0%)	
	Severe	63 (43.8%)	
	Profound	3 (2.1%)	
Hearing deterioration after ITG	Yes	47 (25.0%)	188
	No	141 (75.0%)	
Relapse	Yes	121 (53.5%)	226
	No	105 (46.5%)	
Time-to-relapse(months)	6–12	38 (31.4%)	121
	12–24	38 (31.4%)	
	>24	45 (37.2%)	
Drop attack after ITG	Yes	46 (18%)	255
	No	209 (82.0%)	
Head thrust test after ITG	Negative	52 (22.6%)	230
	Positive	178 (77.4%)	
Labyrinthectomy after ITG		48 (18.8%)	255
Follow-up time(years)	Min	0.5	255
	Max	12.8	
	Mean ± SD	3.7 ± 2.9	
Lingering disequilibrium	Yes	26 (10.2%)	255
	No	229 (89.8%)	

received two injections, and 87 (34.1%) subjects received between 3–10 injections.

Audiometric Outcomes

Prior to ITG treatment, mean pure tone average (PTA; average threshold at 0.5, 1, 2 and 3 kHz) was 57.0 ± 13.7 dB HL and mean word recognition score (WRS) was 49 ± 27 %. 118 patients had audiograms performed after the injection. Of this cohort, 47 (25%) had an objective decline in the performance on audiogram. Of these patients, 11 (23.4%) had one injection, 12 (25.5%) had two injections, and 24 (51.1%) underwent three or more. In these patients, mean PTA increased by 18.6 ± 11.3 dB HL, and mean WRS decreased by 33 ± 21 %.

Vestibular Outcomes

Before ITG treatment, 81 (31.8%) subjects had experienced at least one drop attack. It is noteworthy that only 11% of all MD patients in the senior author's practice fail diet/lifestyle and diuretic therapy, thereby qualifying for ITG treatment. Thus, a drop attack prevalence of 31.8% is really 31.8% of 11%, or approximately 3.5% of all MD patients. After treatment, 46 (18.0%) patients experienced vertigo and/ or drop attack(s).

We have an elaborate custom cVEMP testing system developed in our Audiology Department over the last 20 years. We test cVEMP threshold for 500, 750, and 1,000 Hz tonebursts. We report these thresholds as "normal" if they fall within the 95% confidence interval for our normative data set, and "abnormal" if they exceed the 95% confidence interval at more than one of the three test frequencies. Of the 189 subjects who underwent pre-treatment cVEMP testing, vestibular hypofunction (i.e. abnormally elevated threshold) was confirmed in 162 (85.7%) affected ears. A total of 255 patients had documented subjective history of their symptoms in the one month following ITG treatment. Of the 202 patients who experienced a "tipsy disquilibrium" reaction, 181 (89.6%) had a successful treatment response of >6 months of adequate vertigo control, and 21 (10.4%) failed. Onset of this reaction varied from days (50.4%) to weeks (39.7%).

Of the 255 patients included in this study, 226 (88.6%) were deemed to be treatment successes (e.g. >6 months of vertigo control) and did not relapse within the observation time window of this study, while 29 (11.4%) were considered treatment failures, and 121 (47.4%) relapsed after an initially successful response. Among the 226 successfully treated patients, 141 (62.4%) required only one injection to achieve vertigo control, 63 (27.9%) required two injections, and 22 (9.7%) required between 3–7 injections (two patients required 5 injections and one patient required 7 injections). Of the 121 patients who eventually relapsed, 38 (31.4%) relapsed in one year, 38 (31.4%) relapsed between one and two years, and 45 (37.2%) relapsed after two years. Among relapsed patients, 100 patients (82.6%) elected to repeat the ITG treatment, with 59 patients achieving successful treatment (e.g. ≥6 months vertigo control), 16 patients failing retreatment, and 25 patients without adequate follow-up time.

Of our 255 patients, 48 patients (18.8%) ultimately underwent surgical transmastoid labyrinthectomy for control of their vertigo attacks after relapse and/or failure of ITG treatments. Twenty-six (10.2%) patients complained of persistent disequilibrium or oscillopsia requiring vestibular physical therapy or chronic and regular use of benzodiazepine central vestibular suppressants.

HTT Outcomes

Baseline Data Analysis

A total of 148 subjects had documented pre-treatment negative HTT. Following ITG treatment, 103 subjects (69.6%) converted to positive HTT (i.e. converted HTT), indicating vestibular hypofunction, while 45 subjects (30.4%) remained negative (i.e. non-converted HTT). Of the 148 subjects, 83 (56.1%) were males with a mean age of 57.3 ± 10.4 yrs old. The mean duration of symptoms is 6.8 ± 7.1 yrs. Disease laterality occurred slightly more frequently on the right side (52 vs. 48%). The mean age of the converted HTT and non-converted HTT groups were 59.0 ± 9.9 yrs and 53.5 ± 10.8 yrs, respectively. See **Table 2** for details.

Clinical Treatment Data Analysis

After adjusting for baseline data, including gender, age, laterality, and number of treatments, a logistic regression was used to compare the converted and non-converted HTT groups. Notably, patients who reported experiencing a "tipsy disequilibrium" following drug administration were more likely to convert to positive HTT (*beta* = 1.851, OR 6.363 [95% CI: 1.615–25.080], $p = 0.008$).

There were no significant differences between the groups in drop attacks or conventional MD vertigo attacks ($p > 0.05$). See **Table 3** for details.

Comparison of Time-to-Relapse

Survival curve of time-to-relapse (TTR) in the 148 patients with initial negative pre-treatment HTT and a recorded post-treatment HTT result was used to compare those with a converted HTT vs. non-converted HTT after ITG treatment (see **Figure 2**). Patients were included in this analysis regardless of whether treatment was successful or not, as long as the pre-treatment HTT was negative and the post-treatment HTT was available. By definition, all patients who "relapsed" in less than 6 months were treatment failures and those relapsing after 6 months were initially scored as treatment success. The survival curves of the two groups were significantly different ($p = 0.009$). The mean TTR of the converted and non-converted HTT groups was 49.7 (95% CI: 39.0–60.5) months vs. 27.0 (95% CI: 18.4–33.6) months, respectively. The median TTR of the converted and non-converted HTT groups was 34 (95% CI: 15.7–52.3) months vs. 15 (95% CI: 7.884–22.116) months, respectively. After adjusting for baseline characteristics, such as gender, age, laterality, duration of symptoms, and number of ITG treatments, the TTR of the converted HTT group was still significantly longer than that of the non-converted group (HR 2.047 [95% CI: 1.277–3.283]).

Indicators of Drug Effect

After adjusting for baseline characteristics, logistic regression was used to compare the subjective drug effect of post-treatment disequilibrium reaction and objective drug effect of hearing decline (threshold elevation and/or decreased word recognition

TABLE 2 | Baseline characteristics and head thrust response (%) of patients with negative HTT pretreatment.

Variable		Total (%)	Post-ITG HTT (+) $n = 103$ (%)	Post-ITG HTT (–) $n = 45$ (%)	Chi-Square	*p-value*
Gender	Male	83 (56.1)	57 (55.3)	26 (57.8)	$\chi^2 = 0.076$	0.783
	Female	65 (43.9)	46 (44.7)	19 (44.7)		
Side	Left	71 (48.0)	55 (53.4)	16 (35.6)	$\chi^2 = 3.995$	0.046
	Right	77 (52.0)	48 (46.6)	29 (64.4)		
Number of Treatments	Once	103 (69.6)	74 (71.8)	29 (64.4)	$\chi^2 = 0.810$	0.368
	> Once	45 (30.4)	29 (28.2)	16 (35.6)		
Age (yrs ± SD)		57.32 ± 10.46	58.98 ± 9.92	53.53 ± 10.78	t = 2.993	0.003
Duration of symptoms (yrs ± SD)		6.76 ± 7.09	6.87 ± 7.08	6.50 ± 7.18	z = −0.330	0.741

TABLE 3 | Comparison of treatment response in patients who did and did not convert to head thrust (+) after ITG. (%)*.

Variable		Post-ITG Head Thrust		*B*	*P*	*Exp(B) 95% CI*
		(+)	(–)			
Treatment reaction	Yes	93 (95.9)	29 (78.4)	1.851	0.008	6.363 (1.615,25.080)
	No	4 (4.1)	8 (21.6)			
Drop attack control	Yes	24 (58.5)	8 (47.1)	−0.532	0.483	0.588 (0.133,2.598)
	No	17 (41.5)	9 (52.9)			
Effect	Yes	92 (89.3)	43 (95.6)	−19.171	0.996	–
	No	11 (10.7)	2 (4.4)			

**Logistic regression analysis was used to adjust baseline data such as gender, age, laterality, duration of symptoms, and number of treatments. Treatment reaction refers to the experience of "tipsy disequilibrium" of post injection deafferentation. Effect refers to whether the symptoms of vertigo were adequately controlled.*

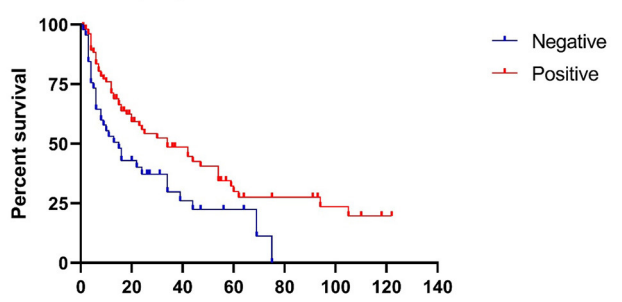

FIGURE 2 | Survival proportions: Survival of ITG treatment patients with different head thrust test results.

score) between the converted vs. non-converted HTT groups. There were no significant differences ($p > 0.05$) between the two groups. See **Table 4** for details.

DISCUSSION

This study had two primary aims: (1) to characterize the audiologic and vestibular outcomes after ITG treatment in individuals with unilateral MD and (2) to study the value of HTT in predicting durability of ITG treatment benefit. Following drug administration, treatment success, failure, and relapse occurred in 41.2%, 11.4%, and 47.4% of patients, respectively. After ITG treatment, about one-quarter of patients developed worsened hearing. Of the patients who had documented pre-treatment negative HTT, 69.6% converted to positive HTT after treatment. Notably, the mean time-to-relapse in the converted HTT group was significantly greater than that of the non-converted HTT group. These results suggest that an abnormal post-treatment result on HTT may predict a longer-lasting treatment effect. This finding did not change even after statistical adjustments were made to account for differences in age and the number of ITG treatments. The converted and non-converted HTT groups did not differ significantly in other audiometric or vestibular (number of vertigo episodes or drop attacks) metrics nor on subjective symptoms such as persistent disequilibrium.

Although Schuknecht et al. reported use of intratympanic aminoglycosides for MD in the 1950s (13), this form of therapy did not gain widespread popularity until the past several decades. Gentamicin is an aminoglycoside antibiotic that has both vestibulotoxic and cochleotoxic effects, specifically targeting the sensory cells of the vestibular apparatus and the hair cells in the cochlea, with a stronger predilection for the vestibular system (14). Current clinical practice guidelines suggest that intratympanic gentamicin be offered to patients with MD who do not respond to more conservative measures, such as trigger management and diuretics (1). There have been two double-blinded randomized control trials investigating the effect of ITG on vertigo control (15, 16). Both studies reported a significant reduction in vertigo complaints, with an average increase in hearing loss of 18.1 dB HL following ITG. As in prior studies, we found a significant reduction in vertigo symptoms following ITG, with a mean threshold shift of +18.6 dB HL in the 25% of ITG-treated ears who suffered hearing loss.

TABLE 4 | Comparison of side effects between the positive and negative groups of the post-ITG treatment HTT (%)*.

Variable		Positive HTT	Negative HTT	*B*	*p-value*	*Exp(B)* 95% *CI*
Post-ITG Disequilibrium	Yes	8 (7.8)	5 (11.1)	−0.658	0.317	1.930 (0.532–6.996)
	No	95 (92.2)	40(88.9)			
PTA Worse	Yes	29 (42.0)	14 (60.9)	−0.108	0.853	0.898 (0.285–2.826)
	No	21 (58.0)	9(39.1)			
WRS Decrease	Yes	31 (62.0)	14 (60.9)	0.229	0.698	1.257 (0.395–4.001)
	No	19 (38.0)	9 (39.1)			

**Logistic regression analysis was used to adjust baseline data such as gender, age, side, duration of symptoms, and number of treatments.*

The head thrust test (HTT) is a widely accepted clinical test that may be used to assess the angular vestibulo-ocular reflex (VOR). In this study, the HTT was used to evaluate the function of the horizontal semicircular canal, as described by Halmagyi and Curthoys in 1998 (17). In individuals with normal horizontal semicircular canal function, abrupt rotation of the head toward the unaffected side has no effect on gaze targeting. However, when there is hypofunction of the horizontal semicircular canal, abrupt rotation toward the affected side will cause the gaze to deviate off target in the same direction as the head movement followed by a corrective saccade to re-establish gaze fixation. For patients with complete unilateral vestibular hypofunction, the sensitivity and specificity of HTT is 100% (18). However, in patients with non-surgically-induced unilateral vestibular hypofunction, such as may occur in cases of vestibular neuritis or following administration of vestibulotoxic medications (e.g. gentamicin), the sensitivity and specificity is estimated to be around 34–39% and 95–100%, respectively (19, 20).

Prior studies have attempted to determine whether vestibular function testing can predict the outcome of ITG treatment. Indeed, greater vestibular dysfunction has been found to correlate with better long-term vertigo control (21, 22). In a study of 20 patients with unilateral MD, Martin-Sanz et al. sought to determine whether changes in the VOR gain after ITG could be correlated with vertigo control (23). The authors found a significant correlation between the 1-month post-treatment VOR gain and the rate of vertigo recurrence after the first ITG treatment. A prospective cohort study of 25 patients with MD with VEMP and caloric testing pre- and post-treatment with ITG showed that absent VEMPs and caloric responses after treatment were correlated with significant symptom improvement at 6-month follow up (24).

Although routine use of formal vestibular function testing for patients with MD is not required, these tests may provide complementary information to help lateralize MD and assess the vestibular system prior to, during, and after ablative procedures. However, not all clinics have the access nor resources to provide vestibular function testing for patients and moreover, patients may refuse to undergo testing due to cost, time considerations, or discomfort. By contrast, the HTT is a simple clinical test that requires no specialized equipment. In our study, we found that the development of a positive (abnormal) HTT response after ITG was correlated with a significantly longer median time-to-relapse (34 vs. 15 months).

The mechanism of relapse after ITG treatment or "gentamicin resistance" is not known. Some authors have suggested that variability in the permeability of the round window or the presence of a pseudo-membrane over the round window may account for cases of relapse or failure (25, 26). Several animal studies have demonstrated that vestibular hair cells may regenerate after injury or damage, but it is unknown whether this regenerative process would lead to functional recovery in humans. Successful ITG treatment causes significant reduction of peripheral vestibular function in the treated ear and effectively mitigates Meniere vertigo attacks in the majority of cases. Recovery from the acute effects of this peripheral vestibular hypofunction depend upon central vestibular compensation, which in turn depends in part upon integrity of vestibular function in the contralateral ear. Since no less than 25–30% of patients with unilateral MD are expected to eventually develop involvement of the second ear, it is possible that the asymptomatic ear may already be slightly affected. If so, ITG treatment could result in bilateral hypofunction, a much more debilitating condition. Pre-treatment vestibular testing can help spot such cases and at least with cVEMP, can offer some predictive information (but not certainty) about future involvement of the second ear. Informed consent discussion with each patient includes this information. However, it is the disabling vertigo or drop attacks from the currently active ear that impacts each patient's quality of life and justifies ITG treatment. Rarely do considerations of hypothetical future problems alter treatment recommendations for current and actual symptoms.

Limitations of this study include the retrospective study design, the subjectivity of the HTT test, and the lack of complete pre- and post-treatment vestibular function testing in this patient population. Of note, all HTT tests were performed by a single, senior physician with expertise in vestibular disorders. There may have been some inter-subject variability as quantitative data was not obtained from the HTT. A formal video head impulse test (vHIT) (25), which is a well-validated clinical measure of the vestibulo-ocular reflex, was not performed. However, the vHIT machine is not easily accessible in all clinics, whereas the HTT, which can be performed in the clinical setting without specialized equipment, has tremendous utility, particularly in resource-limited settings.

ITG treatment is effective in reducing the number of vertigo episodes and drop attacks in MD. HTT is a valuable clinical tool that is predictive of the durability of the ITG treatment benefit.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Partners Healthcare IRB Protocol# 2019P003735. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YG, DC, Y-HL, and SR contributed to study design, data analysis and interpretation, and writing of the manuscript. YG collected all the study data and created the figures and data tables. All authors contributed to the article and approved the submitted version.

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A Historical Perspective on Surgical Manipulation of the Membranous Labyrinth for Treatment of Meniere's Disease

*Calvin J. Kersbergen and Bryan K. Ward**

Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, United States

Meniere's disease is an inner ear disorder without a known cause. Endolymphatic hydrops is a swelling of the endolymph spaces that has been observed consistently on post-mortem histology in patients with a history of Meniere's disease but can occur in asymptomatic individuals and in association with other diseases. Since its discovery, Meniere's disease has been a disorder managed primarily by otolaryngologists. Surgical treatments, therefore, have accompanied attempts at medical management. Inspired by patients' sensations of ear fullness and later by the histologic findings of hydrops, surgeons began manipulating the membranous labyrinth to relieve episodes of vertigo while attempting to preserve hearing. This review highlights this history of manipulation of the membranous labyrinth. These procedures indicate a rich history of innovation that parallels developments in otologic surgery. The studies involving patients are uniformly retrospective, with some procedures performed first in animal models of endolymphatic hydrops. Many approaches were endorsed by eminent otologic surgeons. Surgeries on the endolymphatic sac are performed by some surgeons today; however, procedures on the membranous labyrinth resulted in similar symptomatic relief through a minimally invasive technique, in many cases performed using only local anesthetic. Episodic vertigo in patients with Meniere's disease is a distressing symptom, yet spontaneous remissions are common. The reports of procedures on the membranous labyrinth reviewed here consistently indicated fewer vertigo episodes. Variable degrees of hearing loss were common following these procedures, and many were abandoned. Additional innovative surgeries are inevitable, but we must understand better the relationships among endolymphatic hydrops, Meniere's disease pathophysiology, and patient symptoms.

Keywords: Meniere's disease, hydrops, membranous labyrinth, endolymph, cochleosacculotomy, vertigo, hearing loss

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****Correspondence:***
Bryan K. Ward
bward15@jh.edu

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INTRODUCTION

Meniere's disease is a disorder of the inner ear consisting of intermittent, spontaneous episodes of vertigo in combination with other fluctuating ear symptoms including low-frequency sensorineural hearing loss, aural fullness, and tinnitus. The condition is associated with Prosper Meniere who in 1861 identified the inner ear labyrinth as a likely source for symptoms of a syndrome involving episodic vertigo and hearing loss (1). Meniere's disease has a complex and highly variable natural

course in which spontaneous remission of vestibular symptoms is common and there is slow progression to end-organ damage.

The etiology of Meniere's disease remains unclear. Histopathologic investigation identified a swelling of the membranous labyrinth called endolymphatic hydrops in temporal bone specimens from patients with Meniere's disease (2, 3), leading to the hypothesis that increased fluid volume within the membranous labyrinth triggers the symptoms of vertigo, hearing loss, tinnitus, and aural fullness. The presence of greater endolymph volume has often been interpreted as an imbalance in fluid homeostasis, resulting from either abnormally increased generation of endolymph or impaired absorption. Excess endolymph might lead to mechanical impairment of sensory transduction, or to ruptures of Reissner's membrane or other areas of the membranous labyrinth, subsequently mixing endolymph and perilymph. The severity of hydrops correlates with the duration of disease and severity of both hearing loss and vestibular symptoms (4, 5). Endolymphatic hydrops, however, is observed also in asymptomatic individuals and in individuals with many different disorders, suggesting that while hydrops is associated with Meniere's disease, it may not cause the disorder (5–9).

Since the etiology remains unknown, targeted medical therapies for Meniere's disease are not possible. Treating physicians address symptoms and often suggest lifestyle modifications in attempts to prevent recurrent episodes of vertigo. Today, physicians often prescribe oral diuretics and betahistine, followed by offering steroid perfusion of the middle ear for patients with recurrent episodes of vertigo. If these treatments fail to control the episodic vertigo, otolaryngologists often consider ablative procedures of the inner ear, invoking the logic that the brain can adapt better to constant asymmetry in vestibular neural activity than to fluctuating activity (10).

Meniere's disease is a disorder primarily managed by surgeons (i.e., otolaryngologists) and since its discovery surgical innovation has accompanied attempts at medical management. In the 20th century, pioneering surgeons, inspired by the observations of endolymphatic hydrops as well as patient descriptions of "fullness" and "pressure" within the ear, developed conservative surgical approaches for those patients with persistent, disabling symptoms despite medical therapy. There were two goals for these procedures: (1) preserve hearing function, and (2) improve homeostasis between endolymph and perilymph by reducing the excess volume of endolymph. These novel procedures included decompression or microsurgical manipulation of the endolymphatic sac and membranous labyrinth. This narrative review will encompass several procedures on the membranous labyrinth, comparing historical success rates for the control of vertigo episodes, and providing perspectives on the historical influences of these procedures and the future of surgery on the membranous labyrinth for treatment of Meniere's disease and other conditions of the inner ear.

EARLY APPROACHES TO MANIPULATE ENDOLYMPH IN MENIERE'S DISEASE

In 1871 Knapp comprehensively synthesized the symptoms of patients like those described by Meniere, drawing analogies from Meniere's disease to ocular glaucoma and suggesting surgical relief of pressure could be helpful (11). As early as the 1890s Burnett reasoned that removing the ossicles and tympanic membrane could decompress the labyrinth and provide relief (12, 13). The hearing loss caused by these procedures prompted surgeons to consider new targets to preserve hearing while decreasing the theorized high pressure of the inner ear. The lateral semicircular canal was accessible via the mastoid. Jenkins first decompressed the bony lateral semicircular canal in a patient with active Meniere's disease in 1911, reportedly preserving hearing and vestibular function (14). Similar attempts by Lake to decompress the vestibule, however, often resulted in hearing loss and injury to the facial nerve (15). In the 1920s Portmann, also drawing parallels between Meniere's disease and glaucoma, emphasized decompressing the endolymphatic sac (16). His technique was later expanded by William House and others to inserting materials into the endolymphatic sac to shunt endolymph to the subarachnoid space or mastoid (17). These early surgical attempts to decompress the inner ear gained support by the discovery in 1938 that patients with Meniere's disease had the histologic finding of endolymphatic hydrops. Endolymphatic sac procedures remain in use today by some surgeons, with a success rate for Class A/B vertigo control of 70–80% in retrospective studies across different procedural approaches (18), with a high degree of hearing preservation. Unexpectedly, however, in contrast with both shunting procedures in humans and animal models of hydrops generation (19), procedures that block the endolymphatic duct using titanium clips may also achieve vertigo control in patients with Meniere's disease (20). These contradictory approaches, yet similar clinical observations emphasize our incomplete understanding of physiological endolymph circulation and the role of hydrops in disease (21).

INTRODUCTION OF THE SURGICAL MICROSCOPE AND LEMPERT'S FENESTRATION PROCEDURE

New surgical approaches that manipulated the membranous labyrinth emerged following the adoption by otologic surgeons of the operating microscope and the increased popularity of Lempert's single-stage lateral semicircular canal fenestration procedure for otosclerosis. In 1943 Day attempted to decompress the hydropic membranous labyrinth by inserting a metallic pick through a lateral canal fenestration and into the vestibule. He then cauterized the tissue by running electrical current through the pick (22). Lindsay repeated this approach without cauterization, and reported that patients no longer experienced episodes of vertigo, but uniformly developed hearing loss and sound-induced vertigo (i.e., Tullio phenomenon). He and

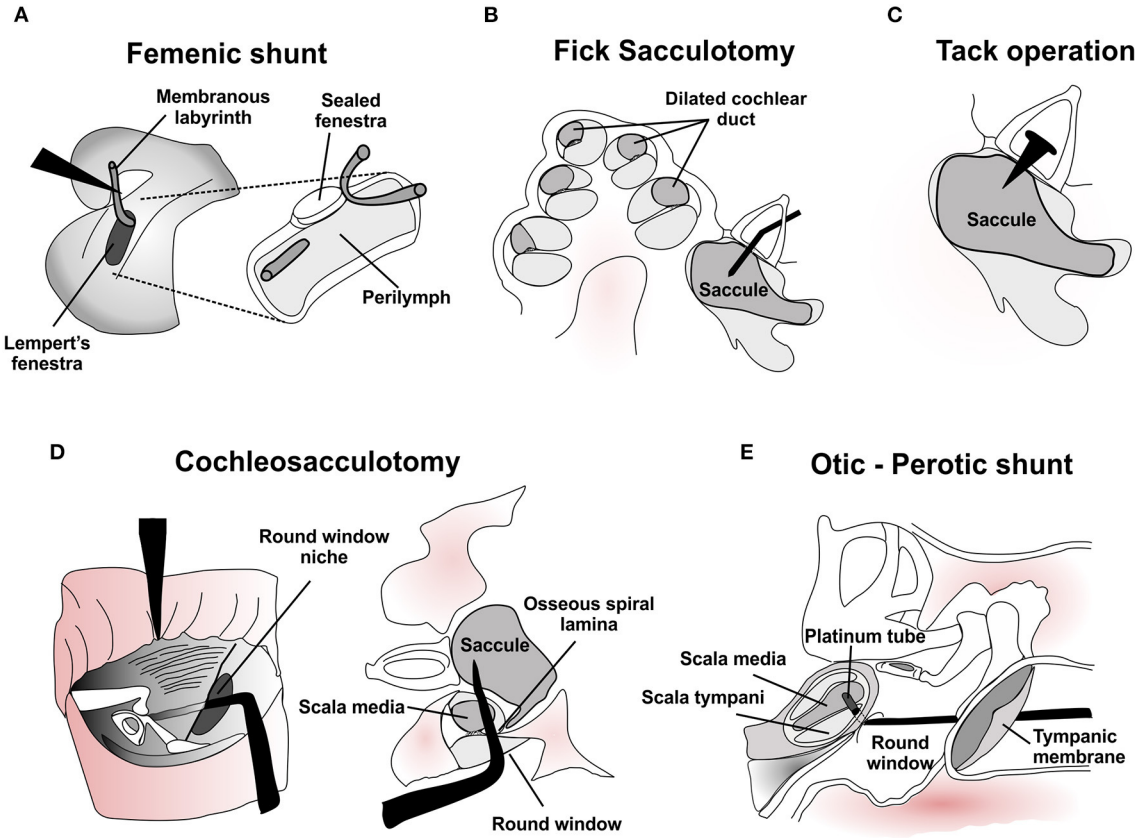

FIGURE 1 | Surgical manipulations of the membranous labyrinth for treatment of Meniere's disease. **(A)** Depiction of Femenic's shunt in the lateral semicircular canal to relieve endolymphatic hydrops and vertigo episodes. Adapted with permission from Femenic (25). **(B)** Histological representation of endolymphatic hydrops in the cochlear duct and saccule, with a Fick sacculotomy needle placed through a fenestration in the stapes to drain excess endolymph. **(C)** Permanent tack placement in the stapes bone was intended to enable repeated decompression of the hydropic saccule in the Cody tack operation. **(D)** Two views of the cochleosacculotomy procedure, where a 90-degree pick is driven through the round window to rupture the cochlear duct and saccule and create a permanent fistula in the osseous spiral lamina. Adapted with permission from Schuknecht (26) and Kinney et al. (27). **(E)** Depiction of the Otic-Perotic shunt procedure, where a platinum tube is placed in the basilar membrane of the basal cochlea to enable decompression of the scala media. Adapted with permission from Pulec (28, 29).

Cawthorne described the Tullio phenomenon that developed in these cases as having been caused by the presence of a "third mobile window" in the inner ear, later associated with the pathophysiology of superior semicircular canal dehiscence syndrome (23, 24). In 1952 Femenic used Lempert's fenestration of the lateral canal to create a permanent drainage of endolymph into the perilymphatic space. Femenic accessed and divided the membranous labyrinth through the fenestration, and then routed the anterior end outside the labyrinth, leaving the posterior end free to communicate with the perilymph (**Figure 1A**). He reports all 4 cases having 'satisfactory' symptom control and preserved cochlear function (**Table 1**) (25).

DECOMPRESSION OF THE SACCULE: FICK'S SACCULOTOMY

The saccule is more commonly affected by endolymphatic hydrops in Meniere's disease than the semicircular canals, and the hydropic saccule can adhere to the stapes footplate (4, 53). As otologic surgeons became comfortable performing stapes surgery in the 1950s and 1960s, the surgical approach to the saccule became feasible. In 1964 Fick proposed a transcanal approach to generate a conduit in the saccule to relieve excess endolymph (30). He inserted a fine needle through a fenestration made in the stapes footplate to puncture the dilated hydropic saccule (**Figure 1B**). Fick reports that rupture of the saccule resulted in immediate decreases in the sensation of aural fullness, but often elicited vertigo and temporary hearing loss lasting up to one week. Early reports of long-term results following the sacculotomy seemed promising. In 60 patients with several years of follow-up, Fick reported a high rate of relief from vertigo, improvements in hearing, and reductions in tinnitus and aural fullness, although nearly a quarter of patients were lost to follow up (**Table 1**) (30, 31). Subsequent reports, however, noted more modest improvements in vertigo, high rates of worsened hearing and cases in which symptoms later recurred (32–35, 37). Notably, sacculotomy procedures in animal models

TABLE 1 | Historical and present outcomes of surgical procedures on the membranous labyrinth for control of vertigo and other symptoms in Meniere's disease.

Procedure	Patient population	Follow-up duration	Vertigo improvement	Aural fullness improvement	Tinnitus improvement	Hearing function	Surgical complications	References
Femenic shunt	NR	NR	4/4 (100%)	NR	4/4 (100%)	Air conduction >30 dB HL, bone conduction 10 dB HL with intact ossicular chain.	NR	Femenic (25)
Fick Sacculotomy	No prior improvement with medical treatments. Symptoms of vertigo, HL, tinnitus, aural fullness.	> 1 year for 90% of cases. 19/79 (24%) lost to follow-up.	55/60 (92%)	49/51 (96%)	49/59 (83%)	39/60 (65%) improved hearing, 3/60 (5%) HL.	Mild vertigo and unsteadiness, immediate hearing deterioration before improvement. 1/60 (1.7%) developed labyrinthitis.	Fick (30, 31)
Fick Sacculotomy	4/4 (100%) had > 65 dB HL, >3 years vertigo.	1-5 months.	4/4 (100%)	NR	1/2 (50%)	4/4 (100%) complete HL.	No postoperative complications.	Proud (32)
Fick Sacculotomy	NR	NR	6/6 (100%)	NR	NR	6/6 (100%) severe HL 10-12 h post-op.	NR	Arslan (33)
Fick Sacculotomy	NR	NR	2/5 (40%)	NR	NR	4/5 (80%) HL, 1/5 (20%) unchanged.	3/5 (60%) required labyrinthectomy to control vertigo.	Ariagno (34)
Fick Sacculotomy	NR	1–10 years.	3/4 (75%)	NR	NR	4/4 (100%) complete HL after operation.	1/4 (25%) had recovery then return of vertigo, underwent labyrinthectomy.	Pavla et al. (35)
Fick Sacculotomy	Middle-aged MD diagnosis.	Mean 17 years.	14/17 (82%) (Class A–C)	NR	NR	HL > 15 dB in 11/17 (64%), 3/17 (18%) had complete HL. 2/17 (12%) had hearing gain >15 dB.	3/17 (18 %) labyrinthectomy due to incomplete vertigo control.	Weilinga and Smyth (36)
Cody Tack procedure	Mean age 50, 52% female. Symptom duration 8 months−7 years.	33% 6–24 months, 67% > 12 months.	38/42 (91%) with > 75% improvement in vertigo frequency.	29/35 (82%)	19/41 (46%)	6/42 (14%) experienced > 20 dB HL, 7/42 (17%) experienced >20 dB hearing improvement. Traumatic cases associated with HL.	2/42 (5%) experienced recurrent vertigo following improvement. Mild postural unsteadiness post-op was common.	Cody et al. (37)
Cody Tack procedure	Unilateral MD	3–6 months.	16/20 (80%)	15/20 (75%)	10/20 (50%), worsened in 2/20 (10%).	2/20 (10%) improved hearing, 7/20 (35%) worsened, 4/20 (20%) complete HL.	3/20 (15%) underwent labyrinthectomy. One experienced large crack in stapes footplate with perilymph leak and hearing loss.	Shea and Cottrell (38)
Cody Tack procedure	67/91 (74%) had > 1 vertigo attack per week, 75/91 (82%) had > 50 dB HL.	1–44 months.	85/91 (93%) with >75% reduction, 64/91 (70%) had no vertigo.	NR	NR	11/91 (12%) experienced air conduction loss >20 dB.	5/91 (5%) patients had improved vertigo after revisional operation. 6/91 (7%) severe vertigo returned after initial recovery.	Cody (39)
Cody Tack procedure	NR	> 6 months.	23/45 (51%)	NR	NR	6/45 (13%) with hearing improvement, 20/45 (44%) with HL.	12/45 (27%) underwent labyrinthectomy.	Pulec (28)

(Continued)

TABLE 1 | Continued

Procedure	Patient population	Follow-up duration	Vertigo improvement	Aural fullness improvement	Tinnitus improvement	Hearing function	Surgical complications	References
Cody Tack procedure	Unilateral MD, unresponsive to medical treatment, severe symptoms (>1 disabling attack/week), desire to avoid labyrinthectomy.	1–3 years.	12/13 (92%) experienced improvement >75%.	9/13 (69%)	8/13 (62%)	3/13 (23%) had >20 dB PTA decrease, 6/13 (46%) had >20 dB SRT decrease. 0/13 (0%) had improvement.	1/13 (8%) underwent labyrinthectomy.	Burgert et al. (40)
Cody Tack procedure	Mean 45 years old. Unsuccessful prior drug therapy.	NR	7/25 (28%) improvement, 17/25 (68%) experienced no change.	NR	NR	17/25 (68%) worsened hearing (> 10 dB), 2/25 (8%) had >10 dB gain.	12/25 (48%) underwent labyrinthectomy.	Jennings et al. (41)
Cody Tack procedure	Middle-aged.	Mean 12 years.	17/19 (89%)	NR	NR	10/19 (53%) had >15 dB HL, 3/19 (16%) experienced complete HL.	1/19 (5%) had cracked footplate with perilymph leak. 2/19 (11%) underwent subsequent labyrinthectomy.	Weilinga and Smyth (36)
Cochleo-sacculotomy	Patients selected for severity: 1–10 vertigo attacks per month.	1–24 months.	45/51 (88%). Three revision procedures included as improvement.	NR	NR	12/51 (23%) had >20 dB PTA loss, 35/51 (68%) had > 20 dB loss at 8 kHz.	1/51 (2%) postoperative otitis media. 6/51 (12%) had vertigo recurrence after improvement.	Schuknecht (26)
Cochleo-sacculotomy	NR	Mean 6 months.	9/14 (64%) fully relieved, 3/14 (21%) improved.	NR	NR	11/14 (79%) experienced severe HL (> 15 dB PTA) in weeks after procedure. 7/14 (50%) experienced HL at 6 months.	8/14 (57%) patients experienced acute unsteadiness. 6/14 (43%) showed unilateral decrease in vestibular function.	Silverstein et al. (42)
Cochleo-sacculotomy	Unilateral MD, > 50 dB HL, unsuccessful medical treatment.	> 12 months.	9/9 (100%)	NR	0/9 (0%)	6/9 (67%) severe HL. 3/9 (33%) low frequency hearing improvement but high frequency HL.	1/9 (11%) experienced positional vertigo post-operatively for 2 weeks.	Dionne (43)
Cochleo-sacculotomy	NR	2–3 years.	19/23 (83%) permanently relieved (3/23 (13%) after repeat procedure.)	NR	NR	2/23 (9%) experienced complete HL	Sense of disequilibrium or giddiness in first postoperative week. 2/23 (9%) underwent labyrinthectomy.	Montandon et al. (44)
Cochleo-sacculotomy	Average age 54 years, unsuccessful prior drug therapy.	NR	14/21 (67%)	NR	NR	10/21 (48%) had >10 dB HL, 5/21 (24%) had complete HL.	3/21 (14%) required a second procedure to control vertigo	Jennings et al. (41)
Cochleo-sacculotomy	Mean age 72.8 years.	6–38 months (mean 17.4).	2/11 (18%) fully relieved, 5/11 (45%) improved. Total 7/11 (64%)	NR	NR	Statistically significant decrease in PTA, SRT, SD among cohort.	4/11 (36%) required second procedure for vertigo control. All patients tolerated procedure well.	Giddings et al. (45)

(Continued)

TABLE 1 | Continued

Procedure	Patient population	Follow-up duration	Vertigo improvement	Aural fullness improvement	Tinnitus improvement	Hearing function	Surgical complications	References
Cochleo-sacculotomy	Mean age 40 years, 48% female, all non-smokers. 9/23 (39%) severe HL, 14/23 (61%) profound HL	NR	22/23 (96%)	NR	No change in tinnitus—0/15 (0%)	No hearing recovery, 9/23 (39%) worsening to profound HL.	NR	Sohielipour et al. (46)
Otic-perotic shunt	MD patients with poor baseline hearing.	NR	16/21 (76%)	NR	NR	5/21 (24%) had significant HL, 2/21 (10%) experienced complete HL.	Mild acute unsteadiness following procedure. 4/21 (19%) required labyrinthectomy.	Pulec (28, 29)
Cryosurgical otic-perotic shunt	Medical treatment ineffective, >40 dB HL at baseline.	6 months −1 year. 11/80 (14%) lost to follow-up.	48/69 (70%) with no HL > 20 dB and relieved of vertigo	NR	"Relieved or improved in about half"	3/69 (4%) had HL > 20 dB, may have been associated with perilymph leak.	8/69 (10%) had temporary facial paralysis during cooling. 7/69 (9%) had tympanic membrane perforation.	House (47)
Intracochlear shunt	NR	NR	9/9 (100%)	9/9 (100%)	9/9 (100%)	8/9 (89%) returned to baseline hearing level, 1/9 (11%) complete HL.	NR	Shea (48)
Lateral canal plugging	MD with functional scales 5 or 6 (severe disability), mean age 48 years (range 22–75) 1.2:1 M:F.	16/28 (57%) > 2 years, 12/28 (43%) > 6 months.	25/28 (89%) for 6 months, 12/16 (75%) Class A or B at 2 years	NR	NR	5/28 (18%) postoperative deafness	3/28 (11%) underwent ablative procedure. 2/28 (7%) unilateral labyrinthitis.	Charpiot et al. (49)
Triple canal plugging	Unilateral MD, previously treated with sac decompression or shunt, ages 46-55.	2–5 years follow-up.	3/3 (100%) two Class A, one Class B.	3/3 (100%)	3/3 (100%)	3/3 (100%) had no changes > 10 dB.	Dizziness and slight vertigo up to 3 days after procedure.	Yin et al. (50)
Triple canal plugging	37 male, 42 Female, ages 29–68 (mean 52).	> 2 years.	78/79 (98.7%) Class A or B.	NR	NR	23/79 (29%) had > 10 dB HL.	NR	Zhang et al. (51)
Triple canal plugging	Severely symptomatic despite medical treatment, ages 45–61, two male, one female.	> 2 years.	3/3 (100%) two Class A, one Class B.	NR	NR	1/3 (33%) > 30 db HL, 2/3 (67%) no change.	NR	Gill et al. (52)

NR, not reported; HL, hearing loss; MD, Meniere's disease; PTA, pure tone audiogram; SRT, speech recognition threshold; SD, speech discrimination.

of endolymphatic hydrops failed to improve hydrops, and significant atrophy of cochlear sensory, neural, and supporting cells was present, observations that could underlie the hearing loss reported by many patients (54). In a long-term follow-up study of patients undergoing Fick's sacculotomy, >80% retained adequate control of vertigo episodes, but 64% had hearing worsened from baseline (36). The location of the membranous wall of the saccule could not have been known during the surgery, and variability in the degree of saccular distension could account for some variability in surgical outcomes (47, 54). Together, publications suggested that the Fick sacculotomy provided relief from episodes of vertigo, but that relief could be temporary, was often accompanied by substantial hearing loss, and sometimes required repeat procedures or a subsequent ablative surgery to control vertigo. Nevertheless, Fick's procedure inspired many similar innovations.

REPEATED AND PERMANENT FISTULA THROUGH THE CODY TACK PROCEDURE AND COCHLEOSACCULOTOMY

A hypothesis for the incomplete long-term benefit following sacculotomy was that the membranous labyrinth of the saccule would heal, or the stapes fenestra would close, potentially resulting in recurrent endolymphatic hydrops and recurrent symptoms of Meniere's disease. Therefore, several procedures were developed with the goals of providing a permanent fistula for endolymph clearance and sustained prevention of vertigo.

In one procedure Cody and colleagues placed a sharp tack through the stapes footplate and directed it toward the saccule (37, 39). Like the Fick sacculotomy, a distended saccule at time of operation should rupture by placing the tack (**Figure 1C**). Cody hypothesized that by leaving the tack in place, the saccule would leak endolymph repeatedly whenever excess volume accumulated, theoretically providing sustained relief of symptoms. Early results in 42 patients revealed that in the weeks following placement of the tack patients experienced improved aural fullness and fewer vertigo episodes, but variable effects on hearing and tinnitus (**Table 1**) (37). Vestibular function—presumably assessed by caloric testing—was unchanged or improved in 39 of 40 patients. The authors deduced that vertigo relief was therefore not due to ablation of vestibular function. A subsequent study with 49 additional patients and longer follow-up (54), as well as reports from other surgeons (38, 40), suggested that more experience with the procedure was associated with better auditory outcomes. The incidence of hearing loss after the operation, however, remained high (41). Long-term outcomes of the Cody tack procedure were excellent with respect to control of vertigo episodes, with 89% satisfied enough with vertigo control to avoid subsequent labyrinthectomy (36). Shorter tack length was associated with recurrent vertigo episodes, supporting the authors' hypothesis for how the tack might work (39). Other groups reported poorer outcomes for control of vertigo episodes, with more patients subsequently pursuing labyrinthectomy (41). In a long-term follow-up study that compared the tack procedure to Fick's sacculotomy, a greater proportion of patients that underwent the tack procedure maintained good hearing [47% class A or B by American Academy of Ophthalmology and Otolaryngology classification vs. 18%, (36)]. A hypothesis for this difference is not mentioned by the authors.

Schuknecht promoted an alternative approach to maintain decompression of the hydropic ear that he called cochleosacculotomy (26). A right-angled pick is inserted through the round window and advanced to fracture the basal osseous spiral lamina to form a fistula, followed by rupture of both the cochlear duct and a dilated saccule (**Figure 1D**). The goal was to create a permanent fistula between perilymph and endolymph compartments. Animal studies suggested that surgically creating a fistula through the basal osseous spiral lamina caused degeneration of cells near the surgery and impaired auditory responses for high frequency sound. Auditory responses to frequencies distal to the lesion site, however, remained unaffected (55, 56). Histological analysis revealed that about half of the animals retained a fistula. In the initial characterization of patients with Meniere's disease who underwent cochleosacculotomy, success rates were high for control of vertigo episodes (**Table 1**), but some experienced recurrent vertigo episodes, and many lost hearing (26).

Later studies of cochleosacculotomy performed by other surgeons and across different patient age groups revealed largely consistent success rates for the control of vertigo episodes (**Table 1**). Severe sensorineural hearing loss was common in the first weeks after surgery, and while modest recovery in hearing was observed with longer follow-up, impaired hearing often persisted more than one year after the procedure (27, 41–43, 46). Unlike the findings in animals, however, hearing loss was not limited to frequencies sensed near the lesion, suggesting that injury to the cochlea in patients was more diffuse than originally anticipated (27). In addition, half of patients had general unsteadiness and vestibular impairment one-month after surgery (42). While the surgery was extremely well-tolerated by elderly individuals, long-term relief from vertigo episodes was poorer than expected in older patients, and hearing loss was experienced at a greater rate (45). In a comparative translational study, cochleosacculotomy failed to resolve endolymphatic hydrops or create a permanent fistula in an animal model of endolymphatic hydrops despite the improvement of symptoms reported by the cohort of patients. The authors suggested that successful outcomes in patients following surgical procedures on the labyrinth may be due to non-specific reactive changes in the ear with endolymphatic hydrops (44) or by "mini-labyrinthectomy" causing impaired vestibular function that had been observed in some, but not all, patients (42, 43).

SHUNTS WITHIN THE COCHLEA: INTRACOCHLEAR SHUNT AND OTIC-PEROTIC SHUNT

Also intending to create a permanent connection between endolymph and perilymph, John Shea, Jr. developed the intracochlear shunt procedure for Meniere's disease in the 1980s (48, 57). Shea had initially proposed a procedure called sacculocentesis, in which the stapes footplate is removed, and

a micropipette is used to extract endolymph from the saccule, without mixing endolymph and perilymph. Most patients (87%) experienced relief from vertigo episodes, but hearing worsened in one-third of patients after 2 years follow up, and he abandoned the procedure (48). In the intracochlear shunt procedure, Shea created a hole in the cochlea between the oval and round windows, opening into the scala tympani. Using a pick, a puncture was then made in the basilar membrane allowing endolymph of the scala media to communicate with perilymph of the scala tympani. According to Shea, patients undergoing this procedure experienced immediate unsteadiness and decreased hearing but reported improved aural fullness and tinnitus as well as relief from episodic vertigo. The hearing loss improved over time, with 8 of 9 patients returning to baseline hearing (**Table 1**) (48). In an animal model of endolymphatic hydrops, creating a fistula using Shea's intracochlear shunt procedure led to less distention of Reissner's membrane one week after the procedure, with only mild degenerative changes in the adjacent region of the organ of Corti (58). One month after the procedure, however, extensive hydrops was present in all animals along with severe degeneration of the organ of Corti and the macula of the saccule, suggesting that creating a fistula in the basilar membrane between endolymph and perilymph is insufficient to reduce endolymphatic hydrops permanently.

To create a permanent shunt between endolymph and perilymph in the cochlea, Pulec—crediting William House—placed a platinum tube through the basilar membrane at the base of the cochlea using only local anesthesia. The tube was loaded on a right-angle pick, introduced through the round window and left in place. Like prior procedures, the aim was to enable pressure equalization and mixing between the endolymph of the scala media and perilymph of the scala tympani (**Figure 1E**) (28, 29). In another attempt to create an otic-perotic shunt, House placed a cryosurgical probe on thinned bone over the promontory of the cochlea. The goal was to destroy tissue of the membranous labyrinth at the saccule and basal cochlear duct, presumably causing a connection between endolymph and perilymph spaces, but without surgically opening into the perilymph space (47). Like other manipulations of the membranous labyrinth, both mechanical and cryosurgical shunt formation relieved patients of episodic vertigo (**Table 1**). However, a severe hearing loss often accompanied the tube placement in the basilar membrane, and patients undergoing cryosurgery had mixed results and other complications including temporary facial paresis (10%) and tympanic membrane perforations (9%). Given the challenge of blindly implanting a tube into the cochlear duct and the challenges associated with implementing cryosurgery, these procedures were not widely adopted.

SEMICIRCULAR CANAL PLUGGING

More recently, surgeons began opening and plugging the semicircular canals in patients with Meniere's disease, drawing lessons from similar procedures performed for the treatment of superior semicircular canal dehiscence syndrome and refractory benign paroxysmal positional vertigo of the posterior semicircular canal. For these conditions, surgeons occlude a semicircular canal to block aberrant stimulation of that canal, while intending to preserve function of the other inner ear structures. Lateral semicircular canal plugging in patients with Meniere's disease is performed with the goal that targeted ablation of endolymph movement in the lateral canal could address hypothesized intermittent high pressure during hydrops and control symptoms of vertigo. A 2 mm fenestra is opened in the bony canal wall, and a plug composed of fibrinogen glue and temporalis fascia is inserted through the fenestra to compress the membranous labyrinth and prevent endolymph movement (49). Prospective studies suggest that long-term canal paresis controls episodic vertigo (∼75%, **Table 1**) (49). Plugging of all semicircular canals on the affected side has also been performed for patients with Meniere's disease (50–52), achieving similar levels of vertigo control to lateral canal occlusion (**Table 1**). A larger retrospective study comparing occlusion of all three semicircular canals to endolymphatic sac decompression suggested higher rates of vertigo control with canal occlusion, but also greater hearing loss (58).

CONCLUSIONS AND FUTURE CONSIDERATIONS

The history of Meniere's disease is rich with surgical innovation. Aside from the frequent association between patients with symptoms of Meniere's disease and endolymphatic hydrops on histology, however, the etiology remains a mystery, making targeted medical treatments impossible. Furthermore, the role that endolymphatic hydrops plays in the disease is uncertain. Nevertheless, surgeons hypothesized that endolymphatic hydrops causes the symptoms of Meniere's disease and have attempted to intervene on this finding. The history of these surgical interventions has paralleled technological developments within otology. Lateral semicircular canal fenestration, the introduction of the operating microscope, the development of stapes surgery, and now increasing experience with semicircular canal plugging have each influenced procedures that aim to address the finding of endolymphatic hydrops. Whether the procedures improved endolymphatic hydrops was unknown, since historically this could be assessed only by histology on post-mortem specimens. The broad goals of these procedures are eliminating episodic vertigo while preserving hearing. Assessing the success of interventions is difficult due to the natural history of Meniere's disease in which cessation of vertigo episodes over time is common (59–61). While hearing loss remains frequent following these procedures, many individuals who underwent procedures experienced relief from vertigo without hearing loss. While this relief might have occurred despite the intervention, other variables such as technical differences among surgeons and other patient-specific factors like extent of hydrops (54) may underly undesirable complications and variable outcomes. Pulec commented in 1969: "one might speculate that if this operation could be accomplished in a more delicate, precise fashion, the desired results in every case could be obtained" (29).

We continue to learn about operating on the membranous labyrinth, now from surgeries for semicircular canal dehiscence (62) and vestibular implants (63). Inevitably, advances in surgical technology including pre-operative imaging, operative robotics and improved magnification will lead to new surgical approaches on the membranous labyrinth. Hopefully, this also will improve outcomes for patients with inner ear disorders like Meniere's disease. Our field, however, must understand better how endolymphatic hydrops relates to the symptoms of Meniere's disease.

AUTHOR CONTRIBUTIONS

Conceptualization: BW; Investigation: CK and BW; Writing: CK and BW. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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MINI REVIEW
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The Role of Wideband Tympanometry in the Diagnosis of Meniere's Disease

Xiangming Meng, Kangxu Zhu, Jing Yue and Chengzhou Han*

Department of Otolaryngology, Wuxi Huishan District People's Hospital, Wuxi, China

Meniere's disease (MD) is a clinical syndrome characterized by spontaneous recurrent vertigo, usually accompanied by hearing loss, tinnitus, and aural fullness. The cause of MD remains unclear and is generally considered to be associated with endolymphatic hydrops. Studies showed that patients with MD could have eustachian tube dysfunction (ETD). ETD can disrupt the pressure balance between the middle and inner ear and impair the inner ear's function. In recent years, several studies have attempted to identify MD by using wideband tympanometry (WBT). However, there are limited studies in this area. There is no consensus on how to use WBT to diagnose Meniere's disease. Therefore, we endeavored to conduct a narrative review in this aspect based on the latest research findings. Reduction in resonance frequency and absorbance are characteristic of MD and can identify Meniere's disease. The use of an increase in the integrated area of absorbance as an indicator for identifying MD is controversial. WBT seems to be ineffective as a diagnostic tool during the acute episodes of Meniere's disease. Patients with MD may benefit from WBT. WBT has excellent potential for future use in Meniere's disease. However, further large sample sizes, multicenter studies are needed.

Keywords: Meniere's disease, wideband tympanometry, endolymphatic hydrops, inner ear, absorbance, eustachian tube dysfunction

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Kimitaka Kaga,
Tokyo National Hospital (NHO), Japan

Reviewed by:
Maria Francisca Colella-Santos,
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****Correspondence:***
Xiangming Meng
xiangming_meng@hotmail.com
orcid.org/0000-0001-8250-9887

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INTRODUCTION

Meniere's disease (MD) is a clinical syndrome characterized by episodes of recurrent spontaneous vertigo, usually accompanied by fluctuating sensorineural hearing loss, tinnitus, and aural fullness (1). This syndrome was initially described by a French doctor named Prosper Meniere in 1861 (2). The prevalence of MD varies widely worldwide, with estimates ranging from 3.5 per 100,000 to 513 per 100,000 individuals (3). MD seriously affects patients' quality of life and produces substantial direct or indirect health care costs (3). The cause of MD remains unknown, but it is considered a multifactorial disease caused by the interaction of genetic, anatomical, autoimmune, and environmental factors (4). Studies have proved that MD is associated with endolymphatic hydrops (EH), which cause an enlarged endolymphatic space in the inner ear (IE) (1, 5). The presence of EH can be verified non-invasively by intravenous injection of delayed gadolinium-enhanced magnetic resonance imaging of the IE (6). The measurement of intralabyrinthine pressure allows a better understanding of MD (7). Currently, techniques such as vestibular evoked myogenic potentials (VEMP), electrocochleography (ECoG), distortion product otoacoustic emissions (DPOAE), and caloric test have been used to assess the condition of MD (8, 9). A study investigating 18F-FDG cerebral uptake in patients with MD vs. healthy controls found lower cortical activity in areas such as the Heschl's gyrus, the posterior part of the insula, and thalamus in patients with MD compared to normal controls (10). A recent study revealed a significant correlation between

low-, mid-, and high-tone hearing thresholds and the grading of hydrops in the cochlea and vestibule (11). Consequently, fluctuating hearing loss in patients with MD may be associated with EH as well as other factors.

In recent years, the possibility of multifrequency tympanometry (MFT) as a new diagnostic tool for MD has been evaluated. The use of MFT to investigate experimentally induced cricoid ligament alterations in guinea pigs revealed significant 2 kHz tympanic conduction curves, which could imply IE pressure (12). Although some meaningful results have been obtained, diagnostic accuracy remains limited (13). The concept of wideband tympanometry (WBT) was first proposed in the 1980s (14). Keefe et al. developed a test method for WBT and obtained data for clinical measurements (15). WBT can provide more sensitive and specific results for middle ear (ME) pathologies such as secretory otitis media, otosclerosis, and ossicular chain disruption, thus helping clinicians differentiate diagnoses (16–18). Changes in IE compartment pressure can induce symptoms in some IE diseases, and WBT has been found to be helpful in the pathological diagnosis of elevated intracranial pressure and IE pressure (8). MD can also cause changes in ME conduction (19). Therefore, several researchers have recently attempted to identify MD by using WBT. However, research is scarce in this field, which is still poorly understood. There is no agreement on how WBT should be used to diagnose MD.

To further the understanding of WBT for diagnosing MD, we have endeavored to produce a narrative review based on the most recent research findings. We searched a variety of literature databases, including PubMed, Scopus, Web of Science, Embase, and Cochrane, using variations of the descriptors WBT, MD, and EH. The inclusion criteria were literature on the use of WBT for identifying MD, which was published in English or Chinese. Non-relevant topic studies, non-English or non-Chinese language articles were excluded. Ultimately, 7 studies met the criteria for inclusion. In this mini-review, we will highlight the role of WBT in the diagnosis of MD.

SUBSECTIONS RELEVANT FOR THE SUBJECT

Properties and Advantages of Wideband Tympanometry

Traditional tympanometry assesses the impedance of the ME at a frequency of 226 Hz. Still, this traditional measurement method yields different results depending on the anatomical characteristics of the ME cavity, which may influence the test results (20). WBT employs 1/24-octave frequency intervals ranging from 226 to 8,000 Hz, delivered into the ear canal by a descending pressure sweep between + 250 to −350 dPa (4). Therefore, WBT is less vulnerable to myogenic noise from the patient movement since the transient stimulus involves multiple frequencies (20). As a result, WBT provides a more trustworthy diagnostic value than traditional tympanometry.

In a WBT test, a microphone-generated sound signal is sent through the external ear canal to the ME, where a portion of it is absorbed, referred to as absorbed sound energy; the remaining portion is reflected by the tympanic membrane, which is referred to as reflected sound energy. The microphone can collect reflected sound energy in the external ear canal, and the absorbed sound energy can be exhibited indirectly via reflected sound energy. The ratio of absorbed sound energy to total sound energy is known as absorbance. The following formula calculates the absorbance. Absorbance (energy) = absorbed power/incident power = 1 – energy reflectance (4). The detection of sounds at different frequencies of WBT can be affected by various ME pathologies, and EA values can reflect abnormalities in the external ear canal and ME (14). Results of WBT measurements are displayed in a three-dimensional figure with simultaneous display of data such as absorbance, frequency, and pressure (**Figure 1**). Various forms of information, such as absorbance, tympanometric peak pressure, and traditional tympanometry, are also available in a single recording. Therefore, WBT addresses a number of the drawbacks and limitations associated with traditional tympanometry.

Relationship Between Meniere's Disease and Eustachian Tube Dysfunction

There may be a link between MD and eustachian tube dysfunction (ETD). The eustachian tube is a natural pressure regulating system that balances the pressure in the ME to the external pressure. It plays a vital role in the ventilation and drainage of the tympanic cavity and the mastoid air cell system. ETD can disrupt the pressure balance between the ME and the IE, impairing the function of the IE (21, 22). The partial pressure of oxygen in the ME is low, significantly lower than the atmospheric partial pressure (23). The oxygen used in the IE is derived in part from the oxygen supply from the ME. Hypoxia may exist in the hydropic IE (23). In a hypoxic state, the pressure of the lymphatic fluid in the IE increases, further aggravating the existing EH and worsening the condition (24). Thus, inserting a ventilation tube (VT) can increase the oxygen supply to the ME and IE, thereby alleviating MD symptoms.

Patients with MD may be associated with ETD. According to a study by Kitajima et al., ∼25% of patients with MD exhibit ETD (21). However, this opinion is highly controversial. It is uncommon to observe adult MD patients with secretory otitis media related to ETD; therefore, the 25% prevalence rate may be exaggerated. Brattmo et al. discovered a significant resistance to opening the eustachian tube in three out of four different provocation tests in their investigation of ME pressure in subjects with MD (19). Park et al. used direct sonotubometric measures to assess the eustachian tube function of MD patients and discovered that these patients showed mild ETD (25). Additionally, the severity of MD is associated with the occurrence of ETD; the more severe the stage, the higher the incidence (21).

VT can affect the pressure mechanism in the IE through the round window membrane. Several studies have demonstrated that inserting a VT is beneficial in treating some patients who have MD. According to a prospective, randomized study, patients with MD who underwent endolymphatic sac shunts and patients who received VT inserted into the tympanic membrane had

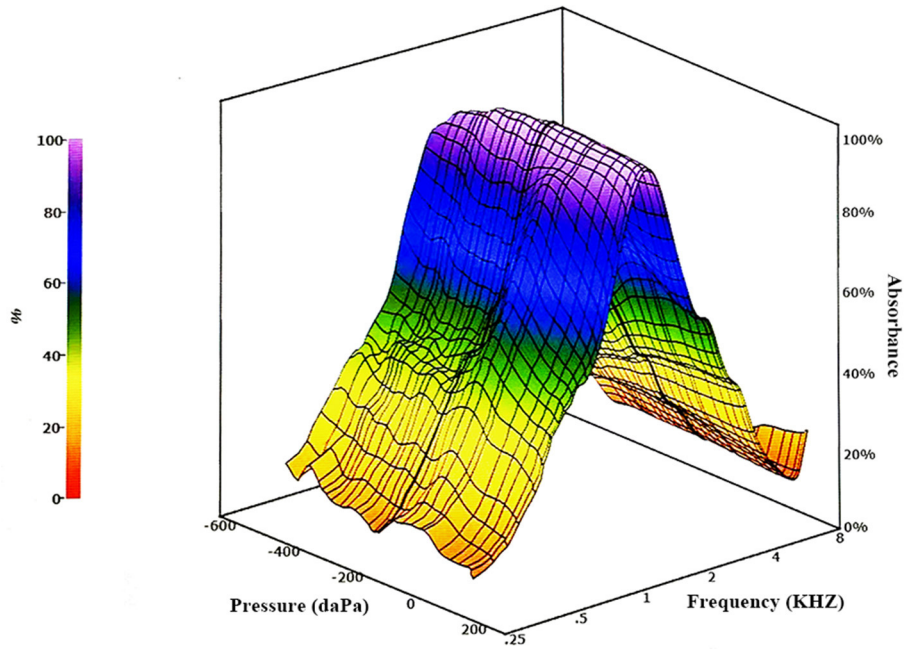

FIGURE 1 | Figure showing a three-dimensional broadband tympanometry image with simultaneous absorbance, frequency, and pressure data.

significantly fewer vertigo episodes at 6 and 12 months post-operatively with no difference between the two treatments (22). The authors believed that in individuals with MD who have severe vertigo symptoms, a VT put into the tympanic membrane should be the primary treatment choice. If this treatment is ineffective, endolymphatic sac surgery should be considered (22). Sugawara et al. studied the long-term outcomes of seven patients with MD who were treated with the insertion of a VT into the tympanic membrane, finding that four patients had significant symptom control and three patients had limited symptom control following 42 months (24). Although this treatment has limited long-term success, it remains a viable therapeutic option for MD because of its simplicity and minimum invasiveness.

Wideband Tympanometry for Meniere's Disease

WBT can be applied to the diagnosis of MD based on the assumption that the stapes footplate and the annular ligament serve as the loudspeaker of the IE (26). EH causes increased perilymphatic pressure, which pushes the stapes footplate toward the ME, limiting the movement of the ossicular chain and thus decreasing the compliance of the ME (26). Here, we highlight the performance and the significance of various WBT indicators and parameters in diagnosing MD.

Resonance Frequency

The resonance frequency (RF) of the affected side of MD patients was significantly lower than that of the asymptomatic ear of the unaffected side of MD patients and the control group (27). The cause of the affected ear's markedly decreased RF in MD patients may be associated with aberrant IE pressure (13). However, some studies suggest that the sensitivity of these data is insufficient for diagnosis and that WBT might be used as a supplementary assessment (13).

Absorbance

Recently, Miehe et al. found that patients with MD had significantly lower absorbance obtained by broadband tympanometry in the frequency range of 2,000–4,000 Hz compared to normal subjects (4). Since this study was a retrospective case-control study, its diagnostic criteria also changed over time, but there were no differences in mean absorbance measurements between all MD patients and the subgroup of patients who met the new criteria for MD. A cross-sectional study by Tanno et al. found significant differences in absorbance in the low-frequency region between symptomatic and asymptomatic patients with MD compared to normal individuals (28). WBT can be used to complement the diagnostic criteria for MD, which meets both the criteria of the previous and the new criteria for MD (4). In addition, WBT allows differentiating between asymptomatic and symptomatic MD patients (28).

Integral Area of the Absorbance

When applying WBT detection, 107 absorbance values from 226 to 8,000 Hz can be obtained, and then the integral area of the absorbance (IAA) of the subject is calculated. Two studies from China compared the difference in IAA between the affected ear and the unaffected ear in MD patients, yielding different results (27, 29). According to a study by Li et al., IAA in the symptomatic ear is larger than that in the asymptomatic ear in patients with

MD, and the difference is statistically significant (29). However, Lan et al. found that IAA in the affected ear of patients with MD was not significantly different from that of the asymptomatic ear but only showed a slightly larger IAA in the affected ear than in the unaffected ear (27). Because of EH in the IE of patients with MD, there is more fluid in the membranous labyrinth on the affected side than on the healthy side. Acoustic energy is more readily absorbed as it passes through the liquid, resulting in a larger IAA in the affected ear than in the healthy ear (29). Whether the increase in IAA can be used to identify MD is controversial and requires further study.

G-Width

G-width is defined as the bimodal width of the waveform obtained when the conductance is measured at 2,000 Hz (30). Several earlier investigations employing MFT discovered a widened G-width in individuals with MD, which may be a diagnostic characteristic (30, 31). However, all the above studies were performed during the quiescence phase of MD. A recent prospective case-control study by Cakir Cetin et al. found no difference in G-width between the acute attacks phase patients with MD and healthy controls (26). Therefore, according to this study, WBT seems to have no diagnostic value in acute episodes of MD.

LIMITATIONS OF THE CURRENT STUDY AND PROSPECTS

WBT is a more comprehensive and relatively new indicator that may provide valuable information for patients than traditional tympanometry or MFT. It has the advantages of being objective, practical, minimally invasive, and rapid (28). However, WBT has been used mainly for research purposes, and its clinical application is still not widespread (4).

Currently, WBT has shown significant advantages in the diagnosis of ME diseases. The absorbance in the WBT systematically decreases with increasing ME effusion accumulation, which is a powerful and sensitive indicator of the volume of ME effusion in children with secretory otitis media (16). However, there are few studies using WBT to diagnose MD, and the sample sizes included in these studies are generally small. Most studies have only measured WBT in patients with MD at rest or the acute attacks phase of the condition, and follow-up WBT data of patients are lacking (13). There were some differences in the normative values of WBT in different age populations (32). In addition, the normative values of WBT parameters vary among different ethnic groups (33). However, no studies have employed WBT to compare ethnic groups of patients with MD. The establishment of a WBT dataset for a specific ethnically healthy adult population will help apply WBT in clinical practice while also serving as a reference for future studies (34).

Other tests have some advantages in diagnosing MD. The VEMP test is used to evaluate the saccule and utricle bilaterally by monitoring the sternocleidomastoid and inferior oblique muscles (4). The interaural amplitude difference ratio of VEMP correlates with the staging of MD and can be used as an auxiliary indicator to determine the stage of MD (35). On ECoG, a ratio of total sum potential to compound action potential >0.40 is regarded as a significant indicator of EH (8). Tone burst ECoG is more sensitive than gadolinium-enhanced MRI scans in diagnosing MD (36). In the DPOAE examination, the reduction of the signal-to-noise ratio at 1 kHz is of some value in the diagnosis of EH (8). Additionally, DPOAE detects cochlear ischemia in seconds and monitors cochlear blood flow indirectly for hearing protection during cerebellopontine angle surgery (37). The caloric test examines the vestibular function at low frequencies (4). According to a recent study, the caloric test complements the horizontal video head pulse test in assessing vestibular disease and plays an important role in suspected EH (9).

Although WBT has some value in the diagnosis of MD, it is essential to note that WBT measurements should be used as part of a test battery and interpreted in conjunction with the patient's history, physical examination, and other objective tests rather than relying solely on WBT results.

The wideband acoustic immittance database (WAI), funded by the National Institutes of Health, has facilitated the development of research in this area, intending to allow audiological researchers to share WAI measurement data and perform comprehensive over multiple datasets (38). Otolaryngologists should strengthen international cooperation, and future prospective multicenter studies on this issue, including larger sample sizes, should be conducted. At present, WBT has already shown a role in recognizing MD as an accurate and rapid test method. With more profound research and better understanding, WBT will have great potential for MD in the future and has a broad application prospect.

CONCLUSIONS

In this review, we would like to emphasize the following points:

- Patients with MD may benefit from WBT, a more comprehensive and relatively new indicator that provides helpful information.
- Patients with MD are likely to have ETD, theoretically allowing for identifying the condition using WBT.
- The reduced resonance frequency and absorbance are characteristic of MD and can identify MD.
- WBT can detect between asymptomatic and symptomatic patients with MD.
- Using an increase in the integral area of absorbance as an indicator for identifying MD is controversial. During acute episodes of MD, WBT appears to be ineffective as a diagnostic tool.
- More research is needed to realize the potential of this technology in clinical applications.

AUTHOR CONTRIBUTIONS

XM conceptualized and drafted the manuscript. KZ, JY, and CH critically reviewed the literature and revised the draft manuscript. All authors contributed to the article and approved the submitted version.

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Changes of Vestibular Symptoms in Menière's Disease After Triple Semicircular Canal Occlusion: A Long-Term Follow-Up Study

Yumeng Jiang[1,2,3†], *Maoxiang Xu*[1,2,3†], *Qingxiu Yao*[1,2,3†], *Zhuangzhuang Li*[1,2,3], *Yaqin Wu*[1,2,3], *Zhengnong Chen*[1,2,3*], *Dongzhen Yu*[1,2,3*], *Haibo Shi*[1,2,3] *and Shankai Yin*[1,2,3]

[1] *Department of Otolaryngology-Head and Neck Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China,* [2] *Otolaryngology Institute of Shanghai Jiao Tong University, Shanghai, China,* [3] *Shanghai Key Laboratory of Sleep Disordered Breathing, Shanghai, China*

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Maoli Duan,
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***Correspondence:**
Zhengnong Chen
jassey@126.com
Dongzhen Yu
drdzyu@126.com

† *These authors have contributed equally to this work*

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Background: The clinical efficacy of triple semicircular canal occlusion (TSCO) and vestibular nerve resection (VNS) for patients with Ménière's disease has been unclear.

Objective: To explore changes in vestibular symptoms after TSCO and its advantages compared to the classical operation of VNS in patients with Menière's disease.

Methods: In total, 36 patients with Menière's disease performed TSCO or VNS at Shanghai Jiao Tong University Affiliated Sixth People's Hospital, China from May 2005 to July 2021, and all of them were enrolled in our study. Twelve of them underwent TSCO, 23 underwent VNS, and 1 had both treatments. We compared the demographic parameters, clinical symptoms, and selected test results between the two surgical methods. Ten patients each who underwent TSCO and VNS completed the follow-up. We collected and compared data pertaining to changes in vestibular symptoms.

Results: No significant difference in demographic parameters, clinical symptoms, or auditory or vestibular test results was detected between the two groups preoperatively. The TSCO group with vertigo as the main complaint experienced less residual paroxysmal dizziness after surgery than the VNS group ($P = 0.020$). Also, 57% of the patients in the VNS group had unsteadiness after surgery, while no such problems were reported in the TSCO group ($P = 0.025$).

Conclusions: Our study shows that TSCO controls vertigo in most Menière's disease patients, and also has the advantage of lower rates of postoperative paroxysmal dizziness and unsteadiness than VNS. Thus, TSCO may be an effective surgery for refractory Menière's disease.

Keywords: vestibular symptoms, triple semicircular canal occlusion, vestibular nerve section, Menière's disease, clinical benefit

INTRODUCTION

Menière's disease is an inner ear disorder characterized by two or more episodes of vertigo associated with fluctuating low- and medium-frequency hearing loss (HL), tinnitus, and aural fullness. The duration of vertigo attacks is between 20 min and 12 h (1). An epidemiological survey in Japan showed that 50–200 out of 100,000 adults suffer from Menière's disease, which mostly occurs in people aged 40–60 years (2, 3). The disease is also characterized by an impaired quality of life (4) and can lead to restricted activity due to refractory vertigo (5).

Both medical and surgical interventions are used in the treatment of Menière's disease, to control vertigo attacks and preserve hearing and vestibular function (6). A series of relatively reliable treatments has been developed for Menière's disease (3). Improving lifestyle and exercising more is the initial treatment step. Previous studies reported that a low-salt diet free from caffeine can help balance the ion concentration in the endolymph of the inner ear (7). The next step of treatment is to reduce the number of attacks and relieve vertigo and dizziness symptoms *via* medications including betahistine, antihistamines, benzodiazepines, ginkgo biloba extract, and corticosteroids (8); diuretics may also be tried to reduce endolymphatic hydrops (9). Most of the symptoms can be stably controlled by medicine, although 15–40% of patients suffer disabling refractory vertigo (7).

For those living with serious vertigo attacks for years, and in whom lifestyle changes and medical therapy have been tried unsuccessfully various surgical treatments are available according to the patient's hearing status (3). Endolymphatic sac surgery (ESS), labyrinthectomy, and vestibular nerve resection (VNS) were recommended by the AAO-HNS clinical guidelines as early as 1985 (10). Dandy performed the first vestibular nerve section in 1942 and advocated selective nerve section for intractable Menière's disease thereafter (11). In 1990 Parnes and McClure described posterior semicircular canal occlusion for benign paroxysmal positional vertigo (12). The purpose is to eliminate the movement endolymph in the canals, so as to eliminate the vertigo attack caused by specific head movement in patients with BPPV. We hypothesize the pathophysiology of Menière's disease is that excessive accumulation of endolymph can cause bulk endolymph movement and episodes of spinning vertigo, and this can be improved by semicircular canal obstruction. Triple semicircular canal occlusion (TSCO) for Menière's disease was advocated by Yin et al. (13), and has been performed in China and elsewhere with good vertigo control and preservation of hearing (14, 15).

However, due to the lack of comparison of clinical efficacy between different surgical methods, it is difficult to determine the optimal approach for refractory Menière's disease (16). Therefore, the aim of the present study is to evaluate the effectiveness of TSCO to control vertigo attacks over the long term and improve quality of life compared to traditional VNS.

METHODS

Study Design

A retrospective study was performed of patients with Menière's disease in Shanghai Jiao Tong University Affiliated Sixth People's Hospital, China from May 2005 to July 2021. The indications for surgery were a pure-tone average of >70 dB Hearing Level (HL) (according to the AAO-HNS clinical guidelines), failure of previous medical therapy applied over at least 6 months, and a strong desire for surgery. The exclusion criteria included a history of any other neurogenic disease, vestibular neuritis, brain tumor, vestibular migraine, BPPV, or any other disease that can cause vertigo.

Before surgery, all patients underwent a series of auditory and vestibular evaluations, including pure-tone audiometry, tympanometry, distortion product otoacoustic emission and glycerol test. Tympanometry is used to test the condition of the middle ear by creating air pressure in the ear canal. Distortion product otoacoustic emission, otoacoustic emission evoked by two pure tones, reflect the integrity of outer hair cell and the function of cochlea (17). The glycerol test was regarded as positive in the audiometry if the pure tone threshold improved at least 15 dB at minimum 3 frequencies after ingesting glycerol (18). Patients seen within the last 3 years also underwent radiological examination, including temporal bone computed tomography and magnetic resonance imaging, and intratympanic gadolinium-enhanced inner-ear magnetic resonance imaging.

Changes of vestibular symptoms were evaluated by telephone follow-up, which inquired about attacks of vertigo after surgery and other symptoms. The specific questions are as follows: Would you please describe the change of your vestibular symptoms during these year after surgery; Was there any vertigo attacked again after surgery and when? Were there any symptoms such as dizziness and unsteadiness appeared? When and how it happened; How about your hearing condition? We calculated the average number of attacks for each ear. In July 2021, we administered four questionnaires by telephone to each TSCO patient: the Dizziness Handicap Inventory (DHI), Activities-Specific Balance Confidence Scale (ABC), Tinnitus Handicap Inventory (THI), and Visual Analog Scale (VAS).

The study was designed and executed in accordance with the recommendations of the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (2020 KY 004).

Patients and Outcome Measures

In the past 16 years, 99 Menière's disease patients underwent surgery, including TSCO, VNS, and ESS, at Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Of these 99 patients, 36 patients underwent TSCO or VNS and all were included in our retrospective study. Ten patients per surgical method who completed follow-up were included and analyzed in this study in terms of the curative effect of surgery, The remaining 16 patients were unable to be contacted or had not returned to our hospital.

Vestibular symptoms, including vertigo, dizziness, and unsteadiness, were assessed before and after surgery (19). The primary outcome was vertigo control as determined by

the number of vertigo episodes. According to the American Academy of Otolaryngology–Head and Neck Surgery guidelines (1), the patient's vertigo control status was determined by comparison of the frequency of vertigo attacks between 6 months before and 18–24 months after surgery. Vertigo control was expressed numerically (number of attacks after treatment divided by the number prior to the treatment) as follows; 0 = A, complete control; 1–41 = B, substantial control; 41–80 = C, limited control; 81–120 = D, insignificant control; and > 120 = E, no control. The postoperative data of all patients were collected by telephone in July 2021. Dizziness and unsteadiness were secondary outcomes. In the TSCO group, the DHI, ABC, and VAS scores were used to analyze secondary outcomes by evaluating vertigo, dizziness and balance; the THI score was used to evaluate the severity of tinnitus. The DHI, a questionnaire exploring the self-perceived handicapping effects of vestibular disease consists of three parts (DHI-P, -E and -F) evaluated separately (20). Visual analog scale (VAS) was administered *via* telephone to measure symptoms or conditions that are not captured by the other measures. We asked the patient to rate their current symptom level on a scale from 0 to 10, with 10 being the patient's symptom at the time when he was most affected by Menière's disease before surgery, and 0 being the patient's symptom when completely healthy. For the VNS group, clinical information including vertigo attacks, unsteadiness, HL, and tinnitus was collected by telephone or outpatient follow-up. All of the information was collected in July 2021.

Hearing (clinical stage) was assessed according to the pure-tone average at frequencies of 0.5, 1, and 2 kHz; this also informed the surgical method, along with clinical guidelines. The hearing of patients was categorized as follows: 0–25 dB HL = stage 1; 26–40 dB HL = stage 2; 41–70 dB HL = stage 3; and > 70 dB HL = stage 4.

Surgical Protocol for TSCO

Yin et al. (13, 14, 21) were the first to modify SCO, which was originally performed in patients with BPPV, and apply it to Menière's disease in 2004. After standard mastoidectomy, three semicircular canals are contoured and a bone island with a diameter of approximately 1 mm is drilled in the non-ampullary arm of each canal. Then, great care is taken while prying off each bone island with a hook, and each canal is completely occluded with a piece of muscle or fascia tissue (**Figure 1A**). Next, the access area is covered by a piece of fascia with some bone dust sprayed on the muscle tissue. Finally, a piece of gelatin sponge is placed on the surgical site.

Surgical Protocol for VNS

Retrolabyrinthine and retrosigmoid approaches were used in the VNS group (22). The difference between these approaches lies in the location in which the dura mater is exposed. The first approach contours the mastoid and opens the internal auditory canal to 270°. The second approach opens a bone window approximately 3 cm × 4 cm in size at the junction of the parietal, occipital, and temporal bones. Then, the dura mater is opened, and cerebrospinal fluid released. The cerebellum is gently pressed to expose the cerebellopontine angle and separate the vestibular and cochlear nerves. The vestibular nerve is then cut. After cleaning the cavity the surgical site is filled with hemostatic silk and gelatin sponge (23) (**Figure 1B**).

Statistical Analysis

Statistical analysis was performed with SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed with the Shapiro–Wilk test. We express normally distributed variables as mean ± standard deviation, and compared the two groups using independent sample *t*-tests; we express non-normally distributed variables as mean ± standard deviation, and used nonparametric tests (Mann–Whitney U test) to compare the groups. We express categorical variables as frequency or percentage and used the chi-square test to compare the groups. We considered $P < 0.05$ statistically significant.

RESULTS

Clinical Symptoms and Tests

During the past 16 years, 99 Menière's disease patients underwent surgery in Shanghai Jiao Tong University Affiliated Sixth People's Hospital, of which 12 and 23 underwent TSCO and VNS, respectively (one patient underwent VNS in 2005 and TSCO in 2017), and were included in our retrospective study. There were no statistically significant differences between the two groups in demographic parameters, including gender and age at surgery, or clinical symptoms, including duration of vertigo attack, number of years of attacks, number of vertigo spells in the 6 months before surgery, worst hearing level, number of years of HL, tinnitus, or affected side (all $P > 0.05$; **Table 1**). Similarly, no significant differences between the groups were detected in the results of auditory tests before surgery, including tympanometry, distortion product otoacoustic emission and glycerol tests.

Vertigo Control

According to the American Academy of Otolaryngology–Head and Neck Surgery guidelines (1), patients who underwent surgery more than 24 months ago ($N = 4$ and 10 in the TSCO and VNS groups, respectively) were analyzed in terms of post-operation vertigo within 2 years; 100% of the patients in the TSCO group achieved complete control of vertigo, compared to 90% in the VNS group (10% achieved substantial control). During the entire follow-up period, four patients in the TSCO group and seven in the VNS group had no vertigo attacks, and three patients in the VNS group had a vertigo attack. There was no significant difference in number of postoperative vertigo episodes in 24 months between the two surgical methods using independent sample *t*-tests ($P = 0.839$). In brief, the surgical methods had similar efficacy for vertigo attack control (number of attacks after treatment divided by the number prior to the treatment) for most patients in two group got an A control in 2 years after surgery using chi-square test ($P = 0.512$; **Table 2**; **Figure 2A**). Six patients in the TSCO group underwent surgery <24 months before this study was completed, and 50% of them had no vertigo attacks after surgery. Although the other 50% of these patients had vertigo attacks, their frequency was much lower than before

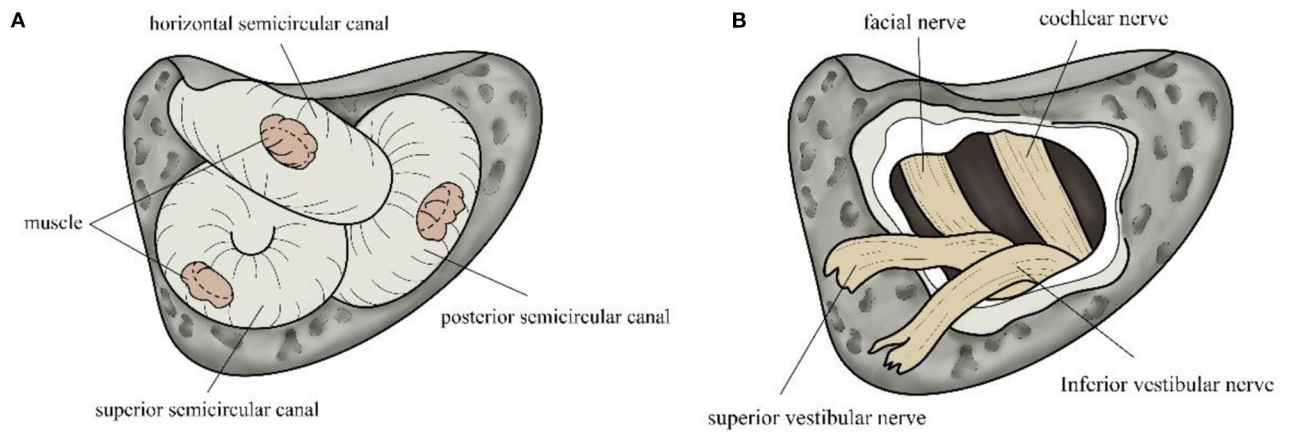

FIGURE 1 | Diagram of triple semicircular canal occlusion and vestibular nerve resection. **(A)** Muscle tissue blocks the three semicircular canals, which are clearly contoured. **(B)** The vestibular is cut off after being separated from the cochlear nerve.

TABLE 1 | Patient demographics, symptoms, and results of tests before surgery.

	Total (*N* = 35*)	TSCO (*N* = 12)	VNS (*N* = 23)	*P*-value
Gender				
Male (*n*/%)	14(40%)	5(42%)	9(39%)	0.884
Female (*n*/%)	21(60%)	7(58%)	14(61%)	
Age at surgery (years)	53.46 ± 9.77	53.58 ± 10.92	53.39 ± 9.38	0.957
Side				
Right (*n*/%)	17 (49%)	7 (58%)	10 (43%)	0.404
Left (*n*/%)	18 (51%)	5 (42%)	13 (57%)	
Vertigo				
Duration (years)	7.55 ± 7.12	6.89 ± 3.59	7.91 ± 8.52	0.68
Average duration of vertigo episode(h)	5.48 ± 6.58	2.78 ± 3.13	4.90 ± 5.81	0.65
Number of spells 6 months before surgery (*n*)	15.26 ± 10.93	16.25 ± 11.68	14.73 ± 10.74	0.71
Hearing loss				
Worst hearing (dB)	67.26 ± 20.61	69.58 ± 13.37	66.04 ± 23.71	0.637
Duration (years)	6.75 ± 6.92	5.53 ± 3.32	7.48 ± 8.38	0.99
Tinnitus				
Duration (years)	8.42 ± 10.27	8.56 ± 13.60	8.34 ± 8.29	0.49
Test				
Tympanogram				
A (*n*/%)	21 (91%)	10 (91%)	11 (92%)	0.949
As (*n*/%)	2 (9%)	1 (9%)	1 (8%)	
Distortion product otoacoustic emission (*n*/%)				
Present	1(6%)	0(0%)	1(12.5%)	0.274
Absent	16(94%)	9(100%)	7(87.5%)	
Glycerol test (*n*/%)				
Positive	10(77%)	3(60%)	7(87.5%)	0.252
Negative	3(23%)	2(40%)	1(12.5%)	

**One patient who underwent both triple semicircular canal occlusion and vestibular nerve resection was excluded from the analyses.*

TSCO. However, one patient whose main complaint was severe dizziness rather than vertigo had no benefit after surgery. We also counted the postoperative vertigo control of the two groups regardless of the postoperative time. The comparison of vertigo control between the two groups was unchanged (*all P > 0.05*; **Table 3**).

Ten patients in the TSCO group completed four questionnaires *via* telephone during follow-up. Based on the

TABLE 2 | Vertigo control after surgery in patients who performed surgery more than 24 months ago.

	Total ($N = 14$)	TSCO ($N = 4$*)	VNS ($N = 10$)	*P*-value
Number of vertigo episodes in 24 months after surgery	0.07 ± 0.28	0.00 ± 0.00	0.10 ± 0.32	0.839
Class				
A	13 (93%)	4 (100%)	9 (90%)	0.512
B	1 (7%)	0 (0%)	1 (10%)	

Four of 10 patients in the triple semicircular canal occlusion group were operated on more than 24 months ago.

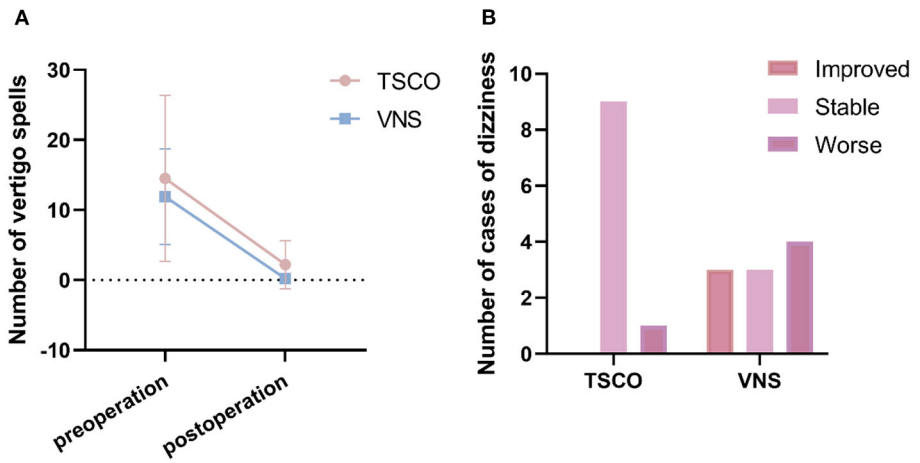

FIGURE 2 | Incidence of postoperative vertigo and paroxysmal dizziness. **(A)** Vertigo spells were controlled by both triple semicircular canal occlusion (TSCO) and vestibular nerve resection (VNS), and there was no significant difference in incidence between the two groups. **(B)** Bar chart comparing the numbers of postoperative cases of paroxysmal dizziness between the two groups.

DHI results, we evaluated the patients' quality of life physically, emotionally, and functionally; a large group difference was found in all three domains ($P = 0.022$, 0.025, and 0.013, respectively). The scores were significantly lower in patients who underwent TSCO more than 24 months ago compared to those operated on more recently. However, no significant differences were found in the ABC, THI, or VAS scores (all $P > 0.05$; **Table 4**).

Postoperative Paroxysmal Dizziness and Unsteadiness

Postoperative problems requiring attention include paroxysmal dizziness (sensation of disturbed or impaired spatial orientation without a distorted sense of motion), unsteadiness (postural instability when sitting, standing, or walking (19)), and vertigo recurrence. As one of the symptoms of vestibular function disorder dizziness may coexist with vertigo in Menière's disease. In terms of paroxysmal dizziness, different patients have different conditions. Using the number of patients with postoperative paroxysmal dizziness to analyze was improper for losing the individual characteristics of patients. All patients were encouraged to exercise and no specific vestibular physical therapy was performed. After surgery we scored the symptoms of our patients as follows: 1, improved: dizziness had occurred before but disappeared after the operation; 2, stable: dizziness existed before and after the operation (or asymptomatic patients); or 3, worse: no dizziness previously, but dizziness onset after the operation. The data indicated that TSCO was significantly better than VNS in reducing dizziness ($P = 0.020$; **Table 5**; **Figure 2B**). unsteadiness, which is a symptom of vestibular dysfunction, only occurred after VNS ($P = 0.025$).

Special Case

One patient in our study underwent both TSCO and VNS. He underwent ESS for recurrent vertigo in 2002 but it recurred. Therefore, in 2005, he underwent VNS and vertigo control was achieved. However, dizziness and unsteadiness occurred after this surgery and lasted for 10 years. In 2016, his vertigo recurred with attacks lasting 2 h. After undergoing TSCO in 2017, his vertigo and dizziness disappeared completely, but functional compensation for the unsteadiness was difficult to achieve.

DISCUSSION

In this retrospective trial, we found no significant difference between TSCO and VNS in terms of the ability to control vertigo. At 24 months after surgery, all patients in the TSCO group achieved class A vertigo control, whereas there were nine cases of class A vertigo, and 1 of class B, in the VNS group. The results confirm the efficacy of the two surgical methods for controlling vertigo symptoms. However, other

TABLE 3 | Vertigo control after surgery in all follow-up patients.

	Total ($N = 20$)	TSCO ($N = 10$)	VNS ($N = 10$)	*P*-value
Number of vertigo episodes	1.15 ± 2.60	2.20 ± 3.43	0.10 ± 0.32	0.218
Class				
A	15 (75%)	6 (60%)	9 (90%)	0.273
B	4 (20%)	3 (30%)	1 (10%)	
D	1 (5%)	1 (10%)	0 (0%)	

TABLE 4 | Dizziness handicap inventory, activities-specific balance confidence scale, tinnitus handicap inventory, and visual analog scale scores of the triple semicircular canal occlusion patients.

	Total ($N = 10$)	Operated on within the last 24 months ($N = 6$)	Operated on more than 24 months ago ($N = 4$)	*P*-value
DHI-P	7.33 ± 8.60	12.40 ± 8.53	1.00 ± 2.00	0.022
DHI-E	11.33 ± 12.73	19.20 ± 12.13	1.50 ± 1.92	0.025
DHI-F	14.67 ± 17.75	26.00 ± 16.37	0.50 ± 1.00	0.013
ABC (0–10)	2.56 ± 3.97	3.20 ± 4.60	1.75 ± 3.50	0.662
THI (0–100)	12.44 ± 20.61	12.40 ± 25.55	12.50 ± 16.20	0.441
VAS (1–10)	3.50 ± 3.32	5.20 ± 3.56	1.38 ± 1.25	0.082

vestibular symptoms including dizziness and unsteadiness were less common among TSCO than VNS patients. It is plausible that the vestibular nerve on the healthy side cannot completely compensate for the balance disorders caused by VNS on the affected side. Our study also showed that the DHI scores of patients more than 24 months after TSCO were significantly lower than those within 24 months, reflecting a change in patient emotional, physical, and functional quality of life. Vestibular function recovery in TSCO patients takes time.

Fan et al. (24) reported a 100% success rate for vertigo control after TSCO, with 81.6% and 18.4% of patients achieving complete and partial control, respectively, after 2 years (25). Setty et al. (26) reported that vertigo was controlled in 97.7% of Menière's disease patients after VNS. Similarly high rates of control of vertigo have also been reported in other studies. However, researchers often ignore postoperative symptoms surgeons can only choose the most effective surgical method by studying the relationships among vertigo and dizziness, unsteadiness, and vestibular disorder.

Surgical ablative therapies are considered an option for patients with active Menière's disease who have failed less definitive treatments and have unusable hearing (3). For nearly a century the VNS operation has been used to treat intractable Menière's disease (since the 1920s (11)). VNS controls vertigo by cutting the vestibular nerve, which sacrifices vestibular function on the lesioned side (11). This could explain why unsteadiness, dizziness attacks, and residual dizziness occur more often in VNS than TSCO patients, with the former group correspondingly showing larger changes in postoperative quality of life. By contrast, TSCO only blocks endolymph flow in three semicircular canals, which decreases vestibular function only on the surgical side (13). Overall, TSCO is equally effective as VNS for vertigo control, but is associated with a lower rate of dizziness.

A major concern with TSCO is postoperative HL. Stultiens et al. (27) assessed the postoperative hearing of patients with a semicircular canal plug and found a difference from the preoperative hearing level of <10 dB HL at the 6-month follow-up. Their study included stage 1–2 patients. In 2015 Zhang et al. (25) reported a rate of hearing preservation of 69.4% for TSCO. In the present study, the patients who underwent TSCO were mostly in stage 4, so it was difficult to determine whether TSCO was helpful for postoperative hearing recovery and preservation.

VNS is an intracranial operation with potential risks for cerebrospinal fluid leaks and facial nerve injury (28). In our patients none of these occurred. Risk for facial nerve injury can be decreased by a retrosigmoid approach (28). Watertight sutures of meninges, use of mannitol, and raising the head to 30 degrees postoperatively will minimize cerebrospinal fluid leaks.

There are some other surgical approaches available for refractory Menière's disease. According to a survey by the American Academy of Otolaryngology–Head and Neck Surgery Foundation, ESS was the initial surgical intervention for the treatment of Menière's disease in 50% of the respondents (7). Portmann et al. (29) first described ESS in 1927. Saliba et al. (30) reported that the vertigo control rate was 37.5% 4 months after ESS. The main advantage of this surgery is that the hearing is preserved, however, no significant difference in symptom improvement was found between ESS and placebo groups in a study by Bretlau (31), although no reported complications or side effects were found either. Despite this controversy over its effectiveness, ESS is still widely used (32).

TABLE 5 | Comparison of postoperative symptoms between the two groups.

	Total ($N = 20$)	TSCO ($N = 10$)	VNS ($N = 10$)	*P*-value
Dizziness				
Improved (*n*/%)	3(15%)	0 (0%)	3 (30%)	0.020
Stable (*n*/%)	12 (60%)	9 (90%)	3 (30%)	
Worse (*n*/%)	5 (25%)	1 (10%)	4 (40%)	
Unsteadiness (*n*/%)	4 (18%)	0 (0%)	4 (36%)	0.025

Parnes et al. (21) found that blockage of a semicircular canal did not influent the function of the other canal receptors. TSCO, which has the same principle, may preserve some vestibular and hearing function on the side of surgery (13). The result of v-HIT showed a decrease of function of semicircular canals, which increased the threshold of vertigo attack (33). Animal models have indicated that endolymphatic movement caused by excessive accumulation of endolymph will decrease or disappear after semicircular canal obstruction theoretically (13). TSCO exerts its effects as follows. Occlusions partially prevent the endolymph from stimulating the semicircular canals, and displacement of the crista ampullaris (which contributes to rotational vertigo). Also, postoperative disequilibrium is quickly compensated for (34). Our study provides guidance on the surgical method for Menière's disease patients, by demonstrating that TSCO is an alternative choice for vertigo control.

LIMITATIONS

There were several limitations to our study. First, we estimated the effects of surgery *via* pre- and post-operative comparison, which limited the sample size given the lack of postoperative auditory and vestibular evaluation results in some cases. This bias may have affected the accuracy of the analysis. Also, we may have underestimated the rate of postoperative vestibular symptoms given the small sample size, and the long follow-up time might have led to recall bias. Finally, postoperative data for pure-tone audiometry, for example, were incomplete, which limited our audiological evaluation. However, these limitations did not prevent us from describing changes of vestibular symptoms after surgery. Large-scale research using the same pre- and post-operative tests applied in the present study is required.

CONCLUSION

The difficulty of treating refractory Menière's disease is well recognized, so selecting the optimal surgical method remains challenging. Our study shows that TSCO controls vertigo in most Menière's disease patients, and also has the advantage of lower rates of postoperative paroxysmal dizziness and unsteadiness than VNS. Thus, TSCO can be considered as an effective surgery for refractory Menière's disease.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanghai Jiao Tong University Affiliated Sixth People's Hospital (2020 KY 004). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DY and ZC: designed and coordinated the study. YJ, QY, ZL, and MX: analyzed the data and wrote the manuscript. DY, ZC, YW, HS, and SY: performed the surgery. ZC and DY: attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors contributed to the article and approved the submitted version.

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A Comparison of Local Endolymphatic Sac Decompression, Endolymphatic Mastoid Shunt, and Wide Endolymphatic Sac Decompression in the Treatment of Intractable Meniere's Disease: A Short-Term Follow-Up Investigation

Guiliang Zheng[1,2,3†], *Yupeng Liu*[1,2,3†], *Jingchun He*[1,2,3], *Shuna Li*[1,2,3], *Qing Zhang*[1,2,3], *Maoli Duan*[4,5*], *Jun Yang*[1,2,3*] *and Yulian Jin*[1,2,3*]

[1] *Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China,* [2] *Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China,* [3] *Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China,* [4] *Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden,* [5] *Division of Ear, Nose, and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden*

Background: Meniere's disease (MD) is an inner ear disorder, characterized by recurrent attacks of vertigo, low-frequency sensorineural hearing loss, tinnitus, and aural fullness. Endolymphatic sac surgery is an effective treatment to control vertigo attacks but without causing a hearing loss for intractable MD. However, the methods and effects of endolymphatic sac surgery have been controversial for many years, and the relationship between the vertigo control rates of different endolymphatic sac surgery methods is not well-documented.

Objectives: This study compared the vertigo control rate, hearing outcome, and quality of life (QOL) among different endolymphatic sac surgery, such as local endolymphatic sac decompression (LESD), endolymphatic sac mastoid shunt (ESMS), and wide endolymphatic sac decompression (WESD).

Materials and Methods: We retrospectively analyzed the patients who underwent endolymphatic sac surgery from January 2008 to June 2019. The control rate of vertigo and QOL scores were compared after 2 years of follow-up. The QOL was scored with validation of the MD patient-oriented symptom-severity index (MDPOSI). The pure tone thresholds of all patients at pre- and postoperation were also compared.

Results: In total, 83 MD patients with complete follow-up data were included in the study, i.e., 20 patients with LESD, 28 patients with ESMS, and 35 patients with WESD. Results showed a better vertigo control with WESD than the other groups (70% with

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***Correspondence:**
Maoli Duan
maoli.duan@ki.se
Jun Yang
yangjun@xinhuamed.com.cn
Yulian Jin
jinyulian8548@xinhuamed.com.cn

†These authors have contributed equally to this work and share first authorship

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LESD, 71.4% with ESMS, and 88.6% with WESD). The QOL was improved after surgery in all groups in which the difference was statistically significant (QOL, preoperative vs. postoperative, 38.2 vs. 10.1 with LESD, 37.8 vs. 9.6 with ESMS, and 37.6 vs. 8.3 with WESD), respectively. After endolymphatic sac surgery, the hearing was well-preserved in the three groups [pure tone averages (PTAs), dB, preoperative vs. postoperative, 41.0 ± 19.3 vs. 40.8 ± 17.9 with LESD, 39.7 ± 16.4 vs. 40.8 ± 18.2 with ESMS, and 38.5 ± 18.7 vs. 36.6 ± 19.5 with WESD].

Conclusion: Wide endolymphatic sac decompression has a higher vertigo control rate, better improvement of QOL, and relatively higher hearing stability or improvement rate after surgery in patients with MD compared with LESD and ESMS.

Keywords: Meniere's disease, endolymphatic sac surgery, local endolymphatic sac decompression, endolymphatic sac mastoid shunt, wide endolymphatic sac decompression

INTRODUCTION

Meniere's disease (MD) is an inner disorder characterized by recurrent vertigo, fluctuating hearing loss, tinnitus, and aural fullness (1, 2). Although the peak age of presentation of MD is between 40 and 60 years old, it can present at any age (3). Endolymphatic hydrops is accepted as the pathological feature of MD. However, the etiology and detailed pathophysiology of Meniere's attacks remain controversial. Conservative medical management is usually the first-line treatment after diet and lifestyle changes. Although most patients with MD can be controlled in the early stages, the patients in the advanced stage become difficult to control. Due to repeated attacks of vertigo, patients with intractable MD cannot go to work and participate in other social activities.

The primary goal of MD treatments is to reduce vertigo attacks (4). Maintaining or improving hearing function and minimizing disability are also important considerations in the treatment of MD. When conservative treatment cannot control the symptoms, there are a series of more active treatment options, such as endolymphatic sac surgery, vestibular neurectomy, and labyrinthectomy (1, 4, 5). Compared with vestibular neurectomy and labyrinthectomy, endolymphatic sac surgery is the most commonly used surgical procedure with minimal damage to normal structures and a low rate of hearing loss (6), however, endolymphatic sac surgery has been controversial. Although the reported control rate of vertigo in patients with MD ranged from 33 to 94%, it was once considered an ineffective operation (7–11). Despite many controversies, Paparella's paper published in The Lancet in 2008 still considered endolymphatic sac surgery as an early recommended surgical method for patients with intractable MD (7). It is commonly recognized that the efficacy of endolymphatic sac surgery in the treatment of MD is related to the patient's hearing stage. For example, endolymphatic sac surgery is certainly not the first option for stage IV patients because its postoperative vertigo control rate is only 40–46% (4, 8).

Endolymphatic sac surgery has a history of more than 80 years since it was proposed in 1927 by Portmann (12) and it has evolved to the present. It is mainly divided into the endolymphatic shunt and endolymphatic sac decompression. According to different shunt routes, endolymphatic shunt includes endolymphatic sac subarachnoid shunting (ESSS) and endolymphatic sac mastoid shunting (ESMS). ESSS has been gradually replaced by ESMS because of its disadvantages, such as the risk of intracranial infection and the stability of endolymphatic pressure, which is vulnerable to intracranial pressure. In practice, some surgeons perform local endolymphatic sac decompression (LESD), while others do wide endolymphatic sac decompression (WESD) according to their understanding of endolymphatic sac decompression. Therefore, currently, there are three procedures of endolymphatic sac surgery, namely, ESMS, LESD, and WESD. There are many reports on the efficacy of MD through endolymphatic sac surgery, but few investigations on the comparison of these three procedures for vertigo control rate, improvement of (QOL), and hearing outcomes.

We reviewed the relevant data of patients with MD who underwent different endolymphatic sac surgeries in single center to analyze their efficacy of them.

MATERIALS AND METHODS

Patients

This is a retrospective study of adult MD patients treated with different endolymphatic sac surgeries at Shanghai Jiaotong University School of Medicine affiliated Xinhua Hospital, from January 2008 to June 2019. All patients in this study were definite MD as defined by 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS): two or more definite spontaneous vertigo attacks lasting for 20 min or longer, at least one occasion hearing loss, tinnitus or fullness of ears, and vertigo caused by other causes were excluded. All patients were treated with diet control, drug treatment (low salt diet, diuretics, oral, or tympanic steroids) for more than 6 months, and their symptoms were still not effectively controlled. Surgeons from the same neuro-otological surgery team performed these surgeries in different periods, ESMS and LESD from January 2008 to September 2016 and WESD from October 2016 to June 2019. The cases of vestibular migraine, bilateral MD, delayed hydrops, and

occupying lesions in the cerebellopontine angle were excluded in this study.

Vertigo class for each patient was calculated from the numerical value (x/y)100: x is the average number of vertigo attacks per month during recent 6 months after surgery and y is the average number of vertigo attacks 6 months before treatment. According to the score, the degree of vertigo control was divided into 5 levels: (A: 0, B: 1–40, C: 41–80, D: 80–120, and E: >120) (13).

Before surgery, each patient's stage of MD was determined. Audiometric parameters used for comparison were pure tone averages (PTA) at 500 Hz, 1 kHz, 2 kHz, and 4 kHz and speech discrimination. Preoperative hearing was defined as the poorest hearing level in the 6 months preceding surgery. The staging was performed according to the average hearing threshold (Stage 1: PTA ≤25 dBHL; Stage 2: PTA 26–40 dBHL; Stage 3: PTA 41–70 dBHL; and Stage 4: PTA >70 dBHL) (13). More than 10 dB differences in PTA before and after treatment were regarded as better, <10 dB differences as worse, and the others as no change.

The QOL was scored with validation of the MD patient-oriented symptom-severity index (MDPOSI). The MDPOSI consisted of 30 items. All the questions were posed with an ordinal response format (14). All patients received a preoperative questionnaire survey and were followed up for 24 months. Patients who could not use the postoperative questionnaire were followed up by telephone.

All data were statistically analyzed using Sigma Stat 4.0 for Windows. The ANOVA was used to analyze the differences among groups. The Mann-Whitney *U*-test was used for non-normal data. As for degrees of control rate, the Pearson and Spearman tests were used for different variables. The difference was considered to be statistically significant when $p < 0.05$.

Surgical Procedure

Local endolymphatic sac decompression: With the patient under general anesthesia, a mastoidectomy was performed in a routine fashion. The mastoid was skeletonized to expose the lateral semicircular canal and the posterior semicircular canal and locate the endolymphatic sac at an intersection angle of the rear lower coordinate quadrant by the long axis of the horizontal semicircular canal and the posterior semicircular canal. The bone just on the surface of the endolymphatic sac in the posterior fossa and around the endolymphatic duct behind the posterior semicircular canal was removed.

Endolymphatic sac mastoid shunt: After a mastoidectomy was performed, the endolymphatic sac was located and the bone just on the surface of the endolymphatic sac in the posterior fossa and around the endolymphatic duct behind the posterior semicircular canal was removed same as LESD procedure. A small incision was opened on the endolymphatic sac with a sharp knife, and a small silicone sheet was embedded at the incision to connect the endolymphatic sac with the mastoid cavity.

Wide endolymphatic sac decompression: A wide mastoidectomy was performed in which the posterior cranial fossa, middle cranial fossa, the sigmoid sinus, and the jugular bulb were widely exposed, such as the dura of the middle cranial fossa, the dura of the posterior cranial fossa in front of the sigmoid sinus anterior to the posterior semicircular canal, which was introduced by Paparella et al. (15). The endolymphatic sac and the endolymphatic duct were then completely visible behind the posterior semicircular canal.

TABLE 1 | Patient characteristics in three groups.

	LESD $n = 20$	ESMS $n = 28$	WESD $n = 35$
Gender			
Males/females	11/9	16/12	18/17
Age	53.35 ± 10.31	52.64 ± 9.89	51.08 ± 11.92
Side R/L	9/11	13/15	18/17
Stage	1 2 3 4	1 2 3 4	1 2 3 4
Patients (*n*)	3 9 7 1	5 12 11 0	6 14 15 0

There was no significant difference in gender, age, side, and stages among three groups.

RESULTS

In total, 83 patients had complete follow-up data. The characteristics of these patients are shown in **Table 1**. There was no significant difference in gender, age, side, and stages among the three groups ($p > 0.05$).

Vertigo Control

The results of the vertigo control rate are summarized in **Figure 1**.

For the LESD group, complete control was achieved in 9 patients (45.0%) and substantial control in 5 patients (25.0%). Overall, 14 patients (70.0%) had satisfactory relief from vertigo. No patient was worse than before surgery.

For the ESMS group, complete and substantial control rates were 39.3% (11 patients) and 32.1% (9 patients), respectively. Two patients were worse at 2 months, and one patient received vestibular nerve section 6 months after endolymphatic sac surgery. It was found that the dissected endolymphatic sac was adhered to the surrounding tissue with a lot of granulation and fibrous tissue hyperplasia in this patient.

In the WESD group, 48.6% (17 patients) of the cases showed complete control, whereas 40.0% (14 patients) showed substantial control. Therefore, the satisfactory control rate was 88.6%. There was no patient worse than before surgery.

Complete and substantial relief rates from vertigo were very similar for LESD and ESMS groups (70.0 and 71.4%, respectively). The vertigo control rate in the WESD group was better than the other two groups. When we take satisfactory control of vertigo (complete and substantial) into consideration, there was a statistically significant difference (WESD vs. LESD/ESMS; **Figure 1**).

Hearing Outcomes

The audiometric evaluation revealed no significant change in PTA at 24 months follow-up in all three groups. PTA in the LESD group was 41.1 dB preoperatively and 40.8 dB at 24 months evaluation. In the ESMS group, PTA was 39.6 dB preoperatively and 40.8 dB at 24 months after surgery. PTA in the WESD

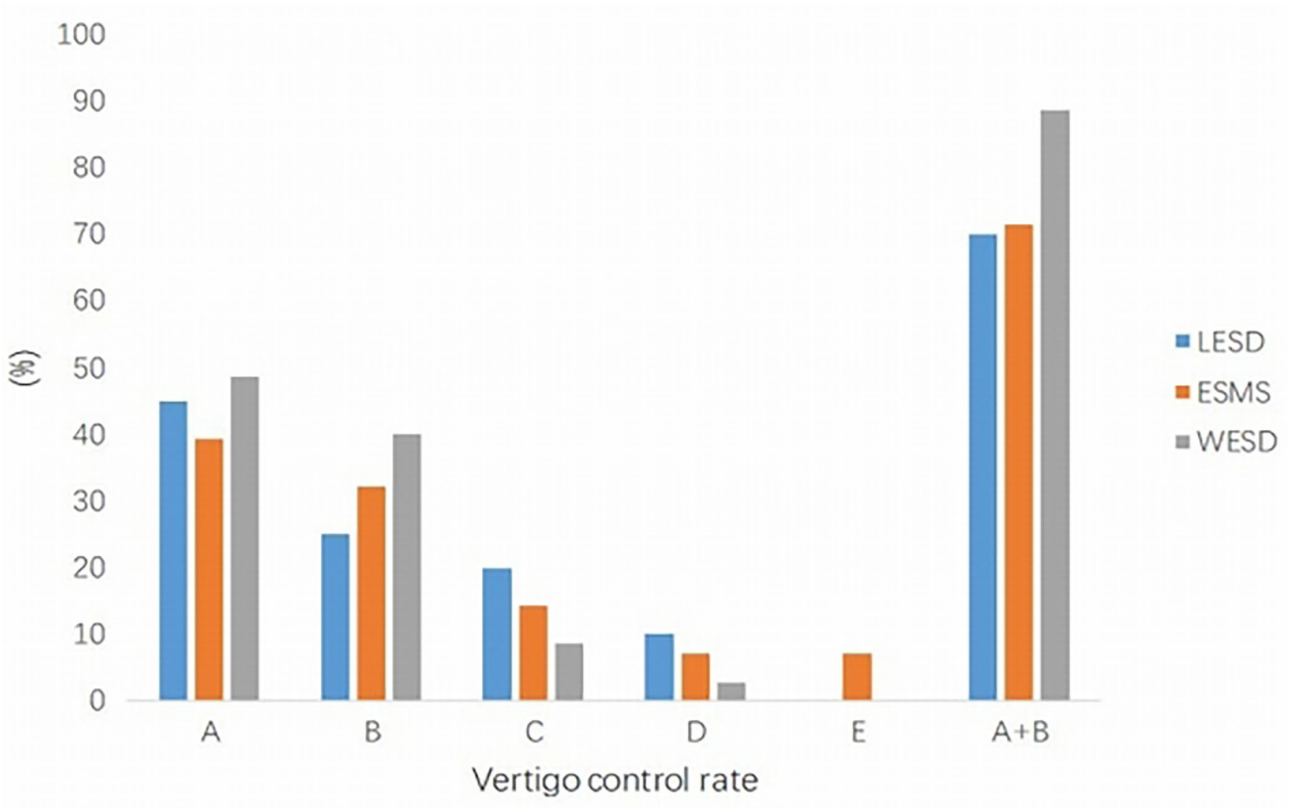

FIGURE 1 | Vertigo control rate in three groups. The satisfactory vertigo control rate (A+B) in the WESD group was better than the other two groups, which were significantly different. WESD, wide endolymphatic sac decompression.

TABLE 2 | Hearing outcome after endolymphatic sac surgery.

	LESD	ESMS	WESD
Improved	4	4	9
Stable	13	19	21
Decreased	3	5	5

Patients with improved or stable hearing in LESD, ESMS, and WESD groups were 85.0, 82.1, and 85.7% after 24 months follow-up, respectively ($p > 0.05$). LESD, local endolymphatic sac decompression; ESMS, endolymphatic sac mastoid shunt; WESD, wide endolymphatic sac decompression.

group was 38.5 dB preoperatively and 36.6 dB at 24 months after surgery. PTA improved or stable was in 17 patients and 3 patients with decreased slightly in the LESD group, however, no patient had a hearing loss of more than 15 dB HL. The audiometric evaluation demonstrated that PTA decreased more than 10 dB in 5 patients in the ESMS group at 24 months after surgery, and one of them was decreased significantly with aggravation of vertigo attack. The hearing level was decreased significantly from 37.5 to 67.5 dB 2 months after surgery. The PTA improved or stable was in 30 patients and 5 patients with decreased slightly in the WESD group. However, no patient had a decreased hearing of more than 15 dB HL (**Table 2**).

QOL Score

The QOL was scored with validation of the MDPOSI. All patients received a preoperative questionnaire survey and were followed up for 24 months. The patients who could not use the questionnaire survey after surgery were followed up by telephone. MDPOSI scores in the three groups were significantly improved (preoperative vs. postoperative, 38.2 vs. 10.1 with LESD, 37.8 vs. 9.6 with ESMS, and 37.6 vs. 8.3 with WESD). However, there was no significant difference among the three groups ($p > 0.05$).

Complications

Cerebrospinal fluid (CSF) leakage occurred in 2 patients with WESD procedure intraoperatively. A piece of temporal muscle was used to repair the defect of the dura of the posterior fossa in one patient. For another patient who failed temporal muscle repair, bone wax was used to seal the entrance of the tympanic sinus, and then abdominal fat was taken to fill the mastoid cavity. There was no CSF leakage after surgery.

Another complication was the sigmoid sinus tearing and bleeding, which occurred in 3 patients also with WESD procedure intraoperatively when bone on the surface of the sigmoid sinus was widely removed. Bipolar coagulation or Surgicel was used to stop bleeding.

There was no facial paralysis and posterior semicircular canal injury in all patients with these three endolymphatic sac surgery procedures.

DISCUSSION

Decision-making of an appropriate surgical procedure for a patient with MD who has failed conservative management is controversial and sometimes difficult. It needs to balance between the control of symptoms and the destructiveness caused by therapeutic modalities. Compared with vestibular nerve section and labyrinthectomy, endolymphatic sac surgery has many advantages, such as less injury and less impact on hearing and vestibular function though relatively low vertigo control (16), which are favorable for patients with MD, especially patients at early or middle stage.

The evolution of endolymphatic sac surgery has experienced a long and tortuous process. As early as 1924, Wittmaack put forward the concept of inner ear hydrops. Guild revealed the key role of the endolymphatic sac in endolymphatic drainage in 1927, which laid an anatomical basis for the establishment of endolymphatic sac surgery. Also in 1927, Portmann, a French doctor, founded the endolymphatic sac opening for the treatment of MD, who achieved certain results and was the first to perform endolymphatic sac surgery for the treatment of MD. Yamakawa et al. (17) modified Portmann's procedure by opening the endolymphatic sac and shunting the endolymphatic fluid to the subarachnoid space in 1954. Twelve years later, Shea made a further modification and developed ESMS. Based on the previous literature (18, 19), the clinical effects of ESMS and ESSS are roughly similar. However, ESSS has been gradually replaced by ESMS because of its distinct disadvantages in intracranial infection and endolymphatic pressure. In the same year of Shea' modification, Shambaugh (20) found that even if the endolymphatic sac was not opened during the surgery, or even without identifying the endolymphatic sac, simply removing the surrounding bone could achieve good results in controlling MD symptoms, Shambaugh therefrom established ESD. An exposure and decompression to the endolymphatic sac is performed in ESD procedure, which does not injure the endolymphatic sac, is more convenient, and has fewer postoperative complications than ESMS. Previous investigations have shown that both EMS and ESD are effective for the treatment of MD, and there is no significant difference in the vertigo control rate between them.

Outcomes of endolymphatic sac surgery have varied from 33 to 94% success for control of vertigo, with most authors reporting success in the range of 70–80% (9, 10, 18, 19). Although endolymphatic sac surgery has been established since 1927, this ambiguity about the effectiveness of surgical intervention in the form of ESD still exists (21–23). Locke (24) reported that the unpredictability of the outcomes of surgical decompression might be related to the difficulty in locating and fully decompressing the endolymphatic sac. Moreover, prolonged exploration of the cystic region may increase the risk of complications due to damage to the cystic cavity and its surrounding structures. Locke recommended that bone should be removed from the superior petrosal sinus to the jugular bulb and from a point medial to the posterior semicircular canal and posterior to the sigmoid sinus (24). The endolymphatic sac was located by measuring the lower limit of the posterior semicircular canal and maintained outside the posterior semicircular canal for decompression in LESD. However, anatomical measurements showed that this was the most variable part. Therefore, decompression limited to this area to reach the endolymphatic sac is unlikely to be reliable (24). Paparella et al. (25) reported that high vertigo control was achieved through wide decompression of the endolymphatic sac and posterior fossa, such as the sigmoid sinus, the jugular bulb, and middle fossa in the study. Gianoli et al. (21) reviewed 35 patients with MD treated by WESD that the complete control rate of vertigo was 85%, and substantial control was 100% in 2 years follow-up. They found that most patients with MD will have an anterior and medial displacement of the sigmoid sinus, and the degree of mastoid pneumatization is generally reduced, reducing the size of the Trautmann triangle and often bringing the sinus in direct contact with the endolymphatic sac. Therefore, extensive decompression, i.e., sigmoid sinus and posterior cranial fossa can better expose the endolymphatic sac and improve endolymphatic drainage. In their study, the vertigo control rate of WESD is higher than that of the LESD. In addition, Ostrowski reported that vertigo control was complete or substantial in 85 and 100% of patients at 1 and 2 years after endolymphatic sac-vein decompression (26).

Although there are many reports on the efficacy of endolymphatic sac surgery in the treatment of MD, few studies compare the effects of ESMS, LESD, and WESD in vertigo control rate and other functional outcomes. ESMS and LESD were performed from January 2008 to September 2016, and WESD from October 2016 to June 2019, respectively, by surgeons from the same neuro-otological surgery team in our single center. The aim of this study was to compare the vertigo control rate, QOL, and hearing outcome among ESMS, LESD, and WESD. Our result showed that the vertigo control rate in LESD and ESMS group was similar (70 vs. 71.3%); however, it was 88% in the WESD group, which was significantly higher than the other two groups.

Another important goal of MD treatment is to maintain or even improve the hearing of the affected ear. Many studies have shown that endolymphatic sac surgery has a slight impact on auditory function (3, 18–21, 24–26). Jameson used round window electrocochleography to measure the electrophysiological changes during ESD and ESS. They found that the low-frequency summating potential (SP) amplitude (500 Hz) had only a small objective change; however, there was no obvious objective change in other measured frequencies or measurement indexes (cm, SP/AP, and CM harmonic distortions). These results suggested that endolymphatic sac surgery has little effect on cochlear electrophysiology (27).

A meta-analysis concluded that endolymphatic sac surgery (sac decompression or mastoid shunt) is effective in controlling vertigo in up to 75% of patients with MD who failed medical treatment, whether short-term or long-term. Once the sac is opened, placing silastic does not add benefit and be deleterious (19). In the present study, the postoperative hearing loss in

the ESMS group was more than that in the other two groups, although the difference was not statistically significant. Whether this phenomenon was related to the placement of silicone sheet remains unknown.

Sood et al. (19) reported in a meta-analysis that an average of 72.8% of patients have improved or stable hearing after ESD, and 68% have improved or stable hearing after EMS. In our study, more than 80% of patients were able to maintain stable hearing function after surgery (85.0% with LESD, 82.1% with ESMS, and 85.7% with WESD), which was higher than other reports, which may be related to the fact that all patients were at stages 1–3 preoperatively except one patient at stage 4 (82/83 (98.8%) in which patients at Stage 1+2 accounted for 59%). However, it was reported that ESMS will increase the risk of further hearing loss (19). In the present study, two patients with significant postoperative hearing loss accompanied by aggravated vertigo attack were in the ESMS group in which hearing decreased from 35 to 70 dB HL in one patient who underwent vestibular nerve section *via* retrolabyrinthine approach 6 months later; and from 28.5 to 40 dB HL in another patient 2 months after surgery.

It should be emphasized that preoperative hearing staging is crucial for the selection of surgical procedures for patients with MD. Only patients at the early and middle stages can benefit from endolymphatic sac surgery, such as vertigo control and hearing stability.

Reducing the impact of recurrent MD on daily life and work is also one of the main goals of MD treatment. At present, the main methods to effectively evaluate the impact of MD on patients' life are DHI, MDOQ, and MDPOSI. Murphy et al. (14) reported that there is a highly statistically significant correlation between MDPOSI scores and the impact of MD on patients' life, which can be used to quantify the impact of MD on patients' health status. In our study, MDPOSI was used to evaluate the impact of MD on patients' life before and after surgery. The results suggested that endolymphatic sac surgery could well-reduce the impact of MD on patients and effectively improve patients' QOL because of its relatively higher vertigo control rate and little impact on auditory function. Although there was no significant difference among the three groups, the postoperative score of patients in the WESD group was the lowest, which was consistent with the effective control rate of vertigo.

Regarding time sequence of different surgical procedures, the main reason that we finally preferred WESD as the current procedure of endolymphatic sac surgery is the postoperative vertigo control rate was higher (with a significant difference), relatively higher hearing stability or improvement rate, and better QOL, which is reasonable and suggested by current results. Although there are complications after this procedure, they are relatively few and acceptable. In addition, it was reported that there is a risk of further hearing loss after ESMS (19). Furthermore, during vestibular neurotomy *via* retrolabyrinthine approach in a patient with recurrent MD who underwent ESMS, we found a lot of granulation and fibrous tissue covering the silicone sheet and the incision of the endolymphatic sac, suggesting that the so-called mastoid shunt did not play a role at all.

As for the choice of surgical methods, the main surgical procedures of endolymphatic sac were LESD and ESMS in our center before 2016. The results showed that the vertigo control rate of these two procedures was close, and hearing outcome after ESMS was worse than LESD. The experience of revision endolymphatic sac surgery showed that granulation and fibrous tissue and formation of new bone reoccurred around endolymphatic sac are the main reasons for the failure of endolymphatic sac surgery. Similar situations have been found in our two patients who underwent a second surgery. These results emphasize the importance of wider decompression during endolymphatic sac surgery. Therefore, we carried out WESD since 2016.

The mechanism of the effect of endolymphatic sac surgery is still inconclusive. Gibson (28) suggested that the operation disrupts the vessels of the endolymphatic sac and weakens the activity of the endolymphatic sac, reducing the attack of vertigo. However, Paparella (29) proposed that endolymphatic sac surgery is likely to enhance the blood supply of the sac and improves its absorption function such that alleviates endolymphatic hydrops. A recent study compared the changes of endolymphatic hydrops after different surgeries through enhanced MRI (30). The results showed that endolymphatic hydrops was improved in some patients after ESMS and endolymphatic duct blockage surgery but not in those patients with ESD surgery (30). Taking all these into account, therefore, we suggest that the possible reasons for the better outcome of WESD for intractable MD are as follows: (1) extensive decompression of the endolymphatic sac and dura is supposed to reduce the local impact of granulation tissue, fibrous tissue proliferation, and new bone formation on the endolymphatic sac after surgery; (2) the local hydrostatic pressure and osmotic pressure are changed; (3) extensive decompression affects the blood supply of the endolymphatic sac, resulting in the alteration of the endolymphatic sac activity; and (4) reduced secretion of glycoprotein, in turn, reduced endolymph influx to the endolymphatic sac such that relieve an attack of vertigo.

This study has a few limitations. The first one is that it is a retrospective analysis rather than a randomized controlled prospective study. There may be some deviation in the sophistication of patient selection and imperceptible improvement in surgical skills since the three types of surgical procedures were carried out in different periods though continuous. The second limitation is that these patients with MD in this study were followed up for only 24 months after surgery. We can only draw such a conclusion that functional outcome in the short term among the three procedures was different. However, the outcome in long term needs further research.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY, MD, and YJ contributed to the study design, critically reviewed, and approved the final manuscript. GZ and YL contributed to the detailed study design and performed data acquisition, statistical analysis, interpretation of results, drafting of the manuscript, and revised the manuscript. JH, SL, and QZ contributed to the methods of statistical analysis and reviewed the manuscript. All authors agree to be accountable for the content of the work, integrity, accuracy of the data, contributed to the article, and approved the submitted version.

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Up-Regulated Expression of Interferon-Gamma, Interleukin-6 and Tumor Necrosis Factor-Alpha in the Endolymphatic Sac of Meniere's Disease Suggesting the Local Inflammatory Response Underlies the Mechanism of This Disease

Chao Huang[1], Qin Wang[1†], Xueying Pan[1†], Wei Li[1†], Wei Liu[1†], Wenqi Jiang[2†], Li Huang[1†], Anquan Peng[1†] and Zhiwen Zhang[1*†]*

[1] Department of Otolaryngology-Head and Neck Surgery, The Second Xiangya Hospital, Central South University, Changsha, China, [2] Department of Anesthesiology, Sun Yat-Sen University Cancer Center, Guangzhou, China

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Edited by:
Pedro Marques,
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Göran Frans Emanuel Laurell,
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University of Canterbury,
New Zealand

***Correspondence:**
Anquan Peng
penganquan@csu.edu.cn
Zhiwen Zhang
zhangzhiwen@csu.edu.cn

† These authors have contributed equally to this work

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Background: Immune mediated inflammatory changes affecting the endolymphatic sac (ES) may underlie the pathology of Meniere's disease (MD). The aim of the present study was to explore the differentially expressed cytokines in ES luminal fluid (ELF) of patients with MD, and the correlation between the expression of cytokines in the ELF with that in the serum was determined by quantitatively analyzing the cytokines in human ELF and serum.

Methods: Human ELF, serum and ES tissues were collected from patients with unilateral MD and patients with acoustic neuroma (AN) during surgery. The Simoa Cytokine 6-Plex Panel kit was used to analyze the levels of cytokines in the ELF and blood samples of the patients. Immunohistochemistry and immunofluorescence were subsequently used to validate the relative expression levels of the cytokines in MD.

Results: Significant differences were identified in the expression levels of interferon-γ (IFN-γ) ($P < 0.001$), interleukin (IL)-6 ($P = 0.008$) and tumor necrosis factor-α (TNF-α) ($P = 0.036$) in the luminal fluid of the ES comparing between the MD and AN groups. By contrast, the levels of IFN-γ, IL-10, IL-12p70, IL-17A, IL-6 and TNF-α in the serum of the MD group were not significantly different from those of either the AN group or healthy control subjects. In addition, no significant correlations in the expression levels of cytokines compared between the ELF and serum were found for the patients in either the MD or the AN group. Finally, the detection of positive expression of TNF-α, IL-6 and IFN-γ in the epithelial cells of the majority of ES specimens from patients with MD confirmed the up-regulated expression of these cytokines in the ES of patients with MD.

Conclusions: The identification of up-regulated expression levels of TNF-α, IL-6 and IFN-γ in the ELF in the present study has provided direct evidence for an increased immunologic activity in the microenvironment of the ES in patients with unilateral MD, may suggest the local inflammatory response underlies the mechanism of this disease.

Keywords: Meniere's disease, endolymphatic sac, ES luminal fluid, cytokines, inflammatory

INTRODUCTION

Meniere's disease (MD) is characterized by episodic vertigo, sensorineural hearing loss, and tinnitus or aural fullness. The primary pathology associated with MD is endolymphatic hydrops (EH) (1). Several of the clinical characteristics associated with MD suggest an underlying inflammatory or autoimmune etiology (2). While the endolymphatic sac (ES) has been convincingly shown to be involved in the initiation of inner ear immune responses (3, 4), various immunological factors have been shown to be involved with the ES, including the immunoglobulins IgG, IgM and IgA, as well as secretory components of the immune system found in the ES, and macrophages and plasma cells residing in the perisaccular connective tissue (2, 5). Whereas high-resolution immunohistochemistry shows that antigens reaching the ear may be trapped and processed by an immune cell machinery located in the ES, providing further proof of the central role of the ES in the immune function of the inner ear (6).

Previous studies have focused on the fact that the immune mediated inflammatory changes to the ES are associated with the production of EH in an animal model (7, 8), whereas the investigation of human ES in patients with MD revealed that mainly viral and autoimmune factors are involved in the pathological mechanism for MD (9–11). However, few studies have been published on the molecular pathomechanism(s) involved in the local alteration of the protein constituents and the composition of the luminal fluids of ES in patients with MD. As EH has been proposed to result from a disturbance in endolymphatic volume regulation that is associated with changes in the microenvironment of luminal fluid of the ES (12), understanding the molecular pathomechanism(s) underpinning the regulation of the immune reaction in the luminal fluids of ES is important both for furthering our knowledge of the physiopathology of EH and for identifying biomarkers for diagnosis or prognosis of pathologies of the MD. Recently, there has been a growing interest in developing a "liquid biopsy" of the inner ear as a surrogate for tissue biopsy to identify molecular biomarkers (13–16). Proteomics analysis in samples of perilymph (13) and ES luminal fluid (ELF) (14, 15) from patients with MD and controls suggested that increased inflammatory reactions in the inner ear may contribute to the pathology of MD. The results of the micro(mi)RNA expression profiles of perilymph from patients with MD and patients with otosclerosis indicated that 12 of the 16 miRNAs unique to MD were directly predicted to regulate inflammation and/or autoimmune pathways (16). However, The MD-specific changes accounting for the observed inflammation in the microenvironment of luminal fluid of the ES have to be validated through additional studies with a larger number of samples, also including the identification of the molecular target(s) of these samples from performing "liquid biopsy" in patients with MD.

The membranous labyrinth consists of the cochlea, vestibule and endolymphatic sac. The sac can be divided into extraosseous, intermediate and intraosseous portions, which is connected to the cochlea and vestibule by the endolymphatic duct (**Figure 1**). Theoretically, the use of cochlear and vestibular endolymph in addition to ELF should enable us to gain a fuller understanding of the processes involved; however, sampling the cochlear and vestibular endolymph in patients with MD would be impossible since the inner ear function of the patients would consequently be destroyed, and the protein concentrations in these compartments would be too low for the analysis (14). Therefore, sampling ELF has been the only viable approach for understanding the composition of inner ear fluid in patients with MD. However, since the amount of luminal fluid in the normal ES is so small (<4 μl) (17), obtaining enough endolymph in ES for analysis by direct aspiration has proven to be very difficult. Nevertheless, based on the fact that the protein concentration of luminal fluid in the ES is extremely high (∼1,600 mg/dl), i.e., ∼40-fold higher than that of cochleo vestibular endolymph (∼38–60 mg/dl) as revealed in animal experiments (18), diluted luminal fluid from the ES would be suitable for use as a surrogate for endolymph in ES for screening the molecular targets of patients with MD. However, sampling luminal fluid of the ES from human subjects demands the highest levels of medical expertise and care to be taken in identifying the lumen of the ES, and in avoiding any contamination of the small sample of luminal fluid taken with the surrounding tissue fluids or with blood.

It has been previously reported that proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β, fulfill an important role in a plethora of middle and inner ear maladies (19, 20), including MD (21). However, the cellular contribution of these cytokines in the ES of MD is poorly understood, and it is not clear whether these cytokines are differentially expressed in the microenvironment of luminal fluid of the ES between patients with MD and control subjects. Additionally, it was reported that one third of MD cases may have a dysfunction of the immune system (22).

Abbreviations: MD, Meniere's disease; EH, endolymphatic hydrops; ES, endolymphatic sac; ELF, ES luminal fluid; AN, acoustic neuroma; EDB, endolymphatic duct blockage; TNF-α, tumor necrosis factor α; IFN-γ, interferon-γ; IL, interleukin; Simoa, single-molecular array; RGP, resorufin β-D-galactopyranoside; PBST, triton-phosphate buffered saline; DAPI, 4′,6-diamidino-2-phenylindole; ANOVA, analysis of variance; IF, immunofluorescence; SNHL, sensorineural hearing loss.

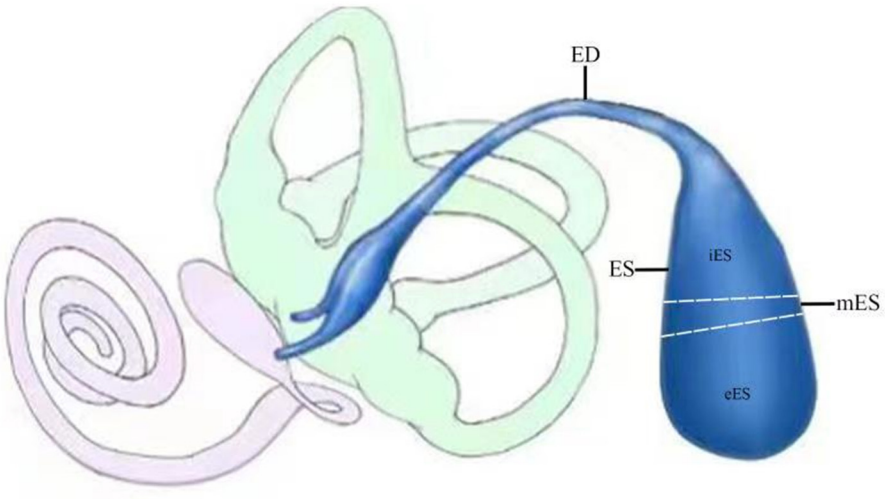

FIGURE 1 | Schematic illustration of endolymphatic sac (ES; blue) and duct (ED; blue) and its relationship to the cochlea (pink) and the vestibule (light green). The sac can be divided into extraosseous (eES), intermediate (mES) and intraosseous (iES) portions.

Although clinical symptoms of systemic autoimmune disorder were not present in patients who were suspected to have autoimmune pathology-associated MD, studies have identified in these patients an excessive immune response due to an attack of the specific inner ear structures by cochlear innate immune cells that recognize self-antigens, which leads to the release of inflammatory cytokines, including TNF-α, IL-1β, interferon-γ (IFN-γ) and IL-17 (23–25). However, previous studies have shown that autoimmune inner ear disorder is confined mostly to the inner ear (23, 24), and whether there is an association between the systemic immune system and local inflammation in the microenvironment of luminal fluid of the ES in patients with MD remains unknown.

In the present study, the first direct quantification of the cytokine levels in the luminal fluid of the ES from patients with MD and patients with acoustic neuroma (AN), and in sera from patients with MD, patients with AN and healthy control patients, is provided in order to analyze the differentially expressed cytokines in the diluted luminal fluid of the ES between patients with MD and patients with AN. The correlation between cytokine levels of the diluted luminal fluid of the ES and of the sera of patients was also examined, and the findings were subsequently validated by analyzing the cellular distribution of cytokines that were expressed differentially in the ES of patients with MD using immunohistochemistry and immunofluorescence techniques.

PATIENTS AND METHODS

Selection of Patients and Controls

In total, 20 patients diagnosed with unilateral MD according to the 2015 criteria of Classification Committee of the Bárány Society for the diagnosis of MD (26) were enrolled in the patient group. Samples of ES luminal fluid and peripheral blood were collected from 20 patients (8 males/12 females; mean age = 52.5 years, age range = 35–65 years) undergoing endolymphatic duct blockage (EDB) to treat their intractable MD with magnetic resonance imaging (MRI)-based visualization of unilateral EH at our University Hospital. In total, 20 patients with AN (11 males/9 females, mean age = 55.3 years, age range = 38–68 years) and 20 healthy volunteers (10 males/10 females, mean age = 48.3 years, age range = 28–62 years) were also enrolled as controls. ELF and peripheral blood were sampled from the 20 patients during the AN surgery via the trans-labyrinthine approach at our University Hospital, and peripheral blood was sampled from the 20 healthy controls. The controls with acoustic tumors had severe sensorineural hearing loss, but no history of sudden vertigo. The healthy volunteer controls had no history of sensorineural hearing loss or vertigo, and their audiograms showed normal hearing levels. None of the patients or healthy controls had a history of systemic autoimmune disease, and all of their laboratory parameters, including the electrocardiogram, chest radiography, blood cell counts (red blood cells, white blood cells and platelets), liver and kidney function tests and urinalysis, were normal. The gender distribution and mean ages of the patients and controls were not significantly different ($P < 0.05$ for the chi square test and t test).

Sampling of ELF and Serum

The EDB procedures used for treatment of MD, as described previously (27), were performed in 25 patients with intractable MD with MRI based visualization of unilateral EH between January 2019 and June 2020. After blockage of the distal intraosseous portion of the ES by applying the ligating clip, the proximal extraosseous ES was opened with an L-shaped incision, and the lumen of the ES was carefully identified (**Figure 2A**). As the amount of luminal fluid is very small (<4 μl) and the luminal fluid is distributed non-uniformly in the lumen of the sac, direct aspiration of luminal fluid proved to be very difficult.

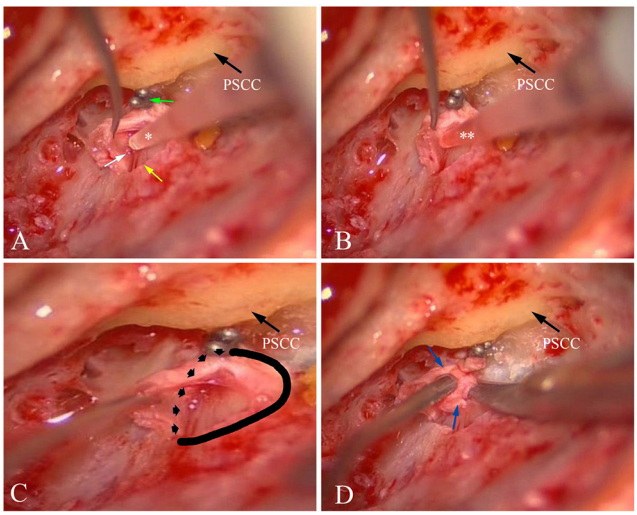

FIGURE 2 | Sampling ELF and collecting ES specimen from patient no. 8 with left MD. **(A)** After blockage of the distal intraosseous portion of the ES using two titanium clips (green arrow) and exposure of the lumen of the ES (yellow arrow), a small amount of fluid (endolymph) could be found (white arrow). Then, 2 μl sterile water (*) was infused into the lumen of the ES. **(B)** 2 μl diluted luminal fluid (**) was aspirated from ES. **(C)** A solid and dotted line was used to mark the border of the ES specimen that would be resected. **(D)** An ES specimen including the distal intraosseous and proximal extraosseous (lateral side) portions (blue arrow) of the ES was resected. PSCC, posterior semicircular canal; ES,endolymphatic sac; ELF, ES luminal fluid; MD, Meniere's disease.

Consequently, 2 μl sterile water was infused into the lumen of the ES (**Figure 2A**), and then 2 μl diluted luminal fluid was aspirated from the lumen of the ES (**Figure 2B**) using a calibrated (1–5 μl) disposable micropipette (Eppendorf, Hamburg, Germany) with an inner diameter of 0.4 mm and an outer diameter of 0.8 mm at the tip, which had previously been scaled with a 2 μl marker and strictly sterilized. The sample was transferred into an Eppendorf tube that had been prefilled with 100 μl sterile water, immediately placed on ice and transferred into an −80°C freezer before further analysis. To avoid contamination by other body fluids, the surgical area was dried using suction and the careful application of haemostatics (13–15). The samples were macroscopically controlled for possible blood contamination, and were discarded if the samples were shown to possess even slightly red-colored fluid. A total of 20 samples of ELF from 25 patients with MD receiving EDB were obtained, as the lumen of the ES in 4 patients with MD could not be identified due to possible hypoplasia or fibrosis of the sac, and one sample was excluded due to possible blood contamination. A total of 20 control samples of ELF from 23 patients with AN were obtained during acoustic tumor surgery via a trans labyrinthine approach between January 2019 and June 2020, as the lumen of ES in one patient was poorly exposed for sampling, and two samples had to be abandoned due to the suspicion of blood contamination.

Blood was sampled from 20 patients with MD and 20 patients with AN, from whom the diluted luminal fluid of the ES was sampled, and 20 healthy volunteer controls for serum cytokine analysis. Following centrifugation at 10,000g for 20 min at room temperature, the supernatant was transferred into an Eppendorf tube and stored at −80°C.

Immunoassay Based on Single Molecular Array

The Simoa Cytokine 6-Plex Panel 1 Advantage kit (cat no. 102958; Quanterix Corp. Billerica, MA, U.S.A.) was used to analyze the cytokines in the diluted luminal fluid of the ES and blood samples. This kit comprises a digital immunoassay based on single molecular array (Simoa) that quantifies the levels of the following human cytokines: IFN-γ, IL-10, IL-12p70, IL-17A, IL-6 and TNF-α. After thawing, the samples were vortex mixed and spun at 10,000 × g for 5 min; subsequently, the supernatant (50 μl) was directly transferred to a Quanterix supplied 96 well plate. The corresponding calibration curves for IFN-γ, IL-10, IL-12p70, IL-17A, IL-6 and TNF-α were constructed, and transferred to the 96 well plate. Assay ranges (pg/ml) were found to be 0.137-353 for IFN-γ, 0.09-152 for IL-10, 0.062-145 for IL-12p70, 0.034-55 for IL-17A, 0.278-500 for IL-6 and 0.176-150 for TNF-α. Control samples and the inter-assay control were also all transferred to the 96-well plate. The 96-well plate was loaded on board, and the desired dilution factor for the samples was created using the Simoa HD-1 Analyzer. Utilizing a 3-step procedure in a reaction cuvette, target antibody-coated paramagnetic beads were combined and incubated with sample alone. Target molecules present in the sample were captured by the antibody coated beads. After washing, biotinylated detector antibodies were mixed and incubated with the beads. The detector antibodies subsequently bound to the captured target during this incubation. Following a second wash, streptavidin-conjugated β-galactosidase (SBG) reagent was added, binding the biotinylated antibodies and leading to SBG enzyme-labeling of the captured cytokine proteins. Following a final wash, the beads were resuspended in resorufin β-D-galactopyranoside (RGP) reagent, transferred to a Simoa disk array and sealed. The cytokine proteins captured by the antibody-coated paramagnetic beads and labeled with the SBG reagent hydrolyzed the RGP substrate, yielding a fluorescence signal. The fluorescence signal values generated from the calibration curve of known concentrations were fitted using a 4-parameter logistic curve and $1/y^2$ weighting. Finally, the concentration of cytokines was determined from their fluorescence signals fitted to the calibration curve.

Tissue Preparation and Immunohistochemistry

Tissue Preparation

i) Sac specimens from patients with MD. EDB surgery provided the opportunity to obtain the sac specimens. A total of 9 small pieces of the intermediate portion of the ES, including the distal intraosseous and proximal extraosseous (lateral side) portions of the ES tissue (**Figures 2C,D**), were obtained from patients undergoing EDB surgery between October 2019 and June 2020. The patients comprised 5 cases with stage III, and 4

cases with stage IV MD, according to staging on the pure tone average at 0.5–3 kHz (28).

ii) Sac specimens from patients with AN. Fresh tissue samples of the human ES were collected during surgery for AN using the trans-labyrinthine approach. After sampling ELF, the bone tissue surrounding ES was dissected and thinned using diamond drills of various sizes. Subsequently, both the intraosseous and proximal extraosseous portions of the ES tissue were resected following removal of a thin shell of bone around the ES, with the exception of the endolymphatic duct and the part of the ES located on the sigmoid sinus. A total of 10 ES specimens from 10 patients were collected between January 2019 and June 2020.

Immunohistochemistry Analysis

Subsequently, tissues were fixed with 4% paraformaldehyde solution for 12 h, and then transferred sequentially to 50, 70, 95 and 100% ethanol baths (1 h each bath) for dehydration. Then, samples were infiltrated by molten paraffin wax in the oven for 1 h, before being embedded into paraffin wax blocks. Paraffin-embedded ES tissues were sectioned at 5-μm thickness for subsequent immunohistochemistry. Slides were deparaffinized and rehydrated in 3% hydrogen peroxide for 5 min. After antigen retrieval by 1% sodium dodecyl sulfate in PBS for 10 min, slides were blocked in 10% horse serum (Abcam) in PBS for 1 h. Primary antibodies (100 μl, 1:400 dilution) against IL-6 [Cusabio Biotech Co., Ltd., TX, USA; cat. no. CSB PA06757A0Rb, rabbit anti-*Homo sapiens* (human) IL-6 polyclonal antibody], IL-10 [IL-10, Abcam, Cambridge, UK; cat. no. AB189392, Rat monoclonal (JES5-2A5)], IFN-γ [Thermo Fisher Scientific, Inc., Waltham, MA, USA; MM700B, murine recombinant] and TNF-α [Abcam, Cambridge, UK; cat. no. AB183218, rabbit monoclonal (EPR19147) to TNF-α] in 0.1% Triton-PBS (PBST) were applied to the samples overnight at room temperature. Negative control samples were processed simultaneously in an identical manner, with the exception that PBST was used to replace primary antibody. Slides were incubated with horseradish peroxidase-conjugated secondary antibody (Beyotime Institute of Biotechnology, Jiangsu, China; 1:200) for 1 h, and then washed three times in PBS. After gently washing in PBS three times, the samples were incubated in diaminobenzidine solution (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan; 1:50) for visualization. Finally, after washing with PBS, the samples were dehydrated and mounted with cover glasses. The immunohistochemical assessment was performed and agreed upon by two pathologists who were blinded to all patient clinical data. The positive immunoreactivity localized at the plasma membrane of epithelial cells was evaluated. Staining was scored for intensity (0: no staining; 1: weak; 2: moderate; 3 and 4: strong) and proportion of cells stained (0: 0%; 1: > 0% to ≤25%; 2: > 25% to ≤50%; 3: > 50% to ≤75%; 4: > 75–100%).

Immunofluorescence Staining

For immunofluorescence staining, the same steps were followed as described above for the staining of the immunohistochemical samples, with the exception that, following incubation with the primary antibodies, the relevant Invitrogen® fluorescent secondary antibodies (Thermo Fisher Scientific, Inc., Waltham, MA, USA; cat. no. A-11034,1:400 dilution) were incubated for 2 h at 37°C. After washing with 0.1 M PBS, the slides were mounted using antifading medium (with DAPI). Slides were then checked via confocal microscopy. Confocal images were acquired using a laser scanning confocal microscope (Leica TCS SP5, Leica Microsystems GmbH, Mannheim, Germany) equipped with 561 and 633 nm lasers for excitation and a 63x oil immersion objective (1.4 NA, Leica). The IF assay was used to examine the expression and localization of TNF-α, IL-6, IFN-γ and IL-10 in ES from the sac specimens of patients with MD.

Statistical Analyses

Data are presented as the mean values ± standard deviation. For statistical analysis, a paired Student's t-test was used for two-group comparisons, whereas Pearson's test was adopted for evaluating the relationship. $P < 0.05$ was considered to indicate a statistically significant value. For cytokine measurements, when variances among the serum groups were equal, one-way ANOVA was used to compare the groups. All data were statistically treated with SPSS version, 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Expression Levels of the Cytokines in the Various Samples

Table 1 shows the levels of IFN-γ, IL-12p70, IL-6, IL-10, TNF-α and IL-17A in the luminal fluid of the ES from the MD and the AN groups, and of the serum from the MD and AN groups and the healthy control group, as detected using a Simoa Cytokine 6-Plex Panel 1 Advantage kit. Data (pg/ml) are presented as the mean values ± SD. All cytokines were detected in samples of the diluted luminal fluid of the ES, including the MD and AN groups, and the serum from the MD, AN and healthy groups. Samples with readings below the minimum detection limit or above the maximum detection limit were assigned values of 0 pg/ml for the minimum value, or 1,000 pg/ml for the maximum value. In samples of the diluted luminal fluid of the ES, no samples were identified that were above the maximum value in either the MD group or the AN group, whereas two samples from the AN group for IFN-γ, one sample from the MD group and two samples from the AN group for TNF-α, one sample from the MD group and two samples from the AN group for IL-17A, and one sample from the MD group and three samples from the AN group for IL-12p70, exhibited values below the detection limit. In the serum samples, no samples with readings below the minimum detection limit or above the maximum detection limit were identified in any of the three groups.

Significant differences were noted in the expression levels of IFN-γ ($P < 0.001$), IL-6 ($P = 0.008$) and TNF-α ($P = 0.036$) in the luminal fluid of the ES compared between the MD and AN groups, whereas no statistically significant differences were observed in the expression levels of IL-10 ($P = 0.154$), IL-12p70 ($P = 0.344$) and IL-17A ($P = 0.659$) in the luminal fluid of the ES comparing between the MD and AN groups (**Figure 3A**).

Cytokine levels of serum in the MD group were then compared with those of the AN group and the heathy control

TABLE 1 | Cytokine levels in ES luminal fluid from MD group and AN group, and the serum from MD group, AN group and healthy control group (mean ± SD).

	IL-6	IFN-γ	TNF-α	IL-10	IL-12p70	IL-17A
MD ELF ($n = 20$)	1.371 ± 0.5427	0.2787 ± 0.0942	0.2656 ± 0.0797	0.1346 ± 0.0296	0.0870 ± 0.0265	0.0721 ± 0.0300
AN ELF ($n = 20$)	0.8939 ± 0.5290	0.1601 ± 0.0610	0.2094 ± 0.0834	0.1551 ± 0.0491	0.0773 ± 0.0367	0.0783 ± 0.0545
AN ELF ($n = 20$)	2.3370 ± 0.8382	1.4361 ± 0.3770	3.291 ± 0.6611	1.5989 ± 0.5002	0.2599 ± 0.1332	0.1528 ± 0.1886
AN serum ($n = 20$)	2.2251 ± 0.8881	1.5293 ± 0.3879	3.4988 ± 0.5981	1.7497 ± 0.4699	0.2077 ± 0.0938	0.1196 ± 0.0679
Control serum ($n = 20$)	2.1033 ± 0.7608	1.5933 ± 0.3208	3.4927 ± 0.7303	1.7255 ± 0.5332	0.2473 ± 0.1136	0.1095 ± 0.0422

MD, Meniere's disease; AN, acoustic neuroma; ELF, ES luminal fluid; SD, standard deviation; n, number.

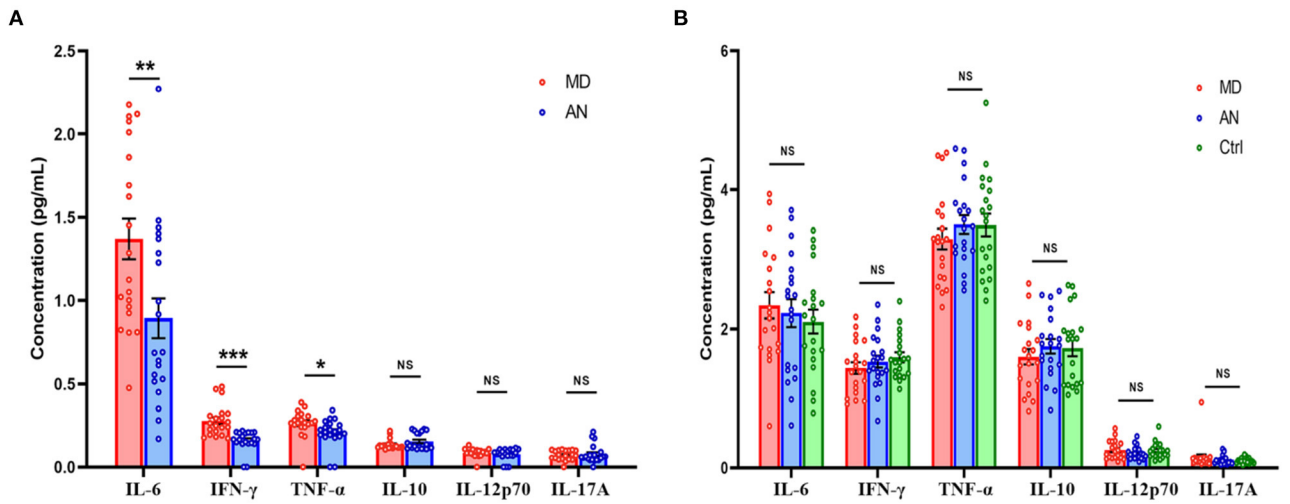

FIGURE 3 | (A) Cytokine levels of ELF in the MD group compared with those in the AN group. **(B)** Cytokine levels of the serum in the MD group compared with those in the AN group and the healthy control group. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ES, endolymphatic sac; ELF, ES luminal fluid; MD, Meniere's disease; AN, acoustic neuroma.

group. No statistically significant differences in the expression levels of IFN-γ ($P = 0.445$), IL-10 ($P = 0.332$), IL-12p70 ($P = 0.160$), IL-17A ($P = 0.464$), IL-6 ($P = 0.684$) or TNF-α ($P = 0.304$) were identified in the serum comparing between the MD and AN groups; neither were there any statistical significant differences found in the expression levels of IFN-γ ($P = 0.164$), IL-10 ($P = 0.444$), IL-12p70 ($P = 0.749$), IL-17A ($P = 0.323$), IL-6 ($P = 0.362$) or TNF-α ($P = 0.365$) in the serum comparing between the MD group and the healthy control group (**Figure 3B**).

No significant correlations were observed in the expression levels of IFN-γ ($r^2 = 0.038$, $P = 0.408$), IL-10 ($r^2 = 0.038$, $P = 0.409$), IL-12p70 ($r^2 = 0.041$, $P = 0.394$), IL-17A ($r^2 = 0.029$, $P = 0.475$), IL-6 ($r^2 = 0.004$, $P = 0.798$) and TNF-α ($r^2 = 0.059$, $P = 0.302$) compared between the ELF and serum in the MD group. Similarly, no significant correlations in the expression levels of IFN-γ ($r^2 = 0.026$, $P = 0.499$), IL-10 ($r^2 = 0.016$, $P = 0.595$), IL-12p70 ($r^2 = 0.004$, $P = 0.401$), IL-17A ($r^2 = 0.024$, $P = 0.512$), IL-6 ($r^2 = 0.113$, $P = 0.147$) and TNF-α ($r^2 = 0.025$, $P = 0.502$) were observed comparing between the ELF and serum in the AN group.

Immunohistochemical and Immunofluorescent Detection of the Cytokines in the Surgically Removed Human ES of Patients With MD and AN

Morphology in all specimens was well preserved at the light microscopic level. The ES specimens in patients with MD only comprised the intermediate portion of the ES, including the distal intraosseous and proximal extraosseous (lateral side) portions of the ES tissue, which is also termed "rugose" since its epithelium is folded and contains secretory-like epithelial tubules, whereas the majority of ES specimens in patients with AN contained a substantial intraosseous and extraosseous portion of the ES (**Figures 4A–C**). Concerning TNF-α, positive immunostaining occurred in the epithelium of the ES, as well as in the subepithelial connective-tissue fibroblasts, showing a positive expression in 9 out of 9 ES specimens from patients with MD, including the strong staining of epithelial cells in 5 specimens (**Figure 5A**), moderate staining of epithelial cells in 3 specimens and weak staining of epithelial cells in 1 specimen, whereas a weak staining of epithelial cells of TNF-α (**Figure 5B**)

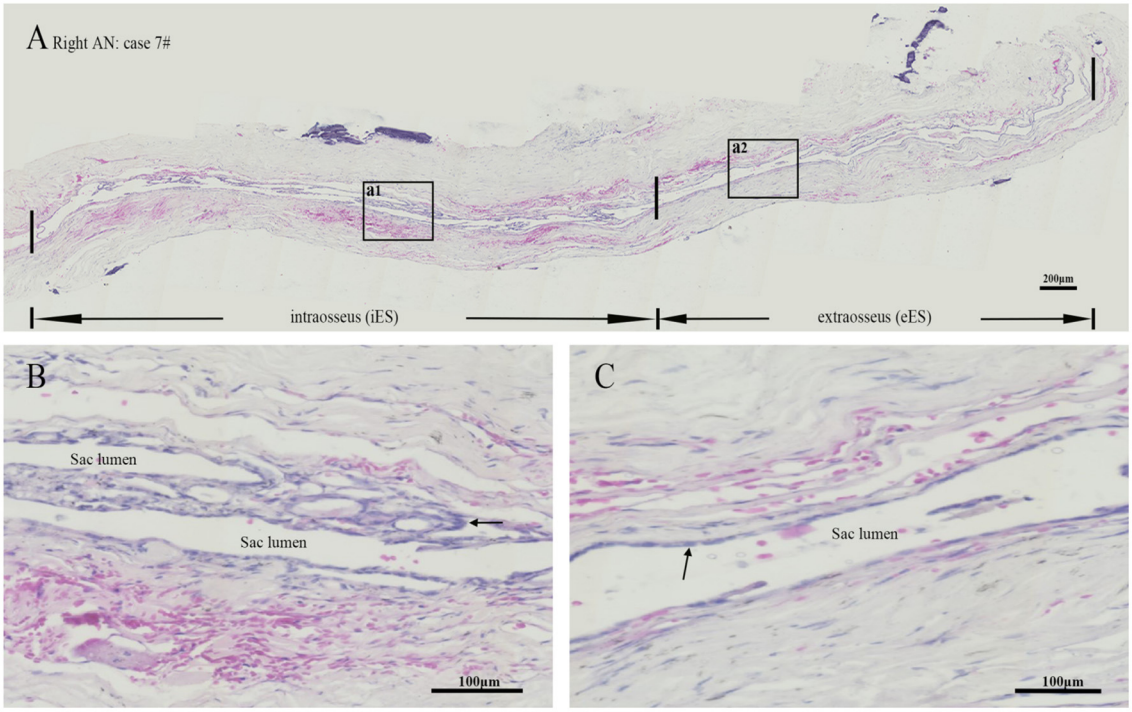

FIGURE 4 | Hematoxylin-Eosin staining revealed a lumen was patent or slit-like in the intraosseous and extraosseous portions of the ES from patient no. 7 with acoustic neuroma **(A)**, whereas the framed area of a1 in **(A)** magnified to show an intact folded epithelial (arrow) lining in the lumen of intraosseous part of ES **(B)** and the framed area of a2 in **(A)** magnified to show a simple cuboidal epithelium (arrow) lining in the lumen of extraosseous portion of the ES **(C)**. ES, endolymphatic sac. Scale bars: **(A)** 200 μm; **(B,C)** 100 μm.

in 4, and a negative expression of TNF-α in 6 ES specimens from patients with AN were detected. Concerning IL-6, this cytokine exhibited prominent staining along the epithelial lining of the sac, demonstrating a positive expression in 7 out of 9 ES specimens from patients with MD, including epithelial cells immunolabeled strongly (**Figure 5C**) in 4, moderately in 2 and weakly in 1, whereas a negative expression of IL-6 in all ES specimens of patients with AN was observed (**Figure 5D**). Regarding IFN-γ, immunoreactivity was seen in the epithelial lining of the ES in 7 out of 9 ES specimens from patients with MD, whereas strong staining in 4 and moderate staining in 3 were shown in the epithelial cells of ES, although no positive expression of IFN-γ was observed in the epithelial lining of the ES of patients with AN (**Figures 5E,F**). Moreover, a negative expression of IL-10 in the epithelial cells of the ES was detected in both the MD and the AN groups (**Figures 5G,H**).

Immunofluorescent staining showed a strong cytoplasmic immunofluorescence signal for IL-6 (**Figure 6A**), IFN-γ (**Figure 6B**) and TNF-α (**Figure 6E**) and a minimal cytoplasmic immunofluorescence signal for IL-10 (**Figure 6F**) along with the marker of nuclei, DAPI (blue) (**Figures 6C,G**) in the epithelial cells of the ES from the sac specimens of patients with MD. Meanwhile, confocal images demonstrated that IFN-γ and IL-6 were mainly expressed in the cytoplasm and membranes of the ES epithelium (**Figure 6D**), whereas TNF-α immunolabeling was localized not only in the cytoplasm and membranes of the ES epithelium, but also in the sub-epithelial tissue and sub-epithelial fibrocytes (**Figure 6H**).

DISCUSSION

To the best of the authors' knowledge, this study has provided the first direct measurements of cytokines in human luminal fluid of ES. The approach of using a Simoa Cytokine 6-Plex analysis of the diluted luminal fluid of the ES was shown to be feasible, and this has provided more refined insights into the microenvironment of the ES in MD where these methods have not been used previously. The present study has highlighted the up-regulated expression of TNF-α, IL-6 and IFN-γ in the luminal fluid of ES in patients with MD through investigating the expression level of the cytokines in the ELF in patients with MD and controls. Moreover, a positive expression of TNF-α, IL-6 and IFN-γ in the epithelial cells lining the sac was detected in the majority of ES specimens from patients with MD through immunohistochemical and immunofluorescent investigation, and this confirmed the up-regulation of expression of these cytokines in the luminal fluid of ES. Additionally, the fact that no significant correlation was identified in cytokine expression between the luminal fluid of the ES and the serum suggested that specialized mechanism(s) exist that regulate the expression of cytokines in the ES. The results of the present study

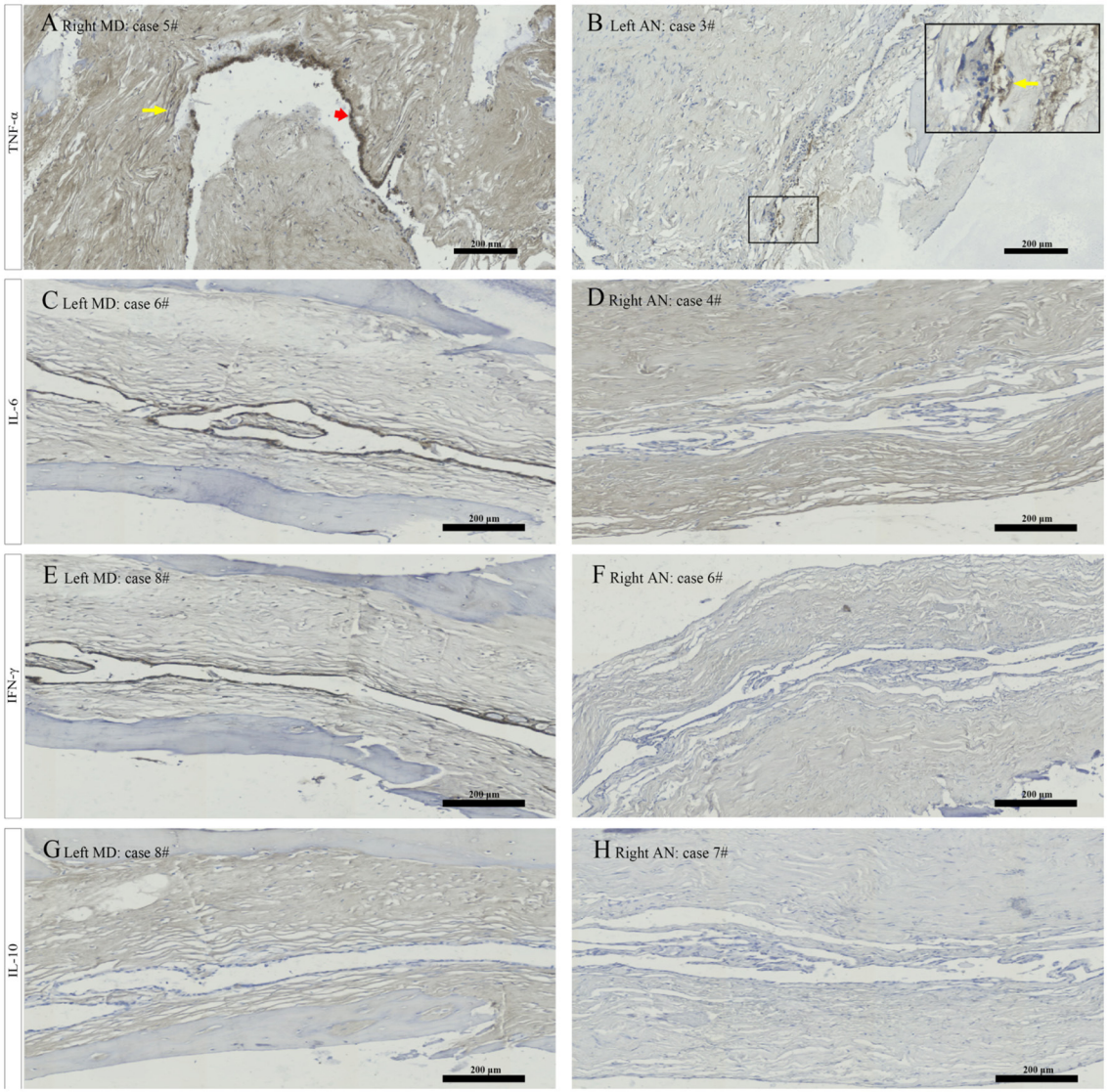

FIGURE 5 | Immunostaining for TNF α showed strong staining of epithelial cells (red arrowhead) and weak staining of the subepithelial fibroblasts (yellow arrow) in patient no. 5 with right MD **(A)**, and weak staining of epithelial cells in the magnified framed area (yellow arrow) in patient no. 3 with left AN **(B)**. Immunostaining for IL 6 revealed strong signal in the ES epithelium in patient no. 6 with left MD **(C)** and no positive expression of epithelial cells in patient no. 4 with right AN **(D)**. Immunostaining from ES specimen in patient no. 8 with left MD showed strong labeling along the epithelial lining of ES for IFN γ **(E)** and a negative expression in the epithelial cells of ES for IL-10 **(G)**. Whereas a negative expression of the ES epithelium for IFN γ in patient no. 6 with right AN **(F)** and IL-10 in patient no. 7 with right AN **(H)** were detected. MD, Meniere's diseae; AN, acoustic neuroma; ES, endolymphatic sac. Scale bars: **(A–H)** 200 μm.

should contribute toward the development of novel strategies for the diagnosis and treatment of MD.

TNF-α and IL-6 are pro-inflammatory cytokines that have key functions in diverse cellular processes, including regulation of the pro-inflammatory responses and maintenance of cellular homeostasis. Previous studies have shown that TNF-α is a harmful factor for cochlea inflammation (7), and IL-6 is necessary both for B-cell development into plasma cells and their antibody production, and this is associated with infections or other inflammatory cascades (7, 29). Several studies have reported that the *in vivo* production of TNF-α, IL-1β and IL-6 has the potential to induce secondary inflammatory responses, including leukocyte infiltration, scar formation or gliosis in injured cochlea (30, 31). Moreover, elevation of the levels of TNF-α and IL-6 are considered to be involved in immune cell proliferation, prolongation of the inflammatory response and tissue remodeling in numerous middle and inner ear maladies (19, 30, 32). In the present study, the elevated levels of TNF-α and IL-6 in the luminal fluid of the ES, and a positive expression of TNF-α and IL-6 in the epithelial cells lining the sac from patients with MD compared with those of the controls, may represent a prolonged immune response and

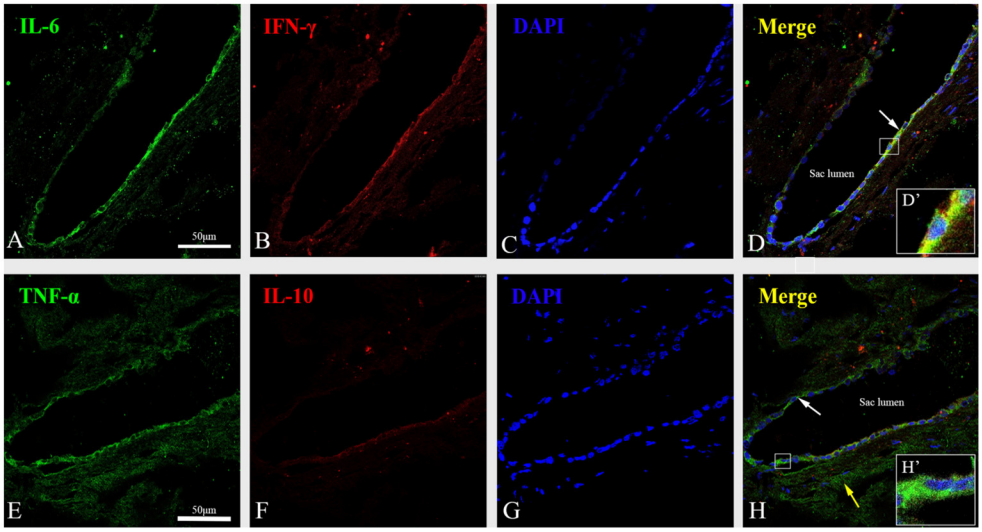

FIGURE 6 | Immunofluorescent staining showed a strong cytoplasmic immunofluorescence signal for IL-6 (green) **(A)**, IFN-γ (red) **(B)** and TNF-α (green) **(E)**, and a minimal cytoplasmic immunofluorescence signal for IL-10 (red) **(F)** along with the marker of nuclei, DAPI (blue) **(C,G)** in the proximal extraosseous part of the ES in patient no. 8 with MD. **(D)** The co-localization regions of IL-6 and IFN-γ showed color in yellow in ES epithelia cells (arrow) in the merged image. The framed area is magnified in (D′), showing that IFN γ and IL-6 were mainly expressed in the cytoplasm and membrane of the ES epithelium. **(H)** Merged image of immunofluorescent labeling for TNF-α and IL-10 showed color in green in ES epithelia cells (white arrow) and the sub-epithelial tissue and Sub-epithelial fibrocytes (yellow arrow). The framed area is magnified in (H′), showing the expression of TNF-α was localized in the cytoplasm and membrane of the ES epithelium. MD, Meniere's disease; ES, endolymphatic sac. Scale bars: **(A–H)** 50 μm.

excessive inflammation with epithelial immunological injury and remodeling in the ES, where the epithelial cells lining parts of the endolymphatic spaces are crucially important for Na^+ transport capacity (33). The ensuing cellular degeneration and dysfunction of the ES may lead to an ionic imbalance in the endolymph, resulting in the accumulation of endolymph at the cochlear duct. Recently, degenerative and hypoplastic changes in the ES of patients with MD have been directly linked to the pathogenesis of EH (34). Interestingly, altered TNF-α expression has been proposed to have a significant role in MD, and TNF-α inhibitors are being preliminarily investigated as a possibility for therapeutic intervention (35). In mouse models, systemic injection of the TNF blocker, etanercept, resulted in a reduction in the cytokine expression levels of a number of cells in the ES lumen (7) and protection against TNF-α-induced sensorineural hearing loss (SNHL) (36), whereas the loss of IL-6 production in knock-out mice was shown to suppress macrophage recruitment and decrease local inflammation (37). In another study, the blockage of IL-6 by specific humanized neutralizing antibodies was clinically used for patients with rheumatoid arthritis or inflammatory bowel disease with promising effects (38). Although the findings of the present study have provided direct evidence for the inflammatory state of the ES, more research is needed for further development of therapeutic strategies for treatment of MD.

IFN-γ is a T-cell cytokine that induces macrophages to produce a variety of inflammatory mediators and reactive oxygen and nitrogen intermediates. Several studies using cultured human ES epithelium have demonstrated changes in Na^+ transport during the application of IL-1β (39, 40). Son et al. (41) reported that the Na^+ transport activity mediated via the epithelial Na^+ channel, Na^+-H^+ exchanger, was significantly decreased following the application of IFN-γ. On the basis of these experimental studies, an up-regulated expression of IFN-γ in the luminal fluid of ES from patients with MD compared with those of controls, and a positive expression of IFN-γ in the epithelial cells lining the sac, could be expected to decrease Na^+ transport in the ES lumen, which may consequently cause higher luminal [Na^+] and an increased luminal fluid volume, since water shift usually accompanies Na^+ movement. Recently, loss or absence of aldosterone regulated Na^+ transport proteins in degenerative and hypoplastic ES pathology has been exhibited in the ES specimens of patients with MD (34). This may support one of the pathological mechanisms for EH under certain inflammatory conditions of the ES. Accumulating evidence supports the link between the pro-inflammatory cytokine profile in peripheral blood mononuclear cells and the pathogenesis of MD, including higher basal levels of IL-1β, IL-6 and TNF-α and a release of TNF-α induced by both *Aspergillus and Penicillium* extracts in several patients with uni- or bilateral MD (35). The allelic variation in rs4947296, at 6p21.33, developing a nuclear factor-κB (NF-κB)-mediated inflammatory response, are supposed to be related to an abnormal inflammatory response at the ES in bilateral MD (21), and there are higher levels of cytokines/chemokines in patients with MD with high basal levels of IL-1β (42). Additionally, significant differences in CD4, CD4/CD8 and CD23 lymphocyte subpopulations and IFN-γ and IL-4 levels in the peripheral blood of patients with MD

were observed when they were compared with controls (43). However, the present study showed no statistical differences in IFN-γ, IL-10, IL-12p70, IL-17A, IL-6 and TNF-α levels in the serum comparing among the MD and AN groups and a healthy control group, indicating an aberrant systemic pro-inflammatory response was not found in these unilateral patients with MD. Moreover, no correlation was found between the expression of cytokines in the luminal fluid of the ES and that in the serum from patients with MD and patients with AN, suggesting the existence of different mechanisms involving the modulation of the expression of cytokines in the ES and blood. Considering that increases in IFN-γ, TNF-α and IL-6 levels were observed in the luminal fluid of ES in these patients with MD, this could indicate that a specialized mechanism independent of the systemic cytokine response may be causing the abnormal cytokine-mediated inflammatory response at the ES, demonstrating increased levels of IFN-γ, TNF-α and IL-6 in the ES lumen and a positive expression of TNF-α, IL-6 and IFN-γ in the epithelial cells lining the sac. On the other hand, this increased production of cytokines could also affect or represent immune activity that is occurring in ES. Several studies have shown the ES could be a target organ attacked by the allergic reaction (5), viral or bacterial infection (9–11), autoimmunity (13–15), otitis media-induced inflammatory products and toxins (44), circulating immune complexes (45), genetic predisposition to altered NF-κB-mediated inflammatory responses (21) and distinct and altered cytokine profiles (16), resulting in the damage of the epithelial layers surrounding the ES space and the dysfunction of ES. However, it was noticed that no statistically significant difference in the expression level of IL-10 in the ELF between the MD and AN group and a negative expression of IL-10 in the epithelial cells of the ES in patients with MD were observed. It is known that IL-10 is a potent anti-inflammatory cytokine. Induction of IL-10 often occurs together with pro-inflammatory cytokines, although pathways that induce IL-10 may actually negatively regulate these pro-inflammatory cytokines (46). The reason for an unaltered expression level of IL-10 in the ES of patients with MD in whom an up regulated expression of TNF-α, IL-6 and IFN-γ in the ES was detected is unclear, which need to be studied further.

The treatment of MD using EDB has been shown to be effective for the control of symptoms of MD without any noticeable cochlear and vestibular damage (47, 48), thereby providing opportunities for sampling ELF and ES specimens in order to investigate the protein composition and molecular biomarkers in human ES of MD. However, superior levels of medical expertise and carefulness are required in sampling the luminal fluid of the ES from human subjects such that contaminating the samples with surrounding tissue fluids and blood is avoided. It must be acknowledged that the samples could have been contaminated from surrounding tissues, fluids and blood. As we have mentioned above, one sample in patient with MD and two samples in patients with AN had to be abandoned due to the suspicion of blood contamination. Recently, Ölander et al. (49) reported an *in vivo* and *in situ* sampling probe technique for collecting ES endolymph samples, which provided a novel way for sampling of proteins in the luminal fluid of the ES. To reduce the risk of contamination of samples, they proposed that the area for sampling was first thoroughly rinsed with Ringer's acetate solution before final drilling and opening of the vestibular aqueduct, and the sampling probe was covered with a metal sleeve that was removed as the probe was inserted into the ES. However, in contrast with the procedure of obtaining 200 μl sample (diluted luminal fluid) from 200 μl normal saline infused into the ES that has been reported in the literature (14, 15), 2 μl sample obtained from 2 μl sterile water infused into the ES in the present study could possibly reduce the risk of the contamination of samples with other body fluids. Moreover, a standard volume (2 μl) of ELF sampled from each person recruited in our study also had an advantage in terms of quantitative analysis of the amounts of protein in the controls and patients. Recently, Warnecke et al. (50) reported that multiplex protein analyses were feasible in very small samples (∼1 μl or less) of human perilymph fluid and was able to identify marker proteins of sterile inflammation as well as of the innate and adaptive immune system using Luminex-based multiplex arrays (human 27-Plex). In the present study, the use of a single-molecular enzyme-linked immunosorbent assay, which has been reported to have the potential to detect soluble immune signaling molecules at an ultralow detection limit of 0.67 fM (0.012 pg/ml) (51, 52), enabled us to perform the quantitative detection of subfemtomolar concentrations of cytokines in 2 μl diluted luminal fluid of ES, thereby demonstrating the feasibility of identifying biomarkers of inner ear disease in very small amounts of diluted luminal fluid of ES using this highly sensitive and specific technique.

There were, however, certain limitations associated with the present study. This is an ambitious experimental setup due to: (i) the difficulties of identification of the lumen in ES, and (ii) the skill needed to take samples of the diluted luminal fluid without any intraoperative contamination occurring. Thus, we need to consider that the area surrounding the sac remains almost dry during luminal fluid sampling, as shown in **Figures 2A,B**. Through using bone wax, electrocautery and careful suction for cleaning, the risk of intra-surgical contamination can be reduced. Theoretically, the use of the luminal fluid of ES from patients with normal hearing as a control would have improved our study; however, sampling the luminal fluid of ES from patients with normal function of the inner ear would have been impossible for ethical reasons. In addition, the interpretation of the results in this study was possibly affected by using the ELF from patients with AN as a control for a comparative analysis of the cytokine levels in the ELF in patients with MD, since an up-regulation of intracochlear levels of TNF-α secreted by tumors possibly present in patients with AN are presumed to result in AN-associated SNHL (53).

In conclusion, the up-regulated expression of TNF-α, IL-6 and IFN-γ in the luminal fluid of ES, in the absence of any aberrant systemic pro-inflammatory response, has provided direct evidence for an increased local inflammatory response at the ES in these patients with unilateral MD, and this phenomenon was validated by demonstrating a positive expression of TNF-α, IL-6 and IFN-γ in the epithelial cells lining the sac in human ES specimens from patients

with MD using immunohistochemical and immunofluorescent analysis. However, no significant correlation was identified between the cytokine levels of the ELF and the cytokine levels of the serum, suggesting that a specialized mechanism for the regulation of cytokines is likely to be operating in the ES.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

CH and ZZ designed and accomplished the experiments together. QW provided technical advice. XP and WLi conducted the experiments. WLiu participated in the revision of the manuscript. AP being the Principal Investigator of the research project, directed the design, and the procedure of the experiments. WJ and LH analyzed data and drafted the paper. All authors approved the final version of the manuscript.

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Efficacy of Resection of Lateral Wall of Endolymphatic Sac for Treatment of Meniere's Disease

*Daogong Zhang, Yafeng Lv, Xiaofei Li, Yongdong Song, Ligang Kong, Zhaomin Fan and Haibo Wang**

Department of Otolaryngology-Head and Neck Surgery, Shandong Provincial ENT Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Background: To explore the long-term efficacy and safety of resection of the lateral wall of the endolymphatic sac for the treatment of intractable Meniere's disease (MD) as an alternative surgical procedure for treating this disorder.

Methods: Data from 73 patients who were referred to our hospital and diagnosed with unilateral MD between January 2015 and June 2019 were retrospectively analyzed in this study. Seventy-three patients who had frequent vertigo even after receiving standardized conservative treatment for at least half a year underwent resection of the lateral wall of the endolymphatic sac. Vertigo control and auditory function were assessed. Pure tone audiometry, caloric test, and vestibular evoked myogenic potential were performed to evaluate audiological and vestibular functions. The post-operative follow-up duration was more than 2 years.

Results: Among the 73 patients (male 34 cases, female 39 cases; age 20–69 years, average 51.4), vertigo was controlled effectively for 66 cases (90.4%) after 2 years of follow-up; 45 cases (61.6%) were completely controlled, and 21 cases (28.8%) were substantially controlled in this study. The patients of 16.4% had hearing loss with more than 10 dB change based on the four-tone average (0.5, 1, 2 and 3 kHz). No patient had a facial nerve weakness, cerebrospinal fluid leakage, or other complications.

Conclusion: Resection of the lateral wall of the endolymphatic sac, which can effectively control vertiginous symptoms in intractable MD patients, represents an effective and safe therapy for this disease. Resection of the lateral wall of the endolymphatic sac is expected to be used as an alternative treatment for MD.

Keywords: Meniere's disease, vertigo, sensorineural hearing loss, resection of the lateral wall of the endolymphatic sac, surgery

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****Correspondence:***
Haibo Wang
whboto11@163.com

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INTRODUCTION

Meniere's disease (MD) is a common inner ear disorder characterized with intermittent episodes of vertigo, fluctuating sensorineural deafness, tinnitus, and/or aural pressure. Its prevalence ranges from 3.5% to 513 per 1,00,000 (1).There is currently no cure for this disease because its pathogenesis has not been established; ∼80% patients can be free from vertigo after changes in lifestyle and medical treatment (1). Surgical procedures are considered when medical

treatment fails to control vertigo. Endolymphatic sac surgery is widely used in patients with intractable MD; however, the rate of vertigo control is only 60–80%, and the benefit of this surgery is still debated (2–4). Vestibular neurectomy has a high rate of vertigo control, but it has several risks (5). Labyrinthectomy is only reserved as a last resort for those MD patients with total deafness (6).

In recent years, we have used resection of the lateral wall endolymphatic sac surgery to treat 73 cases of intractable MD and followed up for more than 2 years. The effectiveness and safety of this method were evaluated to provide a basis for its application to the treatment of intractable MD.

MATERIALS AND METHODS

Patients

This study enrolled 73 patients (34 men, 39 women; age range 20–69 years, mean 51.4 years) diagnosed with ipsilateral MD according to the criterion by Barany society (7) and referred to vertigo clinic of our hospital between January 2015 and June 2019. The average course of these 73 patients was 72.8 months (24–480 months) (**Table 1**). All patients received standard medical treatment, consisting of betahistine 12 mg tid and hydrochlorothiazide 25 mg bid for over 6 months, but they continued to experience vertigo. All the patient had no migraine medical history and performed a battery of tests including auditory and vestibular examination and Gd-enhanced magnetic resonance imaging (MRI) to exclude the patients with vestibular migraine, cerebellopontine angle tumors or other intracranial space-occupying lesions. High resolution computerized tomography (CT) evaluation is performed before the surgery. Surgery is performed only when the anatomical conditions for endolymphatic sac surgery are available. All patients underwent resection of the lateral wall of the affected lymphatic sac. All patients were followed up for 2 years. The evaluation of treatment effects mainly focused on vertigo control and hearing change. The follow-up involved questionnaires, visits, and audiology and vestibular function examinations. Caloric test, vestibular evoked myogenic potential (VEMP) and pure tone audiometry were performed before and 2 years after the surgery.

To better evaluate the efficacy of endolymphatic sac resection, 33 patients who underwent endolymphatic sac decompression at the same time were allocated to the control group. They included 15 men and 18 women, with an average age of 50.1 years (22–70 years) and an average course of 73.3 months (18–444 months). Both the endolymphatic sac decompression and a lateral wall resection were offered to the MD patients with surgical indications. It completely depends on the patients' decision.

The study was approved by the Ethics Committee of Shandong Provincial ENT Hospital. All patients provided written informed consents.

Surgical Procedures

Surgery was performed with a postauricular approach under general anesthesia.

TABLE 1 | The demographic information and outcomes of patients with resection of the lateral wall of endolymphatic sac and endolymphatic sac decompression patients.

	Resection of the lateral wall of endolymphatic sac	Endolymphatic sac decompression	*P* value
Sex			>0.05
Male	34	15	
Female	39	18	
Age	51.4	50.1	>0.05
Disease duration (months)	72.8	73.3	>0.05
Pure tone average (dB) before treatment	49.6	48.1	>0.05
Vertigo control rate (%)	90.4	72.7	<0.05
Hearing loss rate (%)	16.4	9.1	>0.05
Tinnitus improvement (%)	42.5	39.4	>0.05

The middle cranial fossa meninges, sigmoid sinus, sinus meningeal angle, and horizontal semicircular canal were exposed through a mastoidectomy. The endolymphatic sac was found between the sigmoid sinus and the posterior semicircular canal. The lateral wall of the endolymphatic sac was incised and a full blunt separation was performed between the inner wall and the outer wall. The isolated lateral wall of the endolymphatic sac was removed. After the bleeding was completely stopped, the incision was sutured and the surgery was completed.

Evaluation of Vertigo

A definitive episode of vertigo lasting more than 20 min was regarded as Meniere's vertigo according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria issued in 1995 (8). Patients were instructed to record acute spells of vertigo, coexisting symptoms (such as tinnitus, changes in hearing, aural fullness), and other characteristics, including time of onset and duration in a diary for the full 24 months of study. The average number of definitive spells in the last 6 months after therapy/average number of definitive spells in 6 months period before therapy × 100 = numeric value, where the numeric values are: 0 = complete control of definitive spells (class A); 1–40% = substantial control of definitive spells (class B); 41–80% = limited control of definitive spells (class C); 81–120% = insignificant control of definitive spells (class D); and >120% = worse control of definitive spells (class E). Effective vertigo control was defined as class A (complete control) and B (substantial control). After 2 years, patients with scale A and B were considered as having effective vertigo control according to the criteria of the AAO-HNS criteria issued in 1995.

Evaluation of Hearing

Hearing was measured by a pure tone audiometer both using air- and bone-conducted pure-tone detection thresholds. The evaluation was based on the four-tone average (0.5, 1, 2, and 3 kHz) calculated according to the 1995 AAO-HNS criteria

(8). The worst hearing level of the affected ear within the 6 months before surgery was compared with that between 18 and 24 months after surgery. Changes >10 dB were designated as "better" or "worse," and changes <10 dB were designated as "no change" according to the 1995 AAO-HNS criteria.

Evaluation of Tinnitus

According to the severity of tinnitus, tinnitus was divided into six grades. Grade 0, without tinnitus. Grade 1, occasionally tinnitus, but no pain; Grade 2, persistent tinnitus, worse when quiet; Grade 3, persistent tinnitus even in noisy environment; Grade 4, persistent tinnitus with attention and sleep disturbances; Grade 5: persistent severe tinnitus and unable to work; Grade 6, the patient is suicidal due to severe tinnitus. The improvement of tinnitus degree $\geq$1 has clinical significance.

Caloric Test

The procedure of the bithermal caloric test had been reported on our previous study (9). Briefly speaking, each ear was irrigated with a constant flow of air at 24°C and 49°C for 40 s alternatively. The response was recorded over 3 min, and the interval of 7 min between the stimuli was allowed to prevent cumulative effects. A video-based system (Ulmer VNG, v. 1.4; SYNAPSYS, Marseille, France) was used to acquire and evaluate the eye response. The maximum slow-phase velocity of nystagmus after each irrigation was analyzed, and unilateral weakness (UW) was calculated. A UW value of <20% was considered normal.

VEMP Test

The procedure had been reported on our previous study (9). Both cVEMP and oVEMP were tested from 2014 to 2017. Only cVEMP was tested before 2014.

Before 2014, A smart EP device (Intelligent Hearing Systems, USA) was used to record cVEMPs. The electromyographic activity of the sternocleidomastoid muscle (SCM) was recorded when patients lay supine and raise their head up to activate their neck flexors bilaterally. The saccular receptor was excited by air-conducted acoustic stimulation and the recording electrode was placed at the middle third of the SCM ipsilateral to the excited ear. The reference electrode was positioned at the upper edge of the sternum. The ground electrode was positioned at the muscle contralateral to the stimulated side. The amplifier gain was set to 100,000 and the bandpass and signals were filtered from 10 to 3,000 Hz. Short-tone bursts (100 dB n HL, 500 Hz) with a 1 ms rise-fall time and a 5 ms plateau time were delivered monaurally by TDH 49P earphones and the stimulation rate was 5 Hz. The duration of analysis was 60 ms and a total of 128 responses to stimuli were averaged. In order to check the test wave reproducibility, the measurements were repeated twice. A distinctly defined biphasic response was recorded on the SCM ipsilateral to the side of the cathode placement in all patients. We refer to this as p13/n23 response. The amplitudes of the p13-n23 and the peak latencies of p13 and n23 were analyzed. We obtained the averages of the amplitudes and latencies for the two runs. An amplitude ratio over 1.61 for the two ears was considered abnormal. The latencies of p13 exceed 17.3 ms and that of n23 exceed 24.6 ms were considered abnormal.

From 2014 to 2017, VEMPs were recorded by Neuro-Audio auditory evoked potential equipment (Neurosoft LTD, Ivanov, Russia). The test was done with the patients seated. Tone burst stimuli were delivered by an insert earphone (ER-3A). For the cVEMP examination, active recording electrodes were placed within the upper third region of the SCM on both sides. The reference electrodes were positioned on the upper sternum. The ground electrode was positioned on the nasion. The patient was asked to rotate the head toward the contralateral side of the stimulated ear to obtain tonic contraction of the SCM during recording. For the oVEMP examination, active recording electrodes were positioned on the infra-orbital ridge 1 cm below the center of each lower eyelid, and the reference electrodes were placed ∼1 cm below them. A ground electrode was positioned on the nasion. The oVEMP was recorded with eyes open, maximally gazing upward. The stimulation rate was 5.1 Hz and the electrode impedance was maintained below 5 kΩ. We measured the VEMPs with a 500 Hz tone burst and the initial intensity was 110 dB nHL, decreased to the threshold in 5 dB steps. The cVEMP superimposition number was 60 and oVEMP superimposition number was $100 \leq n \leq 200$. The duration of analysis was 0–50 ms and the bandpass filtering of cVEMP was 30–2,000 Hz. The bandpass filtering of oVEMP was 1–1,000 Hz. The latencies of p1 over 17.3 ms and the latencies of n1 over 24.6 ms of cVEMP were considered abnormal. An amplitude ratio over 30% was considered abnormal. The latencies of n1 over 12.6 ms and that of p1 over 17.8 ms of oVEMP were considered abnormal. An amplitude ratio more than 30% was considered abnormal.

Statistical Analysis

The χ^2 test and *t*-test were used to compare the demographic data of the patients who underwent lateral wall resection and sac decompression. *The* χ^2 test was used to compare the vertigo control rates and hearing loss rates of patients who underwent lateral wall resection and those who underwent sac decompression. $p < 0.05$ was considered statistically significant.

RESULTS

In this work, the demographic information for the lateral wall resection and sac decompression groups are presented in **Table 1**. There were no significant differences in sex, age, disease course, and pre-operative hearing level between the two groups.

The total effective rate of vertigo control in the lateral wall resection group was 90.4% (66/73) at the 2-year follow-up, with a complete control rate of 61.6% (45/73) and a substantial control rate of 28.8% (21/73) (**Table 1**). The rate of hearing loss was 16.4% (12/73), hearing improvement was 8.2% (6/73), and hearing was unchanged in 75.3% (55/73). There was no significant difference between the patients with or without hearing loss (**Supplementary Tables 1, 2**). The tinnitus was improved in 31 cases (42.5%) and ineffective in 42 cases (57.5%).

TABLE 2 | Abnormal rate of vestibular function tests pre- and post-operatively in resection of the lateral wall of endolymphatic sac group.

Vestibular function tests	Pre-operative	Post-operative	χ^2 Value	*p* Value
Caloric test	60.3%	63.0%	0.12	$p > 0.05$
cVEMP	53.4%	56.2%	0.11	$p > 0.05$
oVEMP	54.8%	52.1%	0.11	$p > 0.05$

Before surgery, 44 patients (60.3%) had abnormal caloric test results with poor responses on the affected side. Forty-six cases (63.0%) had an abnormal caloric test 2 years after treatment. Thirty-nine cases (53.4%) had abnormal cVEMP before the operation, with a decreased amplitude in the affected ear. Forty-one cases (56.2%) were abnormal 2 years post-operatively. Forty patients (54.8%) had abnormal oVEMP before surgery, with a decreased amplitude in the affected ear, and 38 cases (52.1%) were abnormal 2 years after the operation. There were no significant differences before and after the operation (**Table 2**; **Supplementary Table 3**). None of the patients had any complications, such as facial weakness or cerebrospinal fluid leakage.

The total control rate of vertigo in the endolymphatic sac decompression group was 72.7% (24/33), with a complete control rate of 45.5% (15/33) and a substantial control rate of 27.3% (9/33). The hearing loss rate was 9.1% (3/33). The tinnitus was improved in 13 cases (39.4%).

The vertigo control rate was significantly higher for the lateral wall resection group than for the endolymphatic sac decompression group ($\chi 2 = 4.25$, $p < 0.05$) (**Table 1**). There was no significant difference in the hearing loss rate and tinnitus improvement between the two groups ($\chi 2 = 0.50$, $p > 0.05$; $\chi 2 = 0.016$, $p > 0.05$) (**Table 1**).

DISCUSSION

There is currently no cure for MD; more than 85% of patients with these disorders benefit from changes in lifestyle or medical treatment. Surgery is considered when conservative treatment fails to control vertigo. In this study, we found that vertigo was controlled effectively in 90.4% of the 73 patients with MD who were treated with lateral wall resection of the endolymphatic sac at the 2-year follow-up. The rate of vertigo control with lateral wall resection of the endolymphatic sac was much higher than that of sac decompression in our study, suggesting that lateral wall resection of the endolymphatic sac is effective for the treatment of MD vertigo. However, the mechanism of action is not completely understood. We speculate the following. First, the endolymphatic sac plays a dual role in the formation of endolymphatic hydrops, which absorbs, as well as secretes, endolymph (10, 11). Nordström et al. found that 40% of human endolymphatic sac epithelial cells express Na + -K + -ATPase, indicating that they have considerable secretory ability (12). Immunohistochemical and ultrastructural studies showed that the endolymphatic sac of MD patients had excessive secretion of glycoprotein (13, 14), and the overexpression of aquaporin-2 in the endolymphatic sac epithelium was also involved in the formation of endolymphatic hydrops (15), suggesting that the endolymphatic sac secretion exceeded absorption, increasing the inner ear pressure. Li et al. used micro-computed tomography and high-resolution synchrotron phase contrast non-invasive imaging techniques to image and analyze the structures of the utricular duct and utricular-endolymphatic valve (or Bast's valve) of the human temporal bone specimens, suggesting that there is a two-way exchange of endolymphatic fluid involving the utricle, semicircular canal, and endolymphatic duct. Therefore, the authors speculated that vertigo associated with MD is caused by the sudden increase in endolymphatic pressure caused by the excessive secretion of the endolymphatic sac, which causes the endolymphatic fluid to flow back to the utricle and semicircular canal through Bast's valve (16). Resection of the lateral wall of the endolymphatic sac may reduce endolymphatic hydrops by reducing the secretion of endolymphatic fluid so that it can effectively control vertigo. Gibson et al. reported that 77 patients with MD were treated with partial resection of the lateral wall of the endolymphatic sac; 43 patients were followed up for 2 years, and the vertigo control rate was 83.7% (17). The effective rate in this study was slightly higher than that reported by Gibson. Daneshi et al. reported a new marsupialization technique in endolymphatic sac surgery. The outer layer of the sac was incised, turned around and placed under the anterior bony border, which is very similar with our ways in dealing with the sac wall. The vertigo control rate was evaluated by the vestibular score and deceased in 97.7% of the patients, which is consistent with our point on the vertigo control efficiency. However, there was no control group, only a pre- and post-operative control, and the inadequate evaluation of vertigo control, limiting the evidence effect in the study (18).

Second, the abnormal immune response of the endolymphatic sac may be the cause of MD. More and more studies have shown that the endolymphatic sac may be the "source" of inner ear immune response (19). Through high-throughput sequencing technology, we found that the expression of immune-related factors in the peripheral blood of MD patients was significantly higher than that in normal controls, suggesting that abnormal immune function may be involved in the pathogenesis of MD (20). Endolymphatic sac wall resection may eliminate or block the abnormal immune response of the endolymphatic sac to control vertigo attacks.

Our study also found that the effective rate of vertigo control after lateral wall resection of the endolymphatic sac significantly improved. The mechanism may be that endolymphatic sac wall resection may be more effective at eliminating or blocking the abnormal immune response of the endolymphatic sac than traditional endolymphatic sac decompression to control vertigo. After the resection of the lateral wall of the endolymphatic sac, the drainage of the endolymphatic fluid increased over a wider range, and the pressure of the membranous labyrinth was reduced, so the effect of controlling vertigo was better. The lateral wall resection of the endolymphatic sac is an enhancement of traditional endolymphatic sac surgery (such as endolymphatic

sac decompression and drainage), which improves the control rate of vertigo.

Does excision of the lateral endolymphatic sac affect hearing? Our clinical data shows that hearing is preserved in more than 85% of patients, indicating that endolymphatic sac wall resection can preserve hearing. Prades et al., Darrouzet et al., and other scholars reported that hearing was still preserved with the retrolabyrinthine approach to resection of acoustic neuroma although the endolymphatic vessels were removed, indicating that the removal of the endolymphatic duct does not affect hearing (21, 22). The connection between the endolymphatic sac and the inner ear labyrinth is cut off after endolymphatic resection; therefore, it is speculated that hearing can be preserved after endolymphatic sac resection. Asmar et al. reported that patients who underwent endolymphatic blockage had the lateral wall of their endolymphatic sac removed at the same time, and there was no significant difference in post-operative hearing compared with patients with simple endolymphatic blockage (23). Gibson et al. reported that there was no significant decrease in hearing during the partial resection of the lateral wall of the endolymphatic sac, but ∼56% of the patients had hearing loss during the 2-year follow-up. The authors believe that the cause of hearing loss may be related to the aggravation of membranous labyrinthine hydrops after surgery (17). However, Linthicum et al. reported that patients with endolymphatic sac resection did not develop membranous labyrinthine hydrops (24). In this study, approximately 16% of patients had hearing loss, which may be related to secondary labyrinth infection or aggravation of endolymphatic hydrops. In addition, hearing improved in four patients in this study during follow-up, which may be related to hearing fluctuations. Tinnitus was improved in approximately 40% of patients after resection of the lateral wall of the endolymphatic sac. The specific mechanism is not clear, which may be related to the reduction of membranous labyrinth hydrops and the relative stability or improvement of cochlear function. It may also be related to the effective control of vertigo, the reduction of psychological pressure, and the improvement of mental state and sleep.

In this study, the results of the caloric test and VEMP before and after resection of the lateral wall of the endolymphatic sac showed that this surgery had no significant effect on vestibular function. To date, no significant improvement in vestibular function has been observed with sac wall resection surgery. It is suitable for patients with bilateral vestibular dysfunction, especially those with bilateral MD. The current study is retrospective, and there are limitations in patient selection, control group and statistical methods.

CONCLUSION

The etiology of MD has not been established. The current drug treatment is only to suppress the disease, and there is no complete radical cure. Our study shows that lateral wall resection of the endolymphatic sac is a safe and effective method for the treatment of intractable MD.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Shandong Provincial ENT Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DZ and HW contributed to the conception of the work. DZ, ZF, and YL contributed to the experimental design. YL, XL, YS, and LK collected data and performed the analysis. All authors contributed to the interpretation of the data and were involved in writing the manuscript.

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SUPPLEMENTARY MATERIAL

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Low-Dose Intratympanic Gentamicin for Unilateral Ménière's Disease: Accuracy of Early Vestibulo-Ocular Reflex Gain Reduction in Predicting Long-Term Clinical Outcome

Ricardo Wegmann-Vicuña[1,2], Raquel Manrique-Huarte[1†], Diego Calavia-Gil[1†], Eduardo Martín-Sanz[3,4†], Pedro Marques[5] and Nicolas Perez-Fernandez[1,6†]*

[1] Department of Otorhinolaryngology, Clínica Universidad de Navarra, Pamplona, Spain, [2] Department of Otorhinolaryngology, Hospital Quirónsalud, Barcelona, Spain, [3] Department of Otolaryngology, University Hospital of Getafe, Madrid, Spain, [4] Department of Medicine, School of Biomedical Sciences and Health, Universidad Europea de Madrid, Madrid, Spain, [5] Department of Otorhinolaryngology, S. João Hospital Centre, Porto, Portugal, [6] Department of Otorhinolaryngology, Clínica Universidad de Navarra, Madrid, Spain

Background: The number of intratympanic gentamicin (ITG) injections needed to achieve vertigo control in patients with intractable Ménière's disease (MD) may vary from a single dose to several instillations. Changes in different vestibular test results have been used to define an endpoint of treatment, including the decrease of the vestibulo-ocular reflex (VOR) gain elicited by the head-impulse test.

Objective: To assess the accuracy of the VOR gain reduction after horizontal canal stimulation, as measured with the video head-impulse test (vHIT) 1 month after the first intratympanic injection, in predicting the need for one or more instillations to control vertigo spells in the long term.

Methods: The VOR gain reduction was calculated in 47 patients submitted to (ITG) therapy 1 month after the first instillation.

Results: Single intratympanic treatment with gentamicin has a 59.6% efficacy in vertigo control in the long term. Hearing change in the immediate period after treatment (1 month) is not significant to pre-treatment result and is similar for patients who needed multiple doses due to recurrence. Chronic disequilibrium and the need for vestibular rehabilitation were less frequent in patients with a good control of vertigo with just one single injection of gentamicin. A fair accuracy was obtained for the VOR gain reduction of the horizontal canal (area under the curve = 0.729 in the Receiver Operating Characteristic analysis) in predicting the need for one or more ITG.

Conclusions: Single intratympanic treatment with gentamicin is an effective treatment for patients with MD. That modality of treatment has very limited damaging effect in hearing. The degree of vestibular deficit induced by the treatment is significant as measured by the reduction in the gain of the VOR but not useful for prognostic purposes.

Keywords: vertigo, Ménière's disease, inner ear, ototoxicity, hearing loss

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Shaun Richard Watson, Prince of Wales Hospital, Australia

****Correspondence:***
Nicolas Perez-Fernandez
nperezfer@unav.es

†ORCID:
Raquel Manrique-Huarte
orcid.org/0000-0003-0781-9679
Diego Calavia-Gil
orcid.org/0000-0002-9311-3017
Eduardo Martín-Sanz
orcid.org/0000-0003-1175-3844
Nicolas Perez-Fernandez
orcid.org/0000-0002-1192-5901

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INTRODUCTION

Ménière's disease (MD) is an idiopathic inner ear disorder characterized by episodic vertigo spells lasting from 20 min to 12 h, fluctuating low-frequency hearing loss during the initial spells with associated aural fullness, and tinnitus (1). Current therapies aim to control vestibular symptoms with conservative means, namely, low-sodium diet, diuretics, and vestibular suppressants. For those patients who do not respond, alternatives for alleviating the symptoms include surgical interventions like labyrinthectomy, vestibular neurectomy, or less invasive therapies like intratympanic injection of gentamicin or steroids.

The use of gentamicin delivered intratympanically (ITG) is an effective treatment (2) because it produces a variable degree of vestibular function ablation (3), and this reduces the sensitivity of the vestibular periphery sensors and clinical symptoms. Unfortunately, the amount of damage to the inner ear cannot be predicted, and a trend toward less ototoxic damage has been the interest in current protocols of treatment. As such, different number and frequency regimens and different drug concentrations have been proposed to achieve better vertigo control with the lowest risk of hearing loss and residual instability (4, 5). This can be achieved by using lower doses of gentamicin and fewer injections with longer time intervals between injections. Using a single-shot therapy with an *on-demand* protocol, complete or substantial control of vertigo attacks ranges between 80 and 90%, and complete vertigo control can be accomplished with a single injection of gentamicin in 45–54% of the patients (6–8). It is well tolerated by patients and the amount of post-treatment instability is reduced.

In this modality of treatment, gentamicin gets into the inner ear mainly through the round window membrane and the oval window. It has been shown in the experimental situation that the distribution of gentamicin either in the scala tympani or in the scala vestibuli will be the result of different interactions (9). In experimental studies using gentamicin locally applied in the middle ear it has been shown that it attacks differentially type I receptors in the vestibular end-organs and the dendrites of primary afferent neurons (10). As a result, the vestibulo-ocular reflex (VOR) gain measured, with a scleral search coil or with the video head-impulse test, will be reduced as the response in the caloric test. This gain reduction has been associated with a decrease in the rate of vertigo attacks in patients with MD (11).

Several methods have been used to define a safety endpoint in this modality of treatment, including modification of bedside testing (spontaneous nystagmus, post-head-shaking nystagmus, and refixation saccades on the head impulse test) or vestibular laboratory test results [decreased VOR gain on the quantitative head thrust test, abolished caloric, and vestibular evoked myogenic potential (VEMP) responses]. However, there is yet no consensus on the optimal dose and concentration of gentamicin to be delivered to obtain a significant clinical result. In a previous report, Marques et al. proposed an endpoint of treatment, such that a horizontal canal VOR reduction of at least 17.8% [area under the curve (AUC) of Receiver Operating Characteristic (ROC) curve = 0.843] and a posttreatment asymmetry of at least 7% in the horizontal semicircular canal (AUC = 0.861) was associated with a good vertigo control, which meant that there was no need of further injections during a mean period of 21 months of follow-up (12). However, 13.6% of the patients initially treated with one single ITG injection in that study presented recurrence of vertigo in the long-term follow-up, and the effectiveness of a single dose of gentamicin for vertigo control fell from 71 to 58% (unpublished data).

The first follow-up after ITG is 1 month in different studies based on the short-term dynamics of the vestibulo-toxic effect of ITG. Previous researchers have shown that throughout the first month, there is a significant reduction in the gain of the VOR which stabilizes 1 month after treatment (13).

Our study aimed to assess the following aspects pertinent to the result of the treatment: (1) The effectiveness of one-single dose of gentamicin for long-term vertigo control, (2) How accurately immediate VOR gain reduction (as measured 1 month after the first injection) differentiates patients that need a further injection to achieve long-term vertigo control, i.e., does that change in VOR predict clinical course during the follow-up?, (3) Are there significant short-term changes in hearing after the first ITG treatment?, and (4) Is vestibular rehabilitation more frequently indicated after one or multiple doses of ITG?.

MATERIALS AND METHODS

Subjects

We retrospectively analyzed 47 patients admitted to our clinic who were diagnosed with unilateral definite MD according to diagnostic criteria (1) from August 2011 to July 2017; some of these patients were included in a previous study (12). All patients underwent a complete neurotologic examination and were treated with ITG because of recurrent vertigo attacks which did not respond to conventional medical treatment (salt restriction, diuretics, and/or betahistine). Inclusion criteria were unilateral definite MD, video head-impulse test done before (usually the same day or no longer than a week before treatment) and 1 month after ITG treatment, no evidence of MD and serviceable hearing in the non-affected ear, and no symptoms or signs suggesting central nervous system involvement. All patients were re-evaluated at 1, 3, 12, and 24 months and then annually after the first gentamicin injection. During data acquisition, the following parameters were collected retrospectively: age and sex of the patient, disease duration, number of vertigo spells in the 6 months before treatment, time from the last attack, time of follow up, Tumarkin's attacks, audiometric findings, and migraine history. Additionally, we assessed 6 patients (here defined as untreated) diagnosed with definite unilateral MD without current medication, at baseline and 1 month after. We compared the VOR gain values and hearing test results with those of the patients treated intratympanically to find out to what extent the results of treated and untreated subjects are different and not time-dependent or fluctuant. These patients were selected upon appearance at the hospital and not considered to be age/sex-matched.

Methods

Clinical Evaluation and Bedside Testing

All patients underwent a complete clinical assessment and bedside testing which consisted of microscopic examination

of the eardrum, routine otolaryngological examination, search for spontaneous nystagmus and head-shaking nystagmus under Frenzel's glasses, clinical head impulse test, and positional nystagmus. The Dizziness Handicap Inventory (DHI) was used to evaluate the self-perceived handicapping effects of dizziness; the version used was taken from the original (14) and validated to the Spanish language (15).

Auditory and Vestibular Evaluation

Audiometric findings were reported in terms of the mean pure-tone average (PTA), calculated on air conduction thresholds at 0.5, 1, 2, and 3 kHz of the symptomatic or affected ear and the asymptomatic ear or non-affected ear. Patients were classified into four stages according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) (1).

Vestibular testing was performed with the vHIT (ICS Impulse, Otosuite V 4.0, GN Otometrics, Taastrup, Denmark) for the six semicircular canals, with 20 impulses in each direction according to the canal plane. The parameter evaluated was the VOR mean gain and the presence of refixation saccades, namely, overt and covert saccades. Gain is obtained from the gain value after each of the impulses is performed and is automatically provided for all paired semicircular canals assessed. Data were evaluated from the symptomatic (Gs) and asymptomatic (Gas) ears. Due to modifications in the hardware, horizontal canals were examined in 53 patients, and data from the vertical canals were obtained from 43 patients (38 in the treatment group and 5 in the untreated group).

Treatment

The medication used was gentamicin sulfate (40 mg/ml) buffered with sodium bicarbonate to pH 6.4 and a final concentration of 26.7 mg/ml, and 0.5–1.5 mL (1.06 ± 0.31) of the gentamicin solution was injected slowly in the affected ear through the posterior-inferior quadrant of the tympanic membrane. Care was taken to observe the progressive filling of the middle ear and of the round window niche when possible. The patients were asked to lie in a supine position with the affected ear for up to 30 min and were encouraged not to swallow.

The study was performed according to the following protocol, as previously approved by the Ethics and Medical Deontology Commission at our hospital. All patients that fulfilled the inclusion criteria and signed the corresponding informed consent received the first injection of gentamicin. Patients were then instructed to inform us of any symptoms that developed during the first month after the ITG injection. When necessary, vestibular suppressants were prescribed to treat vestibular symptoms. At the time of the first follow-up visit 1 month after the ITG injection, the clinical status of the patient was reviewed, and bedside vestibular examination, vHIT, and audiometric assessment were performed. After the first follow-up visit, all the patients were instructed to record any vertigo spell resembling those experienced before the treatment in case of chronic disequilibrium impacting daily activities. When new attacks developed, a decision was then made to treat the patient with another injection of gentamicin or with vestibular suppressants. In case of no more vertigo crises but chronic disequilibrium with a high-level handicap as defined by a DHI score >54, then the patient was treated with vestibular rehabilitation. Telephonic contact was maintained with every patient (in between follow-ups at the hospital) to assess any vertigo recurrence. For patients without vertigo recurrences, follow up at the end of the study (2 years) was made mostly by telephonic and/or e-mail contact.

Statistical Analysis

For demographic analysis, differences between normally distributed data were assessed with Student's *t*-test or the one-way ANOVA test. For non-normally distributed data, the Wilcoxon test or the Kruskal-Wallis test was performed. Median and interquartile range (25th and 75th percentiles) are shown for not normally distributed data. Otherwise, mean and standard deviation are shown. Differences between percentages were determined by using Fisher's exact test.

According to the number of injections needed to achieve vertigo control, patients were classified into two treatment groups: one group treated with one single dose of ITG (group 1) and another group who needed during follow-up a subsequent or more ITG injections (group 2). The untreated group was designated as group 0.

The results of the vestibular evaluation were analyzed in terms of VOR gain reduction according to the formula: [(pre-treatment gain – post-treatment gain)/(pre-treatment gain)]*100.

Both data were combined such that patients were classified as "unexpected" when, in group 1, gain reduction was lower than 17.8% or, in group 2, >17.8%, Data were classified as "expected" when, in group 1, gain reduction was >17.8% or, in group 2, lower than 17.8%. A chi-square test was performed to compare the number of expected and unexpected results between treatment groups.

A description of the time course of recurrent vertigo was performed with the Kaplan-Meier survival analysis which allows quantification of the percentage of patients who had adequate control of their vertigo using the need for a second injection as a definition of "failure." ROC curve analysis was performed for vestibular function (VOR gain) reduction regarding treatment outcome. A two-way factorial mixed ANOVA design was performed for VOR gain reduction as dependent variable, treatment groups as between-subjects factors, and ear and time as within-subjects factors. Differences between factors have been tested using contrasts. Cohen's *D* was calculated for assessing the size effect if considered clinically relevant.

All analyses were performed using the STATA 15.0 statistical software (StataCorp, College Station, TX, USA). A value of $p < 0.05$ was considered statistically significant. For interactions terms, a value of $p < 0.1$ has been considered statistically significant.

RESULTS

Patients

The study included 47 subjects (28 women and 19 men) with definite MD that belong to the group of patients treated with ITG and 6 patients in the untreated group. There were 11 additional patients (4 in group 1 and 7 in group 2) not included because the

TABLE 1 | Demographic characteristics of the patients.

Parameter	Group 0	Group 1	Group 2	*P*
Sex §				0.923
Female	4 (66.7%)	16 (57.1%)	12 (63.2%)	
Male	2 (33.3%)	12 (42.9%)	7 (36.8%)	
Age (years)† ¥	58 ± 11	65 ± 13	64 ± 13	0.5401
Affected ear§				0.155
Left	5 (83.3%)	12 (42.9%)	7 (36.8%)	
Right	1 (16.7%)	16 (57.1%)	12 (63.2%)	
Number of crisis in the last 6 months† ¥	8 ± 8	11 ± 5	13 ± 9	0.3345
Time since last crisis (days)* ¥	5(2:7.5)	9(3:14)	5.5(3:9)	0.3618
Duration of disease (years)* ¥	6(2:8)	9(6:16)	10(6:22)	0.1506
Migraine §	1 (16.7%)	4 (14.3%)	0	0.220
Tumarkin §	0	7 (25%)	7 (36%)	0.633
Stage §				**0.015**
Stage I	2	0	0	
Stage II	0	0	2	
Stage III	4	18	13	
Stage IV	0	10	14	
Mean follow up (months)*‡		51(30.5:62.5)	42(35:54)	0.2829

** For not normally distributed data, median, 25th and 75th percentiles are shown.*
† For normally distributed data, mean and standard deviation are shown.
¥ P< 0.05 is considered significant in the one way ANOVA test.
‡ P< 0.05 is considered significant in the Wilcoxon test.
§ P< 0.05 is considered significant in the Fisher's test.
P, significance value for the difference between groups.

first follow-up was not in the expected period of time (1 month) after treatment. There were 6 patients (2 in group 1 and 4 in group 2) who attended the post-treatment visit at the expected time but then lost to follow-up.

Of all those included, 11 were lost to follow-up (4 in group 1 and 7 in group 2) Demographic characteristics by groups are outlined in **Table 1**. The range of follow-up was >24 months in all patients.

There were no significant differences between the three groups of patients regarding sex, age, affected ear, number of spells in the 6 months before treatment, time since last vertigo attack, disease duration, migraine diagnosis, presence of Tumarkin's crisis, or time of follow-up. Regarding the audiometric stage, there was a greater proportion of patients in more advanced stages in the treatment groups with respect to the untreated group ($p = 0.015$). The mean VOR gain after head impulses in the plane of each of the six semicircular canals showed no differences between the three groups of patients when analyzed at baseline in group 0 and before treatment in groups 1 and 2 (**Table 2**).

A survival curve represents a follow-up of treated (groups 1 and 2) patients (**Figure 1**). Twenty-eight patients received one single dose of ITG (59.6% of treated patients, group 1), whereas 19 received more than one ITG injection: 12 patients needed 2, 1 patient needed 3 ITG, 5 patients needed 4 ITG, and 1 patient needed 5 ITG. The mean time interval between the first and the second injection was 10 months ($CI_{95\%}$ 3–16, range 1–51), 5 months ($CI_{95\%}$ 0,7–10, range 1–18) between the second and the third injection, 10 months ($CI_{95\%}$ 0–24, range 1–46) between the third and the fourth injection, and 1 month between the fourth and the fifth ITG injection (1 subject). Among the patients receiving 4 injections, in 2 of them, an exploratory tympanotomy was further performed for direct application of gentamicin to the round window. In both patients, no fibrosis was found in the round window niche which was otherwise normal and access to the membrane was uneventful, and, in both patients, vertigo symptoms resolved after the procedure.

After ITG, 5 patients had to follow a vestibular rehabilitation treatment: 2 (7.1%) in group 1 and 3 (15.7%) in group 2. They mentioned chronic disequilibrium severe enough to limit their activities although there were no more vertigo crises. Those in group 1 had a very intense reduction in the gain of the VOR that affected the three semicircular canals: superior semicircular canal by 44 and 40%, horizontal canal by 82 and 78%, and posterior canal by 50 and 54%, respectively, for each patient. They were each treated 2 and 3 months, respectively, after the first follow-up visit. Those in group 2 were patients that each needed 2 injections (for 2 patients) and 3 injections (for 1 patient). The treatment took place 4 months after the last injection in all three cases.

Results in Group 0

We found that after 1 month and in a stable clinical status (no new vertigo spell), the gain of the VOR showed very small modification as what occurred in the non-affected ear. It is, however, of interest to note an increase of the mean gain of the VOR close to 20% in the case of the anterior canal in the affected ear. The change in mean PTA both in the affected and unaffected ear was not significant and, in all of them, the difference from baseline to 1 month after the initial visit was <10dB. Particularly, it was worse in group 2 and better in group 4.

Analysis of the Effect of ITG on the Gain of the VOR

The change in the gain of the VOR in the first follow-up visit (1 month after ITG treatment), with respect to the pre-treatment value, is shown in **Table 3** and **Figure 2**. The amount of reduction of the VOR gain, in the case of the superior and horizontal semicircular canals, was found to be significantly higher in group 1 than in group 2. Both groups had significantly higher gain reductions compared to the non-treated symptomatic ear (group 0). However, in the case of the posterior semicircular canal VOR gain, in groups 1 and 2, the reduction was equally high, but significantly different from the non-treated group ($p = 0.133$; Cohen's $D = 0{,}41$).

Figure 3 shows the traces of the video head impulse test of a patient belonging to group 1 before and 1 month after the first ITG injection in a subject with a significant reduction of the VOR after treatment.

In the asymptomatic (non-treated) ear, we found a small fluctuation in the value of the VOR gain in the case of head-impulses in the plane of the posterior semicircular canal such that the difference to pre-treatment values was significantly higher in patients in group 1 with respect to patients in the group 2. In

TABLE 2 | Mean VOR gain and standard deviation according to ear and canal stimulation by groups before treatment.

		Symptomatic ear			Asymptomatic ear		
		Superior	**Horizontal**	**Posterior**	**Superior**	**Horizontal**	**Posterior**
Baseline	Group 0	0.75 ± 0.08	0.88 ± 0.07	0.72 ± 0.14	0.89 ± 0.06	0.97 ± 0.04	0.69 ± 0.11
Pre-ITG injection	Group 1	0.84 ± 0.17	0.98 ± 0.15	0.72 ± 0.12	0.88 ± 0.13	1.03 ± 0.13	0.78 ± 0.14
Pre-ITG injection	Group 2	0.81 ± 0.16	1.0 ± 0.19	0.78 ± 0.14	0.91 ± 0.17	1.03 ± 0.17	0.78 ± 0.14
		$P = 0.509$	$P = 0.377$	$P = 0.471$	$P = 0.846$	$P = 0.739$	$P = 0.567$

Mean data and standard deviation are presented.

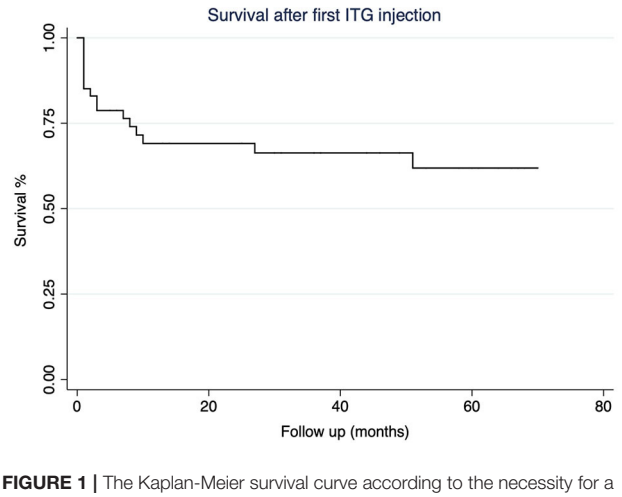

FIGURE 1 | The Kaplan-Meier survival curve according to the necessity for a second intratympanic gentamicin (ITG) injection.

addition, there was a trend toward significance with respect to group 0 but with a great size effect (Cohen's $D = 1{,}64$) (**Table 3**).

The ROC analysis for the reduction of the gain of the VOR of the horizontal semicircular canal of both treatment groups showed an AUC of.729 with a VOR reduction cutpoint of 11.6% (sensitivity = 89.29%; specificity = 52.63%; LR+ = 1.885; LR– = 0.204).

A more detailed analysis of the VOR gain reduction of the horizontal canal in each treatment group and follow-up is shown in **Figure 4**. In group 1, seven subjects (25%) were defined as "unexpected" and twenty-one subjects (75%) were defined as "expected." In group 2, ten subjects (53%) were considered as "expected" and nine subjects (47%) were considered as "unexpected." The VOR reduction of the "expected" and "unexpected" showed no statistically significant differences ($p = 0.582$), not even with group 0 ($p = 0.347$). Also, no differences were found regarding the number of expected and unexpected results in each treatment group (chi-square = 2.52; $p = 0.112$).

No differences were found between the subgroups of subjects with expected and unexpected results in both treatment groups or with the control group regarding age, sex, affected ear, number of crises before treatment, time since the last vertigo spell, duration of the disease, Tumarkin crises, migraine, or time of follow-up.

Further analysis showed that 2 subjects in group 2 showed no changes in the VOR gain, and 6 subjects (1 subject in group 1 and 5 subjects in group 2) showed an increase in the VOR gain in the horizontal canal of the symptomatic ear after the first ITG injection.

Analysis of the Effect of ITG on Hearing

Regarding hearing as shown in **Table 4**, at the time of inclusion, PTA was slightly lower in patients in group 0 than in those in group 1 and showed a trend toward significance when compared with group 2 ($p = 0.075$; Cohen's $D = 0{,}33$). Interestingly, there were no significant differences between those in groups 1 and 2.

After the first ITG injection, the PTA of groups 1 and 2 was significantly higher than that of group 0 or not treated (**Table 4**). However, the PTA did not significantly change 1 month after treatment in any group (**Table 4**). The mean reduction in hearing in the treated ear was 1.3 dB in group 2, whereas in group 1 and in group 0, there was an increase of 0.14 and 2.3 dB, respectively. Eight subjects (4 subjects in each treatment group) showed a PTA modification >10 dB (17%), and 3 of them (2 in group 1 and 1 in group 2) progressed from a moderate to a severe hearing loss (6%). The changes in hearing in the asymptomatic ear were not significant.

DISCUSSION

The questions addressed here are all of interest when counseling patients with unilateral MD to whom we plan a treatment with gentamicin given intratympanically. A low-dose protocol has proved to be an effective method for controlling vertigo attacks with a low rate of hearing loss or persistent imbalance (2, 4, 16–18).

Our study first shows that 59.6% of the patients achieved complete vertigo control after one single dose of ITG after a prolonged follow-up period of up to 6 years, which is an important contribution of this report. This finding is in accordance with previously observed results (6–8).

The main problems when trying to predict an individual outcome in terms of the need for one or several injections in ITG treatments are the unpredictable effect of the drug and the unpredictable recurrence of vertigo after any nonsurgical and sub-ablative treatment. The rationale of this approach is to avoid side effects of unneeded treatments and maximize class A results ("the patient did not suffer any definitive vertigo spell in the 6 months prior to the date of follow-up evaluation," according to the AAO-HNS) but also to provide sufficient information to clinicians and patients about the possible clinical course after a

TABLE 3 | Mean VOR reduction and standard deviation according to ear and canal after ITG injection.

	Symptomatic ear			Asymptomatic ear		
	Superior	**Horizontal**	**Posterior**	**Superior**	**Horizontal**	**Posterior**
Group 0	−19.29 ± 17.94	−5.27 ± 9.05	2.9 ± 11.47	0.17 ± 12.95	−3.17 ± 5.33	−6.96 ± 7.36
Group 1	43.14 ± 22.81	42.48 ± 28.11	42.35 ± 25.19	12.83 ± 21.57	11.13 ± 9.01	14.67 ± 14.01
Group 2	10.78 ± 37.55	20.0 ± 26.56	31.02 ± 30.93	5.33 ± 19.39	4.92 ± 9.85	−2.32 ± 22.44
	P 0 vs. 1 <0.001	*P* 0 vs. 1 <0.001	*P* 0 vs. 1 <0.001	*P* = 0.489	*P* = 0.217	*P* 0 vs. 1 = 0.055
	P 0 vs. 2 = 0.019	*P* 0 vs. 2 = 0.006	*P* 0 vs. 2 = 0.014			*P* 0 vs. 2 = 0.664
	P 1 vs. 2 < 0.001	*P* 1 vs. 2 < 0.001	*P* 1 vs. 2 = 0.133			*P* 1 vs. 2 = 0.028

Mean data and standard deviation are presented. VOR reduction data are presented in terms of percentage.

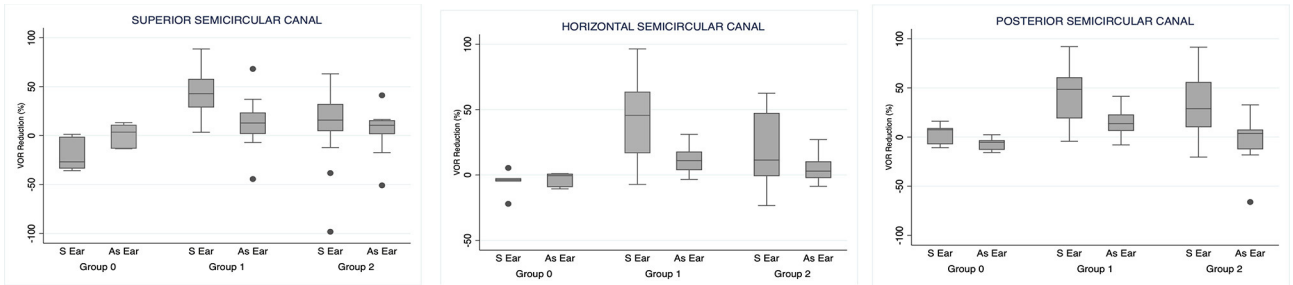

FIGURE 2 | Vestibulo-ocular reflex (VOR) reduction 1 month after the first ITG injection. S Ear: symptomatic ear. As Ear: asymptomatic ear.

given number of injections. In this way, patients could better understand their own disease and expected prognosis after the treatment. All of which contributes to better functioning and well-being during follow-up (8).

There are a limited number of studies assessing the changes of the VOR measured by the quantitative head-impulse test in patients with MD after ITG treatment. Carey et al. observed a correlation between the reduction of the VOR gain as measured with the scleral search coil after fast head impulses and the reduction in the number of vertigo spells (3). Later, Lin et al. observed a significantly greater VOR reduction in the symptomatic horizontal canal after the first ITG injection in the single treatment group than in the multiple treatment groups (11). These findings are in accordance with the second result of our study: we found a significantly greater VOR gain reduction in all the canals in the treated groups than in the untreated group, and in the superior and horizontal canal of the affected ear in the single-dose group than in the group requiring more injections 1 month after the first ITG injection. Many authors have stated that a sub-ablative effect will maintain an optimal relationship between vertigo control and avoidance of side effects such as hypoacusis or chronic disequilibrium. Indeed, such vestibular function preservation may be important in case of subsequent development of bilateral MD.

Given the previously mentioned evidence, the corollary question is whether the amount of change in the gain of the VOR has any significance in clinical follow-up. Despite this, our results do not fully support that purpose, and we shall cover this topic in the next paragraphs.

According to our previous work, we can take into account as the endpoint of treatment at least a 17.8% of VOR gain reduction in the horizontal semicircular canal. In doing that, we found that 75% of patients in group 1 showed a gain reduction above this cut point. On the contrary, group 2 results are more heterogeneous with only 53% of subjects showing a reduction under this value. These discrepancies between the results and the observed clinical course in the present study explain the fair accuracy of the VOR gain reduction (AUC = 0.729) to correctly identify subjects who will have vertigo control with one-single dose of gentamicin and to predict the need for more treatment. Nguyen et al. observed an association between a horizontal canal VOR reduction >60% (clearly higher than our data) and a lower vertigo rate after the first round of treatment with ITG injections. However, they did not find any association between vertigo rate and VOR gain when those values were treated as continuous variables (19). Lin et al. (11) previously reported that partial vestibular ablation appeared to be beneficial by showing that patients who did not suffer vertigo recurrence had significantly greater decreases in ipsilateral horizontal VOR gain 1 year after treatment than those who had recurrent vertigo.

The differences between the findings in our previous study and our current results might be explained by the limited number of subjects in each group of treatment and by the shorter period of follow-up in the former report, since the probability of vertigo recurrence and the probability of needing an additional gentamicin injection increases in time. We have observed a patient who required a second injection after a symptom-free period of more than 4 years from the first treatment that is in accordance with Quaglieri et al. who reported that 10% of

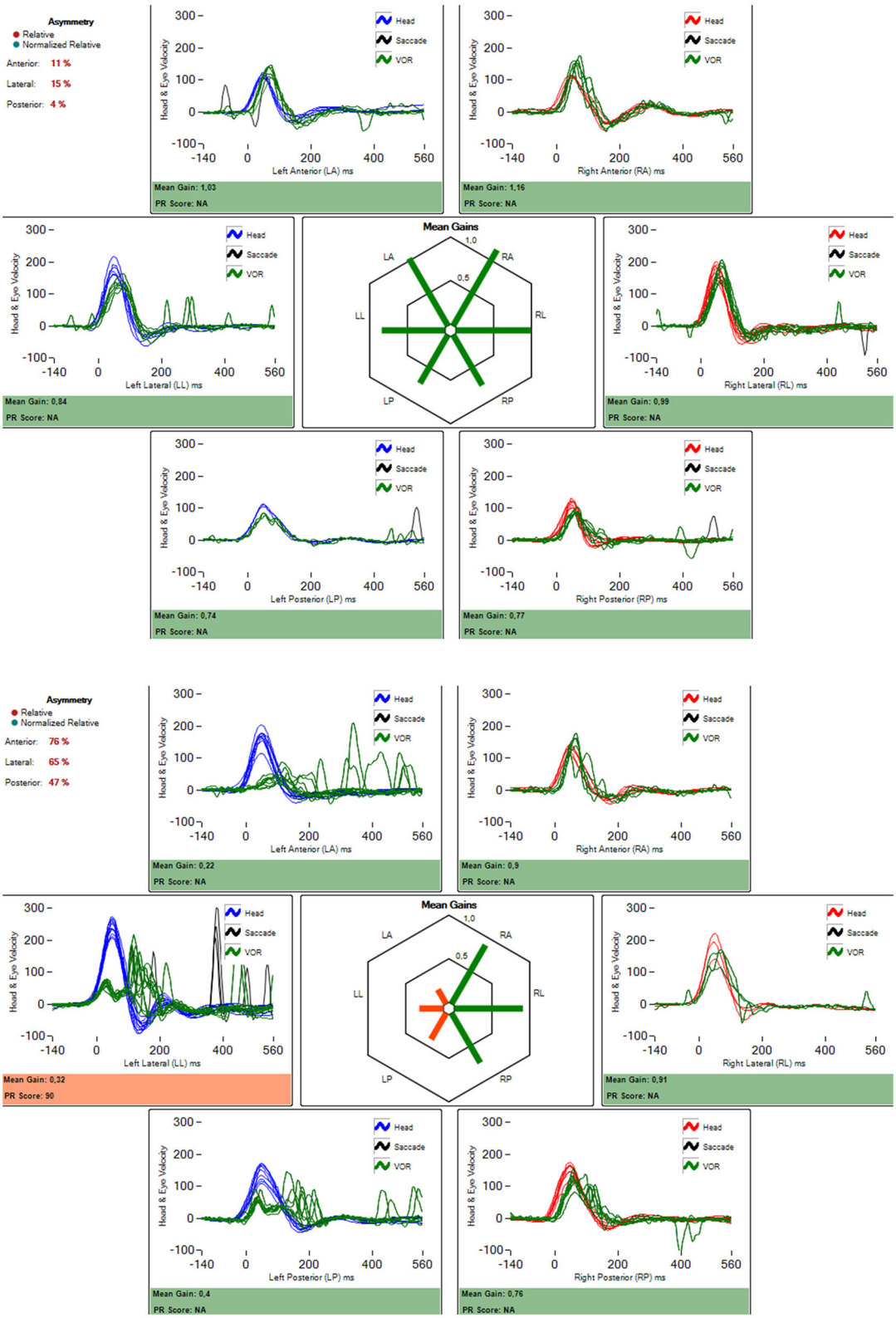

FIGURE 3 | Video head-impulse test result in a patient with left ear Ménière's disease. In 3A before treatment with intratympanic gentamicin (1.1 ml of 27mg/ml). In 3b, 1 month after the treatment. It is an almost complete damage to all three vestibular receptors in the corresponding ampullae. The amount of gain reduction (according to formula in the material and methods section) was 62%.

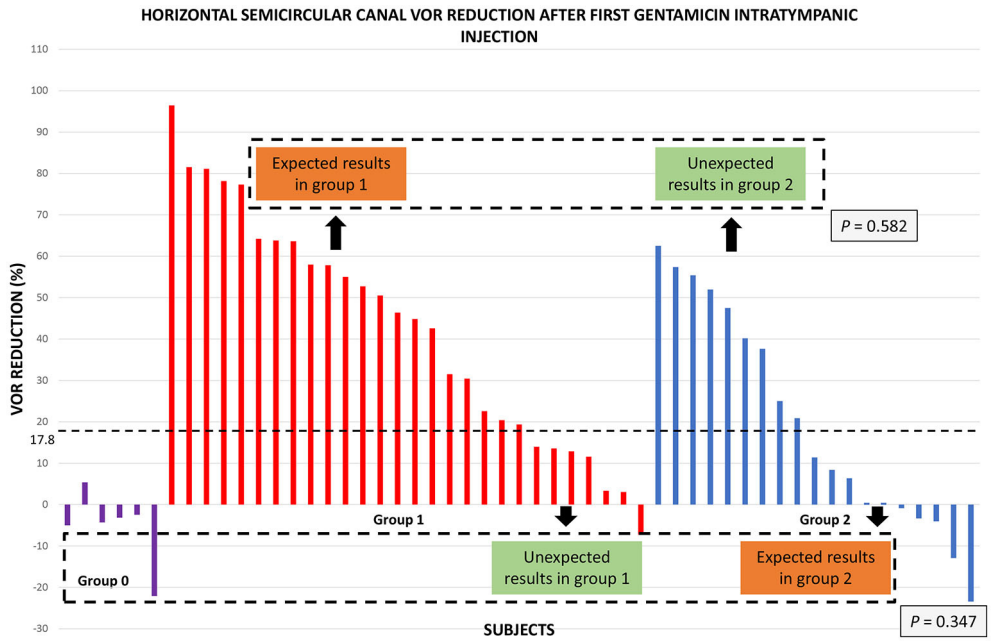

FIGURE 4 | Horizontal semicircular canal VOR reduction 1 month after the first ITG injection. The bars represent the VOR reduction in every subject of the study. The dotted line represents VOR reduction cut point of 17.8% of the previous study which predicted the need for one or more ITG injections for vertigo control. According to this criterion, expected results in group 1 exceed this cut point, and unexpected results are below this cut point. On the other hand, unexpected results in group 2 exceed this VOR reduction value, and expected results are below this cut point. Note that VOR reduction values in the untreated group (group 0) are all of them below this cut-point. Dotted squares represent comparison between subgroups with VOR reduction above the cut-point and between subgroups below the cut-point and the control group (*P* values are located at the inferior right angle).

TABLE 4 | Pure tone average before and after treatment and comparison of pure tone average between groups before and after treatment.

		Symptomatic ear	Asymptomatic ear			Symptomatic ear	Asymptomatic ear
Group 0	Baseline	40 ± 20	12 ± 9	Group 0	Baseline	40 ± 20	12 ± 9
	1 month control	37 ± 21	11 ± 9	Group 1	Pre-ITG injection	65 ± 20	28 ± 28
		P = 0.868	*P* = 0.868	Group 2	Pre-ITG injection	57 ± 17	19 ± 14
						***P* 0 vs. 1 = 0.005**	*P* = 0.171
Group 1	Pre-ITG injection	65 ± 20	28 ± 28			*P* 0 vs. 2 = 0.075	
	Post-ITG injection	63 ± 17	29 ± 29			*P* 1 vs. 2 = 0.156	
		P = 0.868	*P* = 0.868				
				Group 0	1 month control	37 ± 21	11 ± 9
Group 2	Pre-ITG injection	57 ± 17	19 ± 14	Group 1	Post-ITG injection	63 ± 17	29 ± 29
	Post-ITG injection	58 ± 19	18 ± 11	Group 2	Post-ITG injection	58 ± 19	18 ± 11
		P = 0.868	*P* = 0.868			***P* 0 vs. 1 = 0.003**	*P* = 0.072
						***P* 0 vs. 2 = 0.029**	
						P 1 vs. 2 = 0.359	

Mean data and standard deviation are presented (dB).

patients who showed an initial vertigo-free interval of at least 2 years presented a recurrence of vertigo spells after a symptom-free interval up to 5 years (6). However, in our subjects, the mean interval between the first and the second treatment was 10 months, i.e., before the recommended period of follow-up according to the AAO-HNS. We can thus speculate that our observations would not have been different with a shorter period of follow-up but still meet the AAO-HNS follow-up period criteria. In that study (6), they also found that the subgroup of *non-responder* subjects showed vertigo recurrence in the early stages of the treatment, and this can also be observed in our study according to the steepness of the survival curve to the left. The prolonged period of follow-up tries to overcome one of the main drawbacks of studies as it has been shown that vertigo recurrence rates may vary according to the duration of follow-up and that it can recur even after a symptom-free period lasting more than 2

years as said before (6–8). Another important difference relates to the number of patients included in the study. Other researchers found that a small modification (post-treatment to pre-treatment value) in the gain of the VOR for horizontal canal stimulation toward the affected and treated ear was significantly related to the need for further treatments (20). However, the number of patients included in that study was very low compared to ours. The differences in methodology, the age of the population, and disease duration may explain the differences in outcome. Further studies with a broader population and longer follow-up may address this issue.

The previously mentioned spontaneous rate of vertigo remission in MD might explain the cases with complete vertigo control where the VOR gain did not change after receiving a single ITG injection, namely, the patients included in what we have called "unexpected" and are in group 1. Another explanation for this finding could be the supposed damage to the dark cells by gentamicin which would lead to a decrease in endolymph production, limiting the hydrops, and subsequent vertigo (21). Pender described dark cell damage in the vestibular end-organs following gentamicin tympanolisis (22). However, a recent study using electron microscopy did not report significant damage to these cells in the semicircular canals of guinea pigs after a single dose of gentamicin (23).

In the case of those patients with an "expected" result but in group 2, the reasons why ITG does not produce any effect in canal function might be related to the delivery technique, drug concentration, patient positioning, round window obstruction by a second membrane as has been shown by Alzamil et al. (24), or an air bubble, round window membrane thickness, gentamicin loss through the eustachian tube, and inner ear membrane changes due to endolymphatic hydrops that limit diffusion of the drug as previous authors have stated (25).

Finally, as it has been shown by others and in this study, there is a subgroup of subjects who display a significant horizontal VOR reduction after a single dose of gentamicin and, however, continue having vertigo spells that needed more ITG. They are in group 2 and are called "unexpected." This is not completely unexpected as a variable amount of canal function is preserved after intratympanic gentamicin therapy, unlike cases of surgical vestibular deafferentation. We did not assess the severity of vertigo episodes after the treatment, which is an important issue because patients often experience milder episodes following ITG injections. However, our outcome was the presence or absence of spontaneously appearing vertigo episodes after a single dose of gentamicin no matter the severity of the spells, not positional. In these patients, we must also take into account the possibility of spontaneous gain fluctuations related to the disease more than to treatment as can be shown in the affected ear of non-treated patients. That was found not to be homogeneous as we found to be very relevant for the anterior semicircular canal and much lower for the horizontal and posterior. As we relied only on the gain of the horizontal canal, this would preclude a merely causal relationship between the change in the gain and follow-up of the patient.

In our study, the mean VOR gain reduction 1month after the first ITG injection was greater in the single treatment group than in the multiple-treatment group. However, when we consider only the results of subjects with a VOR reduction >17.8% in both treatment groups, we did not observe any statistically significant differences between them. Likewise, when we compare the VOR gain change of the untreated group with the results of subjects having a reduction of the gain of the VOR below 17.8% in both treatment groups, no statistically significant differences were found between them. These observations and our previous results suggest that a VOR gain reduction >17.8% is associated with a good control of vertigo attacks in the first 2 years of follow-up, but not with a particular clinical outcome in the long-term, i.e., the need for one or more intratympanic gentamicin injections to achieve a complete vertigo control.

Besides the semicircular canal function, other variables might account for the reappearance or persistence of vertigo episodes. The question raises about the role of the otolith organs in vertigo episodes in MD, which was not evaluated in the present study. Absent VEMP has been reported in 35–54% of affected ears in MD (26), and a dissociation between oVEMP and cVEMP has been observed during MD attacks compared to quiescence (27). Following ITG therapy, both animal and human studies have shown damage to the otolith organs. In this sense, Liu et al. (28) obtained sensitivity and specificity of 93.5 and 66.7%, respectively, for significant control of vertigo (class A and class B) when combined a positive clinical head-impulse test and abolished cVEMP responses, suggesting the use of this combination as an end-point of treatment of low-dose ITG therapy. Others suggest the association between the persistence of VEMP responses after ITG injections and vertigo recurrence (29).

The possibility to *in vivo* observe endolymphatic hydrops is one of the major achievements in MD in recent years (30). Findings in the MRI are also being considered as an explanation for a reduced response to gentamicin as suggested by Marques et al. (31), such that different degrees of hydrops could indicate corresponding modification of perilymphatic dynamics in the vestibule.

We were also interested in the non-affected or asymptomatic ear. The VOR gain was also reduced in the asymptomatic ear in all the canals in group 1, and, to a lesser degree, in the superior and horizontal canal in group 2 which was also observed by others (3, 12). Büki et al. (32) ascribed this phenomenon to the diminished disinhibition coming from the treated ear through the commissural inhibitory fibers in a similar fashion as in cases of vestibular neuritis described by Weber et al. using scleral search coils (33). However, unlike cases of vestibular neuritis where the contralateral ear is supposed to be a "healthy" one, in MD there is increasing evidence supporting the fact that the asymptomatic ear is not always completely normal. There are histopathological and electrophysiological reports suggesting endolymphatic hydrops in the contralateral ear (34–36). Finally, Pyykkö et al. reported the presence of endolymphatic hydrops in 65% of contralateral ears of subjects with clinically unilateral MD as assessed with gadolinium-enhanced MRI (37), and we also in cases with fluctuating auditory or vestibular symptoms (38). Contrary to these hypotheses (the push-pull mechanism between co-planar canals through the commissural system or subclinical

disease) is our finding that the modification in the gain of the VOR in those ears is not significantly different to the spontaneous modifications as shown when comparing to results in group 0. The number of included patients in that group is small, but findings agree to those recently reported in normal subjects and in patients with MD in whom the gain of the VOR varied little over very short (2 days) periods of time (39), which supports the high test-retest reliability of the measurement (40). This is contrary to what has usually been shown close to a new vertigo crisis (41).

The low overall hearing reduction observed in the treatment groups is our fourth result. It is similar to that observed by Cohen-Kerem (18), probably due to the low cochlear gentamicin levels produced by one-shot application protocols as has been estimated by Salt et al. using a computer simulation program (17). This is an argument for the safety of the use of ITG when indicated and correlates with similar protocol findings (42).

Our work also supports the use of gentamicin according to an on-demand protocol that limits further unneeded treatments based on the good control of vertigo and limited hearing damage but also of the reduced amount of unsteadiness because of the procedure. Although numbers are very small, they replicate the findings of chronic disequilibrium in patients with complete control of vertigo obtained when several treatments (group 2) were performed (5). Interestingly, when that procedure was followed (weekly injections until modification of the results of the vestibular bedside test) no difference was found between patients that needed subsequent vestibular rehabilitation regarding age, pre-treatment PTA and canal paresis, and number of gentamicin injections (43). Now, we have shown that when control of vertigo attacks is obtained with 1 single injection, the number of those that need vestibular rehabilitation is less. Also, that the change in the value of the gain of the VOR from pre-treatment to post-treatment value was very intense in these 2 patients. To further characterize this follow-up, a more in-depth study needs to be performed considering at least other variables as the amount of change induced by gentamicin in the otolithic maculae as measured by VEMP.

LIMITATIONS

This study has some limitations. First, as a retrospective study, there is a risk of selection bias. The prolonged follow-up period in many patients increases the risk of recall bias for the outcome of vertigo recurrence as it is sometimes difficult to remember whether there was a true vertigo episode. Thus, a misclassification of subjects into the wrong group could occur. Nevertheless, if this situation was true, more patients in the subgroup of expected results in group 1 would belong to a subgroup of unexpected results of group 2, supporting the fact that the VOR gain reduction cannot predict the clinical outcome. Second, we have used a measure for cutoff analysis obtained in a previous study. In the actual one, some of those patients are included, and this represents a bias in the analysis that should be taken into account. Third, the lack of information on the vertical canals in 10 subjects has precluded a detailed analysis of the horizontal canal. Very recently, it has been shown that there is a differential effect according to the semicircular canal evaluated such that the reduction in the gain of the VOR was more intense for the posterior and horizontal canal than for the superior semicircular canal (18). Fourth, we did not assess VEMP responses during the vestibular work-up which may bring information about the reasons for the vertigo recurrences in subjects with significant VOR reduction after ITG injections. Finally, another weakness in the present report is the small number of untreated subjects of group 0 because of the difficulty to recruit untreated definite subjects with MD, although the size effect was significant only when comparing the posterior canal VOR reduction between group 0 and group 1 in the asymptomatic ear (Cohen's $D = 1{,}64$). For this reason, these results should be considered with caution.

CONCLUSIONS

Our results show that one single dose of intratympanic gentamicin allows for a good vertigo control in the long term with similar effectiveness to that reported by others. Compared to the untreated group, the mean VOR gain reduction of the horizontal and superior canals, as measured with the vHIT 1 month after the first injection, was significantly higher in the treatment groups. A similar finding was obtained when comparing the single-treatment group and the multiple-treatment group, where the reduction in the former was significantly higher. However, the detailed analysis of the horizontal canal VOR reduction shows that, during the follow-up, many patients do not display the expected clinical course according to our previous endpoint of treatment. This explains the only fair accuracy obtained for the horizontal canal VOR reduction, as measured 1 month after the first injection, in predicting the need for no further instillations in the long term. In other words, a significant reduction of the VOR gain after the first ITG injection is less accurate in predicting the need for only one single dose for complete vertigo control than previously reported. A prospective study with a larger number of subjects and serial VOR assessment following ITG therapy might contribute to better characterizing the effect of gentamicin on canal function in time and help understanding the discrepancy between VOR reduction and vertigo control in the long term.

According to our observations, the protocol of low dosage intratympanic gentamicin as needed has proved to be a safe way to control vertigo attacks with a low risk of hearing loss.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comite de Etica de la Investigación (CEI). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NP-F, RW-V, and EM-S contributed to conception and design of the study. RW-V and DC-G organized the database. DC-G performed the statistical analysis. RW-V wrote the first draft of the manuscript. RW-V, NP-F, RM-H, EM-S, and PM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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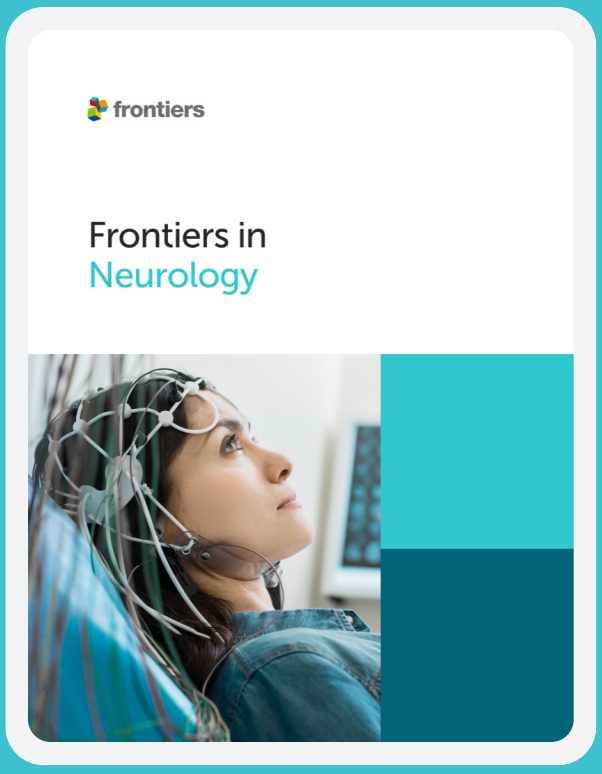

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