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Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms

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Abstract Vertigo patients exhibiting features of vestibular migraine (VM) and Menière's disease (MD) present a difficult diagnostic challenge to the clinician, and the two entities are likely to overlap. The aim of the present study was to investigate the occurrence of endolymphatic hydrops in patients with VM and auditory symptoms. This was an observatory diagnostic study. At an academic interdisciplinary dizziness centre, nineteen consecutive patients with definite or probable VM and auditory symptoms were examined by locally enhanced inner ear MR imaging. MR images were evaluated for the presence of endolymphatic hydrops. Of the 19 included patients, four patients (21 %) demonstrated evidence of cochlear and vestibular endolymphatic hydrops on locally enhanced inner ear MR imaging (three with "definite VM", one with "probable VM"). Locally enhanced inner ear MR imaging may be useful in the diagnostic evaluation of patients with VM and auditory symptoms, as some of these patients have signs of endolymphatic hydrops. Whether these patients suffer from MD only and are misdiagnosed as VM or suffer from both, VM and MD or whether endolymphatic hydrops is a consequence of inner ear damage due to VM are clinically relevant questions that can be evaluated by application of this technique.

Keywords Vestibular migraine · Endolymphatic hydrops · Menière's disease · LEIM · Magnetic resonance imaging

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Introduction

Vestibular migraine (VM) is a disorder characterized by episodic vertigo and typical migrainous symptoms. The currently most widely accepted diagnostic criteria have been suggested by Neuhauser et al. [1] and updated in 2009 [2] and 2012 [3] (Table 1).

The diagnosis is often difficult for three reasons: first, the attacks are associated in only 65 % with typical migrainous symptoms [4]; second, vertigo attacks and headaches may appear simultaneously or independently [5–8]; and third, there is evidently an overlap between VM and Menière's disease (MD) [9, 10]. Attacks are in particular often clinically indistinguishable from MD attacks because all auditory symptoms typical for MD may also be present in VM [11, 12]: aural pressure may be very difficult to be distinguished from headache; phonophobia is a symptom listed in the diagnostic criteria for VM (Table 1), but is also commonly encountered during MD attacks.

Clinical experience in dizziness centres as well as reports in the literature [13] show that there is a remarkable overlap between VM and MD when the diagnosis is based on clinical features and audiovestibular function tests alone. Currently,

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Table 1 Diagnostic criteria for vestibular migraine (from Lempert et al. [3]

Vestibular migraine
A At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h
B Current or previous history of migraine with or without aura according to the ICHD
C One or more migraine features with at least 50 % of the vestibular episodes:
–headache with at least two of the following characteristics: one sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
–photophobia and phonophobia,
–visual aura
D Not better accounted for by another vestibular or ICHD diagnosis
Probable vestibular migraine
A At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h
B Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
C Not better accounted for by another vestibular or ICHD diagnosis

the diagnostic criteria for "definite" MD are based on such clinical and audiometric criteria [14]. To establish a diagnosis of "certain" MD, the histopathologic proof of endolymphatic hydrops (ELH) is required. At the same time, MD is defined as "the idiopathic syndrome of endolymphatic hydrops" [14]. Recent progress has made it possible to reliably visualize ELH in living humans by employing a Locally Enhanced Inner ear MRI (LEIM) technique [15–17]. This paves the way for an in vivo assessment of endolymphatic and perilymphatic structures not only in patients with MD, but also in VM patients, as there may currently be a significant overlap between these two disease entities.

Due to the overlap in diagnostic criteria for VM and for MD and due to the fact that both diagnoses require other causes to be excluded, clinicians currently are often confronted with an unresolvable dilemma when evaluating patients who exhibit features of both VM and MD.

In our study, we aimed to investigate the prevalence of ELH in patients with definite or probable VM with hearing-related symptoms to further elucidate the relationship between these two frequent disease entities using a LEIM technique.

Methods

Setting

Universitary interdisciplinary dizziness centre in a university hospital. The study protocol was approved by the ethics committee of the medical faculty. All patients provided oral and written informed consent prior to inclusion into the study.

Study population

Nineteen consecutive patients with the diagnosis of definite or probable VM, according to the diagnostic criteria by Neuhauser et al. [2] and with auditory symptoms (hearing loss, tinnitus or aural fullness) were included in this study after giving written informed consent.

Clinical evaluation

All patients were evaluated clinically by an otologist and a neurologist, both with more than 8 years of experience in a dizziness clinic. The diagnostic work-up included MR imaging of the brain including the cerebellopontine angle and the brainstem, audiometry, caloric videooculography and electrocochleography. Horizontal semicircular canal function was measured using videooculography (SensoMotoricInstruments, Germany). Caloric responses were assessed according to Hallpike [18] by irrigation with 100 ml of 30 and 44 °C warm water for 30 s, respectively, and the degree of horizontal canal paresis was evaluated according to Jongkees et al. [19]. A canal paresis of >20 % was considered a pathologic result. Electrocochleography was performed using a tympanic membrane electrode and click stimuli [20]; an SP/AP ratio of >0.4 was considered as indicative of ELH. The clinical and functional test results data were extracted from the electronic and paper medical records.

Locally enhanced inner ear MRI (LEIM)

Immediately after audiovestibular function testing, a 1:8 dilution of gadolinium-based contrast agent (GBCA) (Omniscan; GE Healthcare, Amersham, UK) was injected transtympanically, with the patient lying supine and the head turned 45° away from the surgeon. The patient then remained in this position for 30 min, instructed not to speak or chew. After 20–24 h, the MR scan was performed on a 3T MR unit (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) using a 32-channel phased array coil. The following two MR sequences were applied to visualize ELH: (1) 3D-FLAIR sequence with the following parameters: repetition time of 9,000 ms, effective echo time of 128 ms, inversion time of 2,500 ms, constant flip angle echo train with flip angle of 180° for conventional turbo spin echo refocusing echo train, echo train length of 23, matrix size of 384 × 384, 12 axial 2 mm thick slices to cover the labyrinth with a 16 × 16 cm^2 square field of view, acceleration factor of 2 using a

parallel imaging technique, with a Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) algorithm. The resulting voxel size was 0.4 mm × 0.4 mm × 2 mm. The number of excitations was 1, and the scan time was 15 min. (2) 3D-IR-TSE sequence with the following parameters: TR 7,000 ms, TE 128 ms, TI 1,700 ms, constant flip angle of 180°, echo train length of 23, matrix size of 384 × 384, 12 axial slices at 2-mm slice thickness, and number of excitations 1. The labyrinth was scanned with a square field of view of 16 × 16 cm^2, parallel imaging with a factor of 2 was used with GRAPPA reconstruction algorithm. This sequence allows for a better delineation of the endolymphatic space from the surrounding bone, compared with the 3D FLAIR sequence [21]. In addition, a high resolution, strongly T2-weighted, 3D constructive interference steady state (CISS) sequence of the temporal bones was performed to evaluate the anatomy of the whole fluid-filled labyrinthine spaces, with the following parameters: TR 6.24 ms, TE 2.87 ms, flip angle of 70°, field of view of 160 × 160 mm^2, matrix size of 320 × 320, averages 1, and slice thickness of 0.4 mm. The presence of ELH was observed on the 3D-FLAIR images as enlarged negative-signal spaces inside the labyrinth, according to the previously reported method [15]. LEIM evaluation was performed independently by an experienced head and neck radiologist and an experienced neurotologist who were blinded to the clinical patient data and, if discrepancies arose, a consensus was reached by discussion.

Results

An example of the LEIM morphology in a patient with ELH and a patient without ELH is provided in Figs. 1, 2, 3, 4. The clinical features of the study cohort are summarized in Table 2. Of the 19 patients with definite or probable VM, there was morphologic evidence of cochlear and vestibular ELH on MR imaging in four patients (cases no. 1, 2, 6 and 8). Three of these patients had been clinically classified as having definite VM; one patient was classified as having probable VM.

Thirteen of the 19 patients showed a hearing loss of at least 20 dB nHL (PTA 0.5, 1, 2, 3 kHz). This included 3 of the 4 patients with ELH, the remaining patient, however, had a normal hearing function. Tinnitus was the most common auditory symptom, being reported by all but one patient. Thirteen of the 19 patients included in this study were suffering from aural fullness, including all four patients with ELH. In all but two patients, the vertigo attacks lasted longer than 20 min. Two of the four patients with ELH experienced photophobia and phonophobia associated with the attacks of vertigo, the other two did not. Three of the four patients with ELH reported also having a visual aura.

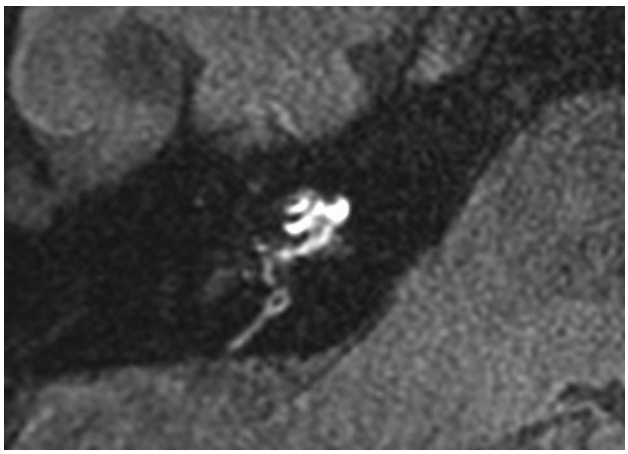

Fig. 1 Inner ear of patient with endolymphatic hydrops (FLAIR). 3D FLAIR image of the right ear of patient no. 1 with ELH. The cochlear perilymphatic space (high signal intensity) is markedly compressed by the endolymphatic space (low signal intensity). The vestibulum shows very weak perilymph signal. The posterior SCC with its ampulla shows normal perilymph signal

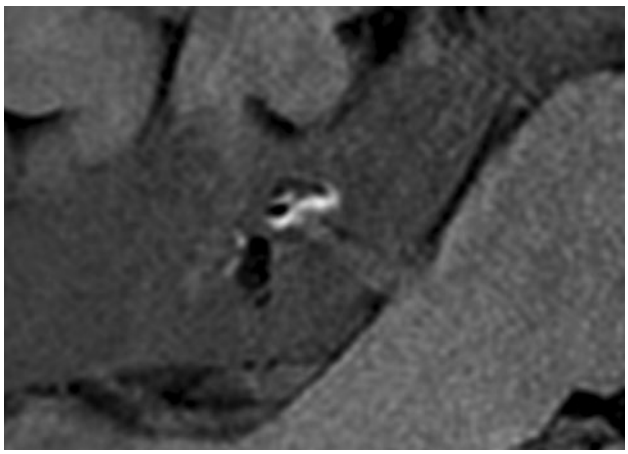

Fig. 2 Inner ear of patient with endolymphatic hydrops (Real-IR). Real-IR image of the right ear of patient no. 1 with ELH. The cochlear endolymph space (low signal intensity) is markedly enlarged and clearly differentiated from surrounding bone (intermediate signal). The vestibulum shows only endolymph signal and no perilymph signal due to severe endolymphatic hydrops

Of the four VM patients with ELH, three also fulfilled the criteria for definite MD [14] and one patient for probable MD. It is important to note that, of the seven patients with definite VM, five also had definite MD, but only two of these five with a diagnostic overlap had endolymphatic hydrops.

Discussion

This study is the first to demonstrate the morphologic presence of ELH in vivo in patients with the diagnosis of definite and probable VM. Our study cohort does not

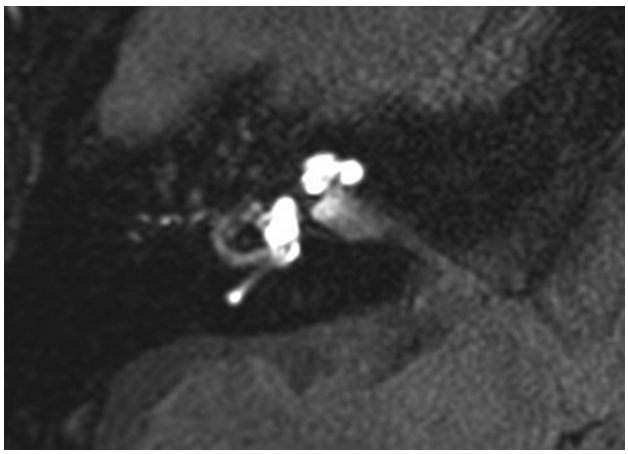

Fig. 3 Inner ear of patient without endolymphatic hydrops (FLAIR). 3D FLAIR image of the right inner ear of patient no. 12 without ELH. The cochlea and vestibulum show a strong perilymph signal (high signal intensity). The physiologically small endolymphatic space is hardly visible

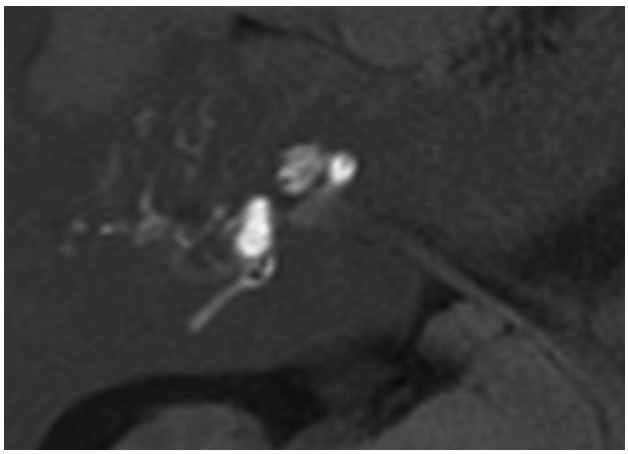

Fig. 4 Inner ear of patient without endolymphatic hydrops (Real-IR). Real-IR image of the right ear of patient no. 12 without ELH. The cochlear endolymph space (ductus cochlearis) appears slim between the larger scala tympani and scala vestibuli. The vestibular endolymph space is too small to be visualized on this section. The posterior SCC shows a regular endolymph space (low signal intensity) in its ampulla

represent an average VM population, since all patients had some sort of auditory symptoms. However, auditory symptoms are not uncommon among VM patients. There is a well-known overlap between the clinical entities of VM and MD, already acknowledged even by Prosper Menière himself [22], which is also reflected by the fact that there is no diagnostic reference standard available for either disease [10, 23]. Electrocochleography has been used to indirectly detect ELH for many decades, but is known to have a low sensitivity and specificity [24] which is in concordance with the results in our study population. In a recent study, Neff et al. meticulously analyzed and categorized the clinical features of VM, MD and chronic subjective dizziness, showing a large overlap between and the many common features of VM and MD. In their study, 28 % of patients diagnosed with MD also had VM and 23 % of patients with VM also had MD. Furthermore, it has been shown that the rate of migraine was significantly greater among MD patients than in matched controls and far higher than the population prevalence [9]. These observations are very much in accordance with our clinical experience gathered at an interdisciplinary dizziness centre and reflect the difficulties that clinicians are facing when patients exhibit features typical for both VM and MD. The four patients with VM found to have ELH in this study had, likewise, various aural symptoms: Case 1: Constant tinnitus, with slight fluctuations independent of vertigo; aural fullness appears isolated, but also sometimes simultaneously with vertigo and with headache. Case 2: Tinnitus appears intermittently and isolated, but sometimes together with vertigo or with headache; Aural fullness and hearing loss are both constant. Case 6: No subjective hearing loss; constant tinnitus and aural fullness. Case 8: Constant hearing loss and aural fullness; Constant tinnitus, with fluctuations during stress and sometimes also during headaches or vertigo attacks.

Recent advances in inner ear imaging now allow us to visualize ELH in a human in vivo. Although it is still a new modality and includes intratympanic application of Gadolinium-based contrast agents, the published data have not shown any evidence of ototoxic side effects so far [25, 26]. Therefore, MR imaging-based diagnosis of ELH will likely become more widely used in the future.

The fact that our study demonstrated ELH to be present in a proportion of VM patients with auditory symptoms underscores the usefulness of LEIM in the diagnostic work-up of patients exhibiting vestibular, migrainous and/or auditory symptoms. As was recently stated in a best-practice-review on the diagnosis of VM, "The Neuhauser et al. criteria presents a broad-based starting point to help guide clinicians…", but "in an ideal world, the pathophysiology of a disease process (e.g., ELH) would dictate its diagnosis." [27]. Very recently, the diagnostic criteria for VM have been updated by the Bárány Society. We have classified our study population according to these new criteria, but for the sake of clarity we are still using the denominator "definite" when referring to VM according to these new criteria, to facilitate differentiation from the category "probable VM" (in the new criteria, "definite VM" has simply become "VM", with slight modifications). These new criteria also acknowledge the widely known overlap of the two disease entities, and they recommend to classify a patient as suffering from MD, whenever the patients fulfills both the criteria for VM and MD. However, our data show that this might be an oversimplification, since only two of

Table 2 Clinical features of study population. All patients had definite or probable vestibular migraine and auditory symptoms

No.	Age	Sex	VM category	MD category	Disease duration (years)	Episodic vertigo	V > 20 min	PTA 0.5-3 kHz	Tinnitus	Aural fullness	HA 4-72 h	Nau/Vo	Photo-phobia	Phono-phobia	Visual Aura	Other Aura	CP	ECochG-ELH	LEIM-ELH
1	68	f	Definite	Definite	30	+	+	70	+	+	+	+	+	+	+	−	−	+	+
2	44	m	Definite	Definite	3	+	+	34	+	+	+	+	+	+	−	−	−	+	+
3	36	f	Definite	Definite	4	+	+	48	+	+	+	+	−	−	−	+	+	+	−
4	70	f	Definite	Definite	1	+	+	78	+	+	+	+	−	−	−	−	+	n.a.	−
5	44	f	Definite	Definite	7	+	+	31	+	+	+	+	+	+	+	+	−	+	−
6	31	f	Definite	Possible	2	+	+	11	+	+	+	−	−	−	+	+	−	+	+
7	32	f	Definite	Possible	15	+	+	14	+	+	+	+	+	−	−	−	+	−	−
8	58	m	Probable	Definite	12	+	+	83	+	+	+	−	−	−	+	−	+	n.a.	+
9	46	f	Probable	Definite	1	+	+	58	+	+	+	+	+	+	−	+	+	+	−
10	31	f	Probable	Definite	15	+	+	48	+	−	+	−	−	+	+	−	−	+	−
11	51	m	Probable	Definite	10	+	+	31	+	−	−	+	−	+	+	−	−	+	−
12	51	f	Probable	Definite	2	+	+	20	+	+	+	+	+	+	+	−	+	+	−
13	42	m	Probable	Definite	18	+	+	10	+	−	+	−	+	−	−	−	−	−	−
14	77	f	Probable	Possible	45	+	−	34	+	+	−	+	−	−	+	−	−	−	−
15	67	f	Probable	Possible	10	+	+	16	+	+	−	+	+	+	−	−	−	−	−
16	60	f	Probable	Possible	2	+	+	13	+	+	+	+	−	+	−	−	−	n.a.	−
17	74	f	Probable	Possible	1	+	+	21	−	−	−	+	+	+	−	−	+	+	−
18	46	m	Probable	Possible	2,5	+	−	25	+	−	−	−	+	−	+	−	+	−	−
19	38	f	Probable	Possible	4	+	+	14	+	−	−	+	+	+	−	−	+	−	−

CP Canal paresis, *EcochG-ELH* SP/AP ratio on electrocochleography indicative of endolymphatic hydrops, *HA* Headache, *LEIM-ELH* Morphologic evidence of endolymphatic hydrops on Locally Enhanced Inner ear MRI, *MD* Menière's disease, *Nau/Vo* nausea/vomiting, *V* Vertigo, *VM* Vestibular migraine

the five patients in this cohort that qualifies for both definite VM and definite MD, had morphological evidence of ELH.

Interestingly, in this study population, EcochG showed evidence of ELH in a larger number of patients (10 of 16) than LEIM, suggesting that LEIM may be less sensitive than EcochG. In general, audiovestibular function tests may conceivably detect physiologic changes (e.g., basal membrane displacement) caused by subtle degrees of or beginning ELH which may be too small to be visualized by current MR imaging techniques. Such a diagnostic "delay" should be examined in long-term follow-up studies on such patients, since we know from cross-sectional studies that ELH is likely to progress over the years during the disease course [16]. It has to be kept in mind, however, that even electrocochleography which has been regarded by many for a long time as the gold standard for the detection of ELH, is not completely specific, since it has been found to give false-positive results in patients with perilymphatic fistula [28] or with superior canal dehiscence syndrome [29].

This study has several limitations that need to be taken into account when interpreting the data. First, the study sample is relatively small. However, all participants in the study were well characterized both clinically and with audiovestibular function tests. Second, we only included patients with VM who also had auditory symptoms. This may artificially increase the prevalence of ELH in a patient cohort with VM. However, the occurrence of auditory symptoms in patients with VM is rather high [30].

In conclusion, LEIM may be useful in the differential diagnosis of patients with VM and auditory symptoms, since it may detect ELH in a proportion of these challenging cases. This has immediate implications for the differential diagnosis in vertigo patients, for the pathophysiologic understanding and the clinical definitions of diseases like VM and MD as separate entities and for their therapeutic management.

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Conflict of interest None of the authors has a conflict of interest to declare. None of the authors has any financial conflict of interest to declare.

References

1. Neuhauser H, Leopold M, von Brevern M, Arnold G, Lempert T (2001) The interrelations of migraine, vertigo, and migrainous vertigo. Neurology 56:436–441
2. Neuhauser H, Lempert T (2009) Vestibular migraine. Neurol Clin 27:379–391
3. Lempert T, Olesen J, Furman J et al (2012) Vestibular migraine: diagnostic criteria. J Vestib Res 22:167–172
4. Dieterich M, Brandt T (1999) Episodic vertigo related to migraine (90 cases): vestibular migraine? J Neurol 246:883–892
5. Neuhauser HK, von Brevern M, Radtke A et al (2005) Epidemiology of vestibular vertigo: a neurotologic survey of the general population. Neurology 65:898–904
6. Cutrer FM, Baloh RW (1992) Migraine-associated dizziness. Headache 32:300–304
7. Cha YH, Lee H, Santell LS, Baloh RW (2009) Association of benign recurrent vertigo and migraine in 208 patients. Cephalalgia 29:550–555
8. Brantberg K, Baloh RW (2011) Similarity of vertigo attacks due to Meniere's disease and benign recurrent vertigo, both with and without migraine. Acta Otolaryngol 131:722–727
9. Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H (2002) Migraine and Meniere's disease: is there a link? Neurology 59:1700–1704
10. Radtke A, von Brevern M, Neuhauser H, Hottenrott T, Lempert T (2012) Vestibular migraine: long-term follow-up of clinical symptoms and vestibulo-cochlear findings. Neurology 79:1607–1614
11. Kayan A, Hood JD (1984) Neuro-otological manifestations of migraine. Brain 107(Pt 4):1123–1142
12. Battista RA (2004) Audiometric findings of patients with migraine-associated dizziness. Otol Neurotol 25:987–992
13. Neff BA, Staab JP, Eggers SD et al (2012) Auditory and vestibular symptoms and chronic subjective dizziness in patients with Meniere's disease, vestibular migraine, and Meniere's disease with concomitant vestibular migraine. Otol Neurotol 33:1235–1244
14. AAO-HNS (1995) Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg 113:181–185
15. Nakashima T, Naganawa S, Pyykko I et al (2009) Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol 129(s560):5–8
16. Gurkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E (2012) In vivo visualized endolymphatic hydrops and inner ear functions in patients with electrocochleographically confirmed Meniere's disease. Otol Neurotol 33:1040–1045
17. Grieve SM, Obholzer R, Malitz N, Gibson WP, Parker GD (2012) Imaging of endolymphatic hydrops in Meniere's disease at 1.5 T using phase-sensitive inversion recovery: (1) demonstration of feasibility and (2) overcoming the limitations of variable gadolinium absorption. Eur J Radiol 81:331–338
18. Hallpike CS (1956) The caloric tests. J Laryngol Otol 70:15–28
19. Jongkees LB, Maas JP, Philipszoon AJ (1962) Clinical nystagmography. A detailed study of electro-nystagmography in 341 patients with vertigo. Pract Otorhinolaryngol (Basel) 24:65–93
20. Ferraro JA, Durrant JD (2006) Electrocochleography in the evaluation of patients with Meniere's disease/endolymphatic hydrops. J Am Acad Audiol 17:45–68
21. Naganawa S, Satake H, Kawamura M, Fukatsu H, Sone M, Nakashima T (2008) Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. Eur Radiol 18:920–924
22. Menière P. Mémoire sur des lésions de l'oreille interne donnant lieu à des symptômes de congestion cérébrale apoplectiforme. Gazette médicale de Paris 1861; 16:88–89, 239–240, 379–380, 597–601

23. Strupp M, Versino M, Brandt T (2010) Vestibular migraine. Handb Clin Neurol 97:755–771
24. Kim HH, Kumar A, Battista RA, Wiet RJ (2005) Electrocochleography in patients with Meniere's disease. Am J Otolaryngol 26:128–131
25. Louza JP, Flatz W, Krause E, Gurkov R (2012) Short-term audiologic effect of intratympanic gadolinium contrast agent application in patients with Meniere's disease. Am J Otolaryngol 33:533–537
26. Louza J, Krause E, Gürkov R (2013) Audiologic evaluation of Menière's disease patients one day and one week after intratympanic application of Gadolinium contrast agent: our experience in sixty-five patients. Clin Otolaryngol 38(3):262–266
27. Kahmke R, Kaylie D (2012) What are the diagnostic criteria for migraine-associated vertigo? Laryngoscope 122:1885–1886
28. Arenberg IK, Ackley RS, Ferraro J, Muchnik C (1988) ECoG results in perilymphatic fistula: clinical and experimental studies. Otolaryngol Head Neck Surg 99:435–443
29. Arts HA, Adams ME, Telian SA, El-Kashlan H, Kileny PR (2009) Reversible electrocochleographic abnormalities in superior canal dehiscence. Otol Neurotol 30:79–86
30. Radtke A, Neuhauser H, von Brevern M, Hottenrott T, Lempert T (2011) Vestibular migraine–validity of clinical diagnostic criteria. Cephalalgia 31:906–913