

Ménière's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops

Ilmari Pyykkö,¹ Tsutomu Nakashima,² Tadao Yoshida,² Jing Zou,¹ Shinji Naganawa³

To cite: Pyykkö I, Nakashima T, Yoshida T, *et al.* Ménière's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. *BMJ Open* 2013;**3**:e001555. doi:10.1136/bmjopen-2012-001555

► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-001555>).

Received 8 August 2012
Revised 3 January 2013
Accepted 8 January 2013

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

¹Department of Otolaryngology, University of Tampere, School of Medicine, Tampere, Finland

²Department of Otolaryngology, Nagoya University School of Medicine, Nagoya, Japan

³Department of Radiology, Nagoya University School of Medicine, Nagoya, Japan

Correspondence to

Professor Ilmari Pyykkö; Ilmari.pyykko@uta.fi

ABSTRACT

Objectives: To evaluate the onset of vertigo, hearing loss and tinnitus in Ménière's disease and the associated endolymphatic hydrops (EH) of the inner ear.

Design: Multicentre evaluation of three patient groups.

Settings: Disease-specific symptoms were reviewed among referred patients in a tertiary referral hospital in Finland and in members of a Finnish Ménière Association in Finland. The MRI of a separate group of patients was undertaken in a tertiary referral centre in Japan.

Participants: 340 patients were reviewed in the referral hospital along with 740 members of the Ménière Association. MRI was undertaken in 224 patients in Japan.

Primary and secondary outcome measures:

Latency and symptom development in Ménière's disease, and the appearance of EH of the inner ear in monosymptomatic patients and in Ménière's disease.

Results: The mean age of the first symptom was 43.8 years, with 10% of the patients being older than 65 years. The time delay between hearing loss and vertigo was more than 5 years in 20% of the members and of the patients. Gadolinium-contrasted MRI demonstrated EH in 90% of the patients with Ménière's disease, in which 75% was bilateral among patients with unilateral symptoms. In monosymptomatic patients with vertigo, tinnitus or hearing loss; EH was demonstrated in 55–90% of the patients either in the cochlea and/or the vestibulum of the symptomatic ear.

Conclusions: Ménière's disease often shows bilateral EH and comprises a continuum from a monosymptomatic disease to the typical symptom complex of the disease. We suggest that a 3T MRI measurement should be carried out in patients with sensory-neural hearing loss, vertigo and tinnitus, 4 h after the intravenous injection of a gadolinium-contrast agent to verify the inner ear pathology. This may lead to a better management of the condition.

The cardinal symptoms of Ménière's disease form a disease entity consisting of episodic vertigo, fluctuant hearing loss and tinnitus.¹ Patients also often complain of

ARTICLE SUMMARY

Article focus

- Variability of symptom occurrence and diagnostic difficulties of Ménière's disease in two patient groups.
- Appearance of endolymphatic hydrops (EH) in Ménière's disease in symptomatic and asymptomatic ears.
- Appearance of EH in monosymptomatic patients.

Key messages

- A reappraisal of the diagnosis of Ménière's disease: in about 20% of patients, it takes more than 5 years before a diagnosis can be made.
- In unilateral Ménière's disease, the appearance of EH is often bilateral. MRI is a key measure in the assessment of EH.
- In the monosymptomatic ear, EH can be frequently shown.

Strengths and limitations of this study

- While this is the first large study in this field in the world, the three study groups are collected in separate places.
- There is no longitudinal follow-up of the MRI results—repeated MRIs could indicate the possible fluctuation of EH.

fullness in the ear, gait problems, postural instability and nausea. Ménière's disease is a chronic illness affecting about 190/100 000 patients in a US Health-claims database, but in population studies a prevalence as high as 513/100 000 has been shown.² The severity of the symptoms varies. Ménière's disease originates in the inner ear and can be demonstrated in histological studies as an enlargement of the endolymphatic space, called endolymphatic hydrops (EH).^{3 4} The aetiology of the disease is unknown and the condition has a chronic course.

Symptom-based classification methods have been used to make the diagnosis.⁵ Indeed, in

a taxonomic investigation of patients with vertigo, after the exclusion of neurological and middle ear conditions, head trauma and ototoxicity, Hinchcliffe⁶ found that those with 'classical' Ménière's disease (meeting the 'probable' definition below) fell into a single nosological entity with all other cases of vertigo. He later argued that Ménière's disease included 'forms frustes', where the triad of symptoms is not complete.⁷ The American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) has proposed the currently used classification (table 1).⁵ It defines 'Possible Ménière's disease', 'Probable Ménière's disease' and 'Definite Ménière's disease'. 'Certain Ménière's disease' is diagnosed by the symptom entity and histological verification of EH in the inner ear. To define the condition clinically, however, the existing AAO-HNS classification is unhelpful.

The recent development of 3T MRI with gadolinium chelate (GdC) as the contrast agent provides a tool for the visualisation of EH. This technique was first developed in animal experiments⁸ and adapted in patients with inner ear diseases.⁹ For human imaging, specific algorithms using Fluid Attenuation Inversion Recovery sequences (FLAIR) can demonstrate minute amounts of contrast agent in the inner ear.¹⁰ Three-dimensional (3D)-inversion-recovery turbo spin echo (TSE) with real reconstruction (3D-real IR) showed a higher contrast between the non-enhanced endolymph and the surrounding bone.¹¹ With new imaging techniques, EH can be demonstrated in vivo in most cases and can thus confirm the diagnosis.

It is important that doctors and patients become aware of the possibilities of removing the uncertainty of the diagnosis of recurrent attacks of vertigo or hearing loss when the symptom profile does not fit 'classical' Ménière's disease. We shall demonstrate that Ménière's disease is characterised by a variable course and onset of symptoms. The disease appears to be a continuum from an initial single symptom disease to a fully developed disease entity. With the development of inner ear imaging, the diagnostic work-up can be performed even

in patients of advanced years, which can lead to better management of the condition.

INDIVIDUALS AND METHODS

Symptom clustering of patients referred to a tertiary referral hospital

We evaluated all of those patients referred to the vestibular unit of Helsinki University Hospital while developing a computer-aided diagnostic system for vertigo.^{12 13} The study was approved by the local ethical committee (HYKS 7.5.97). All patients enrolled in the vestibular unit completed a questionnaire concerning their symptoms, accidents and earlier disease among others. A nurse supervised and instructed them with the questionnaire. The information was then supplemented by data from clinical examinations and the results of audiological, neurotological and imaging studies. All 1730 patients were enrolled in the study. During follow-up, we were able to assess the diagnosis in 1030 cases, of whom 340 had Ménière's disease. For this study, we evaluated the symptoms that the patients presented when seeking help from healthcare specialists for their disease. The mean age of patients with Ménière's disease was 51.9 years (range 21–83 years). Their first symptom occurred on average 7.4 years prior to entering the clinic (range 0–47 years). The group consisted of 249 (73.2%) women and 91 (26.8%) men.

Cross-sectional study

Permission was obtained from the Finnish Ménière Federation to contact their members, asking them to complete an extensive questionnaire on symptoms related to Ménière's disease. Some of the patients who were included in the clinical study were also included in the cross-sectional study. The mean time difference between these studies was 12 years. (Under Finnish law, a questionnaire-based patient association study does not require ethical approval.)

They were sent a 26-page questionnaire^{14 15} by mail, together with a stamped, addressed envelope for their

Table 1 Diagnostic scale for Ménière's disease of the American Academy of Otolaryngology—Head and Neck Surgery

Evidence of the class of Ménière's disease	Vertigo	Hearing loss	Tinnitus/aural fullness	Other
Certain Ménière's disease	Two or more episodes of vertigo of at least 20 min	Audiometrically defined hearing loss at least once	Yes	Histological confirmation of endolymphatic hydrops
Definite Ménière's disease	Two or more episodes of vertigo of at least 20 min	Audiometrically defined hearing loss at least once	Yes	
Probable Ménière's disease	One definite episode of vertigo	Audiometrically defined hearing loss at least once	Yes	
Possible Ménière's disease	Episodic vertigo Vertigo without definite episodes	Not documented SNHL, fluctuating or fixed		

SNHL, sensory-neural hearing loss.

responses. Those not responding within 12 weeks were sent reminders. In total, 740 (62%) of 1200 questionnaires sent out were returned and of these, 726 were adequately completed and included in the database. The study group consisted of 571 (78.6%) women and 155 (21.3%) men. Their mean age was 62.3 years (SD 11.5 years). Their Ménière's disease-like symptoms had lasted an average of 16.2 years (SD 11.2 years). Thirty-five individuals with only Ménière's disease-like symptoms had 'possible Ménière's disease', while the other 691 fulfilled the AAO-HNS criteria of 'probable or definite Ménière's disease'.⁵

MRI evaluation of patients with suspected EH

All 224 patients with symptoms of tinnitus, hearing loss and/or vertigo were measured with GdC-enhancement of the inner ear MRI in a tertiary referral centre in Japan. The patients included in the study either had symptoms attributable to Ménière's disease or had inner ear symptoms without any obvious cause. All patients seen in the clinic who met these criteria were invited to participate in the study. The mean age of the individuals was 53.3 years (range 16–82 years); 115 were women and 109 were men. All patients gave informed consent to participate in the study. The study protocol was approved by the Ethics Review Committee of Nagoya University, Japan.

The individuals received GdC, either gadodiamide hydrate (Omniscan) or gadopentetate dimeglumine (Magnevist), for visualisation of the cochlear partitions. Two different application routes were used. A transtympanic injection of 0.3 ml was performed only in the symptomatic ears of 119 patients (119 ears). MRI was performed 24 h after the transtympanic injection of GdC. An intravenous application of 0.2 ml/kg was used in 105 patients (210 ears). MRI was performed 4 h after the intravenous GdC administration. Overall, 328 ears were evaluated (table 2). One ear had a congenital hearing loss and was excluded. If the patient had no complaints in the contralateral ear, it was called an 'asymptomatic ear'. When the patient had episodic vertigo without hearing loss, a diagnosis of 'possible Ménière's disease' was used.⁵

Table 2 Classification of patients included in MRI-study based on symptoms

Symptoms of the ear evaluated	Number
Asymptomatic	45
Hearing loss	43
Sudden deafness	13
Tinnitus	9
Vertigo and dizziness	13
Possible Ménière's disease	122
Probable Ménière's disease	15
Definite Ménière's disease	68
Totally	328

The same MRI protocol was performed on patients with symptoms of tinnitus, hearing loss and/or vertigo in Finland. Detailed results obtained from the study will be reported in the future when the local ethical committee approves the permission. Therefore, these data are not included in the current report.

Conventional 3D FLAIR of the inner ear was performed after either transtympanic or intravenous injection of GdC as previously reported.¹⁶ In order to improve the sensitivity of imaging EH after the intravenous injection of GdC, a heavy T2-weighted FLAIR sequence was optimised as follows: repetition time (TR) of 9000 ms, echo time (TE) of 540 ms, inversion time (TI) of 2350 ms. The initial refocusing flip angle was 180° and rapidly decreased to a contrast flip angle of 120°. For the TSE, refocusing the echo train was set in a SPACE sequence, with an echo-train length of 144, matrix size of 270×320, and 72 axial 0.8-mm-thick slices covering the labyrinth and with a 15×18 cm field of view. A GRAPPA acceleration factor of 2 was used; it had a voxel size of 0.56 mm×0.56 mm×0.8 mm, four excitations and a scan time of 10.7 min. More detailed information on the imaging has been published elsewhere.¹⁰

The vestibule and cochlea were analysed separately for each patient, based on previously documented criteria.¹⁷ The normal range of the ratio of the endolymphatic area over the vestibular fluid space (sum of the endolymphatic and perilymphatic areas) is 33%, and any increase in the ratio would be indicative of EH. According to the criteria; mild EH in the vestibule covers a ratio of 34–50% and significant EH covers a ratio of more than 50% in the vestibule. The respective evaluation of the ratio of the endolymphatic area over the total fluid space of the cochlea is correlated to the displacement of Reissner's membrane. Normally, Reissner's membrane remains in situ and is shown as a straight border between the endolymph-containing scala media and perilymph-containing scala vestibuli. Mild EH displays an extrusion of Reissner's membrane towards the scala vestibuli and results in an enlargement of the scala media with an area of less than that of the scala vestibuli. Significant EH causes an increase of the scala media with an area larger than that of the scala vestibuli.

Statistics—a χ^2 test was used to compare the appearance of EH between the cochlea and vestibulum.

RESULTS

Symptom profile and onset of the disease

The symptoms of patients on their first visit to the tertiary hospital for evaluation and treatment were examined. Based on the initial symptoms, 38% of the 340 patients could be classified as definite Ménière's disease. In 62%, a definite diagnosis was not possible. Within this group, the mean age of onset of the first symptoms was 42.5 years among the 340 patients referred. Table 3 shows the clustering of symptoms on referral for treatment.

Table 3 Symptoms of Ménière's disease when first seen in a tertiary referral hospital (n=340)

Symptom	Prevalence (%)
Vertigo, tinnitus and hearing loss	38
Vertigo	21
Hearing loss	13
Tinnitus	5
Tinnitus with hearing loss	15
Vertigo with hearing loss	4
Vertigo with tinnitus	4
Total	100%

Onset of symptoms

The age of onset of symptoms was evaluated among 726 patients belonging to a Finnish Ménière Association. This group comprised 35 individuals who had only Ménière's disease-like symptoms and 'possible Ménière's disease'. The mean age of onset of the first symptoms was 43.8 years. In about 10% of the individuals, the symptoms started at an age of over 65 years (figure 1).

We asked the individuals to recall the first symptoms associated with Ménière's disease. Most commonly, the symptoms started with vertigo, with or without tinnitus and pressure in the ear. Hearing loss, as an initial symptom, occurred significantly less frequently than vertigo (figure 2). Vertigo without hearing loss developed as an initial symptom among 300 individuals, and hearing loss without vertigo in 109 individuals. In Fisher's exact test, the onset of the disease with vertigo was significantly more common than onset with hearing loss (p=0.031).

Latency of the disease entity

Among the members of the Finnish Ménière Association, the time delay between the onset of vertigo

and hearing loss, with or without tinnitus, was long in many cases, irrespective of whether the disease started with vertigo (figure 3A) or with hearing loss (figure 3B). In 21% of the patients, the time delay in assigning a probable diagnosis was 1–4 years. In 11% of the individuals, the time difference between the occurrence of both hearing loss and vertigo was 5–10 years, and in 9%, the difference was longer than 10 years. Thus, in about 20% of the patients, the time delay between the development of the disease entity of probable Ménière's disease was more than 5 years.

MRI of Ménière's disease and different inner ear-related complaints: patients with a symptom entity referable to Ménière's disease

EH was present in 190 of 205 ears (93%) with symptoms attributable to Ménière's disease (as shown by MRI enhanced with both transtympanically and intravenously administered GdC). Of the 45 asymptomatic contralateral ears, 29 (65%) showed EH on MRI with intravenously administered GdC. Table 4 shows the site of EH in patients investigated with GdC-enhanced MRI. The vestibule showed the presence of EH more frequently than did the cochlea (p<0.004).

Figure 4 shows a representative inner ear MRI from a Finnish patient with EH, acquired with a 3D-FLAIR sequence at 24 h post-transtympanic injection of GdC. In this, the inner ear fluids of the unenhanced ear showed as a dark image, and the eighth nerve and bone were imaged as grey. The perilymph of the injected ear displayed a bright signal as a result of GdC contrast. Since GdC failed to pass the perilymph-endolymph barrier, the endolymphatic space in the vestibular and cochlear regions remained dark and obvious EH was visualised.

Figure 5 is a representative MRI of a Japanese patient with Ménière's disease, acquired by a heavy T2-weighted

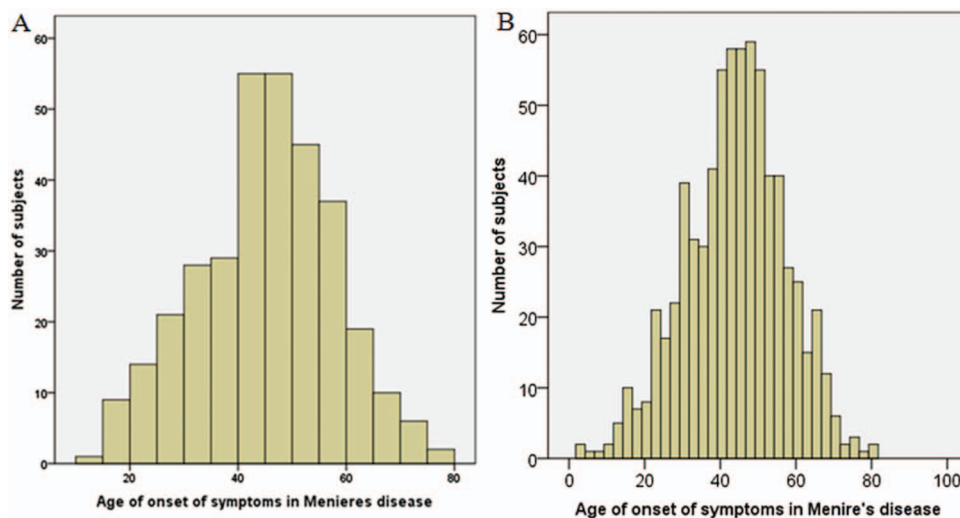
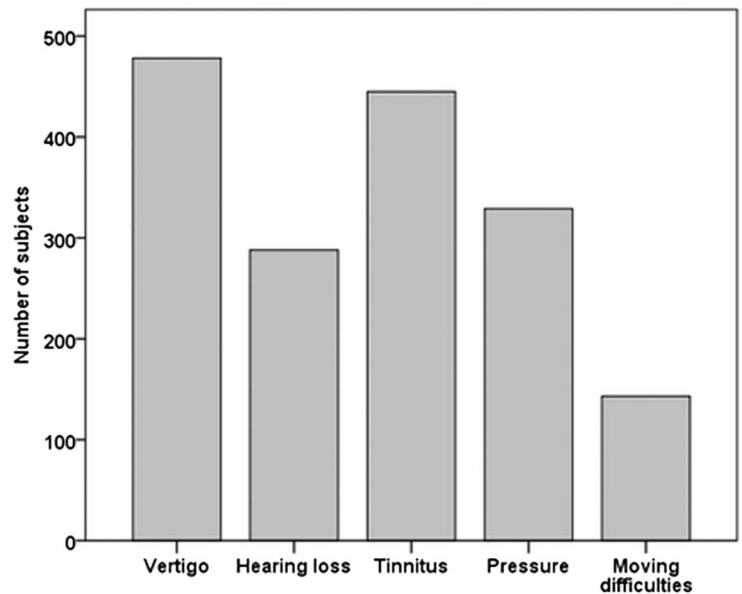


Figure 1 The onset of symptoms of Ménière's disease and age of the individual—(A) in the tertiary referral centre (n=340), (B) in the Ménière Association (n=726).

Figure 2 Onset of symptom among patients with the Finnish Meniere Association (n=726). The patients could have one or several symptoms in the onset of the disease.



3D-FLAIR sequence and 4 h postintravenous injection of GdC. The border between the endolymphatic and perilymphatic spaces was not as distinct as seen following transtympanic GdC administration.

Patients with monosymptomatic inner ear diseases

Patients with a single inner ear symptom such as vertigo, fluctuant hearing loss or tinnitus comprised a heterogeneous group on MRI findings. Fifty-three per cent of patients with sudden hearing loss showed a presence of EH. In total, 69–95% of the other patient groups showed EH (table 5). EH was more frequently observed in the vestibulum than in the cochlea ($p=0.025$).

The data were reclassified according to the AAO-HNS criteria of Ménière's disease (1972) with cochlear Ménière's disease and vestibular Ménière's disease. Thereafter, the extent of EH in the cochlea and vestibule among patients with cochlear and vestibular

symptoms was classified (table 6). In both groups, the vestibulum showed a more significant EH presence than the cochlea, and among patients with vestibular hydrops, usually no cochlear symptom was complained of (χ^2 , $p=0.003$).

DISCUSSION

The current study is composed of two different ethnic patient groups in different geographical areas. Studies in Finland and Japan are the warp and the weft, respectively. A Finnish study revealed that monosymptomatic patients occasionally have typical Ménière's disease after a long period. A Japanese study revealed that most of the mono-symptomatic patients have EH, which is a characteristic sign of Ménière's disease. The outcome of the study points out that there is a large group of patients with Ménière's disease in whom the disease is neither recognised nor diagnosed correctly. The current

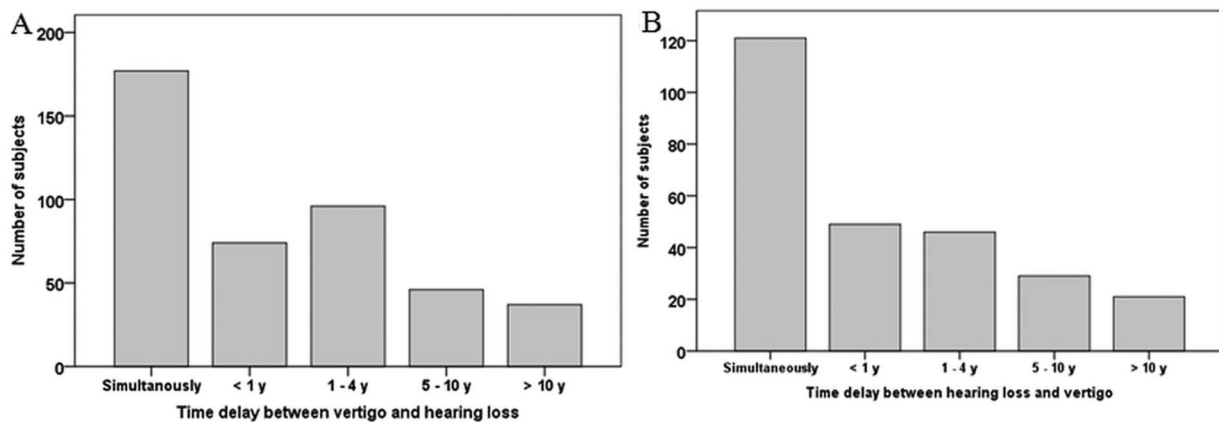


Figure 3 Distributions between the onset of hearing loss and the onset of vertigo—in the Finnish Ménière Association (n=726). (A) Indicates individuals who had vertigo as the initial symptoms and diagram (B) individuals who had hearing loss as the initial symptom.

Table 4 Endolymphatic hydrops (EH) in patients with symptoms associated with Ménière's disease classified with the American Academy of Otolaryngology—Head and Neck Surgery as possible, probable and definite Ménière's disease

Symptom/diagnosis	EH in the cochlea only	EH in the vestibule only	EH in both	Total with EH	No EH
Possible Ménière's disease (n=122)	8	43	57	108	14
Probable Ménière's disease (n=15)	2	4	8	14	1
Definite Ménière's disease (n=68)	1	4	63	68	None
Total (n=250)	11	51	128	190	15

In total, 205 ears with symptoms and 45 contralateral ears without symptoms are included. The cochlea and vestibule are analysed separately.

strict diagnostic criteria for definite Ménière's disease include only representative cases which are at the end stage of the disease. Those with an 'uncharacteristic disease' are seldom correctly diagnosed.^{18 19} In several individuals, different imaging studies may be carried out, mainly to exclude tumours and vascular derangements

and which seldom provide diagnosis. 3T MRI of the inner ear with FLAIR imaging sequences after GdC enhancement can now be used to remove uncertainty and to provide an accurate diagnosis. This will help to clarify the terminology and avoid symptom descriptors such as vestibular or cochlear EH without definite proof.²⁰ Eventually, this should lead to better therapy. The results from clinical data and MRI both indicate that Ménière's disease is a continuum from mono-symptomatic cases to full-blown Ménière's disorder. Therefore, the AAO-HNS classification of 1995, which is based on a full-blow symptom entity and EH is inadequate as this classification requires the involvement of a semicircular canal fault by neglecting the fault in the otolith organ in the vestibulum with or without hearing loss. Now, 3T MRI provides an instrument for a more detailed analysis of the inner ear. This should be used, especially when in practice all patients are diagnosed as having suspected Ménière's disease.

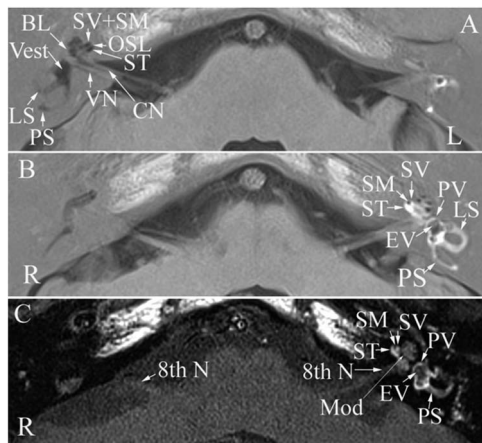


Figure 4 MRI comparison of inpatients with Ménière's disease between three-dimensional (3D)-real IR and conventional 3D-FLAIR sequences following transtympanic injection of Gd-DOTA. The ears were imaged 24 h post-transtympanic injection of Gd-DOTA (0.1 M, 0.5 ml) in the left ear with 3T MRI. Using 3D-real IR sequence, the non-contrasted inner ear fluids showed black and can be distinguished from the surrounding bone which displayed grey in the right ear (A); Gd-DOTA-enhanced perilymph was singled out from the non-contrasted black endolymph and grey bone in the left ear (B). Using 3D-FLAIR sequence, the contrast between the Gd-DOTA-enhanced perilymph and the non-enhanced endolymph was higher than that imaged using 3D-real IR sequence, broader Gd-DOTA enhancement was detected, which was in the higher turns and modiolus (C). In the figure, the EH is seen in the cochlea and in the vestibulum (black areas), which showed enlargement of the endolymphatic spaces. CN, cochlear nerve; 8th N, cochleo-vestibular nerve; EH, endolymphatic hydrops; EV, endolymph in the vestibulum; FLAIR, Fluid Attenuation Inversion Recovery sequences; L, left ear; LS, lateral semicircular canal; Mod, modiolus; PS, posterior semicircular canal; PV, perilymph in the vestibulum; OSL, osseous spiral lamina; R, right ear; SM, scala media; ST, scala tympani; SV, scala vestibuli; VN, vestibular nerve.

Symptom delay

General practitioners, otolaryngologists and audiovestibular physicians face a challenge in making the diagnosis of Ménière's disease. The symptoms can be variable and occur over different time spans, and any hearing loss can recover before audiometric measurements are made. A concurrency between the tertiary referral centre patients and those members of the Ménière's Association, in terms of the onset age of the disease and symptom development, was identified. Interestingly, cases with Ménière's disease recorded in a tertiary reference centre and in Ménière's Association had an almost identical onset pattern of the disease with a similar symptom complex and latency of the disease. The association of cardinal symptoms for Ménière's disease followed the same pattern irrespective of whether the symptoms had started with vertigo or hearing loss. Diagnostically confirmed cases, however, represent just a part of the individuals with the disease, as is reflected in the variability between prevalence studies.^{2 21} Ménière's disease started with vestibular symptoms more frequently than with hearing loss supports the findings of MRI that indicated more frequent EH in the vestibulum than in the cochlea.

Symptom onset at an advanced age is frightening and may raise a suspicion of vascular derangements

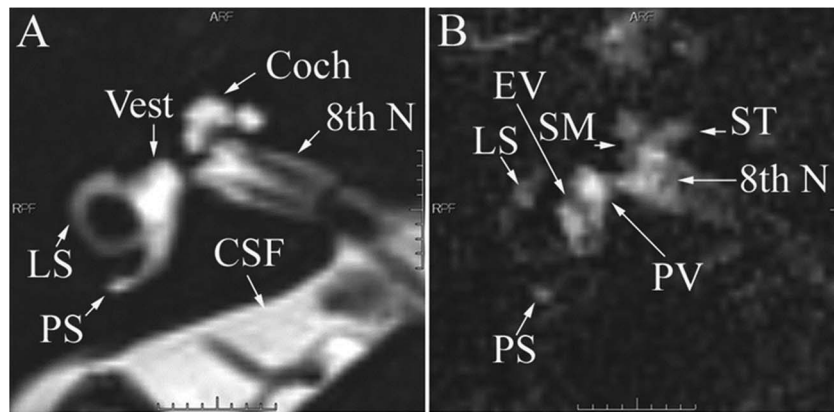


Figure 5 MRI of a 72-year-old patient with Ménière's disease on the right side at 4 h post-intravenous injection of Gd-DTPA-BMA at a single dosage. Anatomy was demonstrated by T2-weighted MRI (A). Uptake of Gd-DTPA-BMA in the inner ear was shown using a heavy T2-weighted FLAIR sequence (B). Obvious enlargement of the scala media (SM) at the basal turn is a sign of endolymphatic hydrops and was observed in the cochlea. Coch, cochlea; CSF, cerebrospinal fluid; 8th N, cochleo-vestibular nerve; EV, endolymph in the vestibulum; FLAIR, Fluid Attenuation Inversion Recovery sequences; LS, lateral semicircular canal; PS, posterior semicircular canal; PV, perilymph in the vestibulum; Vest, vestibulum.

interpreted as presbyequilibrium and so result in an incorrect prognosis and therapy for the patient, as Ménière's disease does not limit life expectancy.^{18–22} We therefore encourage the use of the possibilities provided by 3T MRI with GdC enhancement in assessing patients with symptoms indicative of Ménière's disease. One of the limitations of the comparison of Finnish and Japanese patient data is that all the MRI results published were carried out in Japan. However, based on clinical needs, a vast number of inner ear MRIs were carried out in the Finnish patient group using the same methods. Owing to the recommendations of the Finnish ethical committee, systematic research on MRI has not been performed yet. Basically, however, the results of MRIs conducted in Finland and Japan are comparable.

The old nomenclature of 'cochlear or vestibular Ménière's disease' was abandoned with the 1995 update of the AAO-HNS criteria, as there was insufficient evidence that these monosymptomatic diseases share the same pathophysiology with Ménière's disease.⁵ Owing to a short follow-up period, many of these patients were not correctly diagnosed as having Ménière's disease since diagnostic criteria were needed for the involvement of both auditory and vestibular systems.²⁰ However, Ménière's disease is a diagnosis of exclusion as EH can also be found in several

other related conditions including trauma, semicircular canal dehiscence, sudden deafness and vestibular Schwannoma.^{23–25} Thus, EH does not signify Ménière's disease, but is associated with it. We would argue that the current classification of inner ear diseases⁵ is misleading as the disease pattern takes a long time to develop and the symptoms are a continuum from isolated symptoms to a more complex disease, changing over time.²⁰ We do not advocate the term 'cochlear hydrops' for atypical Ménière's disease but prefer the terms 'cochlear Ménière's disease' and 'vestibular Ménière's disease' according to the older AAO-HNS definition of 1972.²⁶ Based on the greater involvement of the vestibulum than the cochlea both in mono-symptomatic patients and in Ménière's disease, we suspect that vestibular Ménière's disease may be the initial form of developing Ménière's disease. We also hypothesise that cochlear EH is gradually building up in vestibular hydrops patients with the development of cochlear symptoms.

MRI in Ménière's disease

Based on previous MRI studies in normal individuals, we used 33% as the upper limit for the enlargement of the endolymphatic space of the vestibule.¹⁷ In cadavers without symptom history, the ratio of the endolymphatic

Table 5 Endolymphatic hydrops (EH) in patients with monosymptomatic diseases

Diagnosis	EH in the cochlea only	EH in the vestibule only	EH in both the cochlea and vestibule	Total with EH	No EH
Sudden deafness (n=14)	3	1	3	7	7
Fluctuant hearing loss (n=43) (see table 6)	5	13	22	40	3
Tinnitus (n=9)	0	3	5	8	1
Vertigo (n=12)	0	6	2	8	4
Total (n=78)	8	23	32	63	15

The vestibule and cochlea are analysed separately.

Table 6 Degree of endolymphatic hydrops in patients with cochlear and vestibular Ménière's disease based on the 1972 AAO-HNS classification on vestibular hydrops and cochlear hydrops

Diagnosis	EH in the cochlea only	EH in the vestibule only	EH in both the cochlea and vestibule	Total with EH	No EH
Cochlear Ménière's disease (n=43)	5	13	22	40	3
Vestibular Ménière's disease (n=17)	0	8	7	15	2

AAO-HNS, American Academy of Otolaryngology—Head and Neck Surgery; EH, endolymphatic hydrops.

space to the vestibular fluid space ranged from 26.5% to 39.4%, as reported by Nakashima *et al.*¹⁷ In the study of Liu *et al.*²⁷ the authors considered 40% as the normal range. However, they reformatted their MRI images, whereas we have used original MRI figures. Their calculation method was also different from ours; however, the normal values that we use have been recently confirmed by other reports.^{27 28}

The transtympanic administration of GdC allows penetration of the contrast agent into the inner ear perilymph in about three-quarters of patients, and reduces the risk of systemic toxicity, although it may cause local irritation and toxicity.^{8 29 30} In most cases, the scala media is impermeable for GdC, and as such, a bulging of Reissner's membrane allows the precise quantification of the degree of EH present. The transtympanic injection of GdC cannot, however, demonstrate a dysfunction of the blood–inner ear barrier, which can be visualised after an intravenous delivery of GdC.^{31 32} The current challenges in inner ear imaging are to improve the delivery of the contrast agent so that the concentration of GdC in the inner ear exceeds the detection limit. However, a blood–inner ear barrier impairment may recover over time, and so the uptake of GdC in the inner ear fluids may become insufficient (Zou J *et al*, unpublished data). In trying to improve the detection sensitivity of MRI, Naganawa *et al.*¹⁰ showed in human studies that a heavily T2-weighted 3D FLAIR is superior to the conventional 3D FLAIR in demonstrating EH in patients 4 h postintravenous injection with GdC. With a single dose of GdC, it was possible to demonstrate EH in patients¹⁰ and a leakage of gadolinium from the stria vascularis.^{8 33 34} The dose of GdC allows the determination of the cochlear compartment when using a 3D-FLAIR sequence. There is, however, some uncertainty of distinguishing GdC enhancement from pure perilymph when the uptake of GdC is faint, and so the assessment should be undertaken by an expert radiologist. A relatively low concentration of GdC in the cochlea can be enhanced by increasing the dose of GdC or/and developing more sensitive parameters for the MRI. In our opinion, transtympanic and intravenous administrations have different indications. If the aim was to demonstrate an EH, then transtympanic injection of GdC is preferred. However, when seeking aetiological factors for EH, an intravenous administration is

preferred. In comparing the sensitivity of the two administration techniques, the uptake of GdC in the inner ear is usually seen to be much less after intravenous injection than after transtympanic administration, but the indications for use are different. In principle, the sensitivity of the intravenous and transtympanic methods to demonstrate EH in the inner ear should be similar, as both methods measure the same phenomenon. Usually the intratympanic administration provides stronger uptake and is easier to assess. As intratympanic administration is an off-label for the use of GdC, intravenous use is preferred. Recent advances in evaluation technique have improved the image quality of intravenous administration of GdC. Using this technique, the images of inverted Gray-scale positive endolymph were subtracted from images with native positive perilymph images. This subtraction significantly improved the contrast-noise ratio and assisted in separation of the endolymph, perilymph and bone.³⁵

The presence of EH in 'asymptomatic contralateral ears' indicates that EH is a frequent finding (65%) and that the symptom in the majority of cases (in 79% of our study) is bilateral. This would indicate that Ménière's disease is a systemic disease, as has been argued elsewhere. Analysis of temporal bone specimens has shown variability in the presence of EH.³⁶ Patients with Ménière's disease, who did not have EH on histological examination, have also been reported, and Salt and Plontke³⁷ questioned whether the presence of post-mortem EH is either essential or specific to Ménière's disease. On the other hand, Nakashima *et al.*³⁸ and Fiorino *et al.*²⁸ demonstrated with MRI that EH was present in all living patients with definite Ménière's disease.

In the present study, EH was detected in 54% of the patients with sudden hearing loss. EH was also frequently demonstrated in patients with spontaneous tinnitus. Whether EH will develop in all forms of tinnitus and hearing loss is not known but is worthy of future study. In this respect, EH in the ear resembles raised intraocular pressure in the eye which, in the population, occurs 10 times more frequently than glaucoma.^{39 40} For that, early treatment is recommended to prevent the development of symptoms of glaucoma during the asymptomatic period. It remains to be documented, however, whether a salt-free diet can prevent further development of the symptom complex in patients showing EH.

CONCLUSIONS

The aim of the present work was to provide an insight into the assessment of Ménière's disease for medical practitioners. Ménière's disease is a difficult condition to define clinically, and the existing AAO-HNS classification is unhelpful. GdC-enhanced inner ear MRI may be beneficial to identify Ménière's disease in its early stages. Ménière's disease started with vestibular symptoms more frequently than with hearing loss supports the findings of MRI that indicated more frequent EH in the vestibulum than in the cochlea. In contrast to existing beliefs, the present study suggests that Ménière's disease is essentially a bilateral condition. The previously used terms 'vestibular Ménière's disease' and 'cochlear Ménière's disease' should still be used in patient work-up, and in cases in which the diagnosis is unclear, GdC-enhanced inner ear MRI with a transtympanic or intravenous administration should be carried out instead of the current conventional MRI. However, Ménière's disease is a diagnosis of exclusion and EH can also be found in several other related conditions.

Acknowledgements Professor Dafydd Stephens, Cardiff University, participated in the writing of this manuscript but passed away during its preparation.

Contributors IP participated in writing the paper, collecting and evaluating patients visiting the university hospital and collecting and analysing data from patients belonging to the Finnish Ménière Association. TN participated in writing the paper, collecting and analysing clinical data for patients undergoing MRI. TY participated in the clinical assessment and analysis of data of patients entering MRI and in writing the paper. JZ participated in establishing models for inner ear MRI and identifying EH, collecting and analysing data from patients belonging to the Finnish Meniere Association as well as in writing the paper. SN participated in the evaluation of MRI in patients entering the study and in writing the paper. All authors have accepted the final submitted version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Ethics approval Under Finnish law, a questionnaire-based patient association study does not require ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement (1) Tertiary Referral Centre: Data were applied in the development of artificial intelligence programmes to establish the diagnosis of disease causing vertigo. Also, the data regarding symptoms such as Tumorin attacks were retrieved from this study group. (2) The data from the Finnish Ménière Association were used to describe the impact of the disease. There were several reports concerning the quality of life, impact of tinnitus, personality trait, positive aspects of the disease, effect on significant others and the classification of the impact by using ICF criteria (ICF-WHO 2001). (3) The MRI of Ménière's disorder has been reviewed in a paper (Pykkö *et al* 2010), and a part of the patient data has been published in several detailed analyses by Nakashima *et al* and Naganawa *et al* (2007–2012).

REFERENCES

- Atkinson M. Meniere's original papers reprinted with an English translation with commentaries and biographical sketch. *Acta Otolaryngol (Stockh)* 1961;(Suppl 162):1–78.
- Havia M, Kentala E, Pykkö I. Prevalence of Meniere's disease in general population of Southern Finland. *Otolaryngol Head Neck Surg* 2005;133:762–8.
- Yamakawa K. Über die pathologische Veränderungen bei einem Ménière-kranken. *J Otorhinolaryngol Soc Jpn* 1938;44:2310–12.
- Hallpike CS, Cairns HBW. Observations of pathology of Meniere's syndrome. *Proc R Soc Med* 1938;31:1317–3636.
- Committee on Hearing and Equilibrium, American Academy of Otolaryngology-Head and Neck Foundation, Inc. Guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg* 1995;113:181–5.
- Hinchcliffe R. An attempt to classify the primary vertigos. *J Laryngol Otol* 1967;81:849–57.
- Hinchcliffe R. Ménière's syndrome. In: Ransome J, Holden H, Bull TR, eds *Recent advances in otolaryngology*. Edinburgh: Churchill Livingstone, 1973;12:127–43.
- Zou J, Pykkö I, Bretlau P, *et al*. In vivo visualization of endolymphatic hydrops in guinea pigs: magnetic resonance imaging evaluation at 4.7 tesla. *Ann Otol Rhinol Laryngol* 2003;112:1059–65.
- Nakashima T, Naganawa S, Sugiura M, *et al*. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope* 2007;117:415–20.
- Naganawa S, Yamazaki M, Kawai H, *et al*. Visualization of endolymphatic hydrops in Meniere's disease with single-dose intravenous gadolinium-based contrast media using heavily T (2)-weighted 3D-FLAIR. *Magn Reson Med Sci* 2010;9:237–42.
- Naganawa S, Satake H, Kawamura M, *et al*. 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* 2008;18:920–4.
- Kentala E, Pykkö I, Auramo Y, *et al*. Computer assisted data collection in vestibular diseases. *Acta Otolaryngol Suppl* 1995;520 (Pt1):205–6.
- Kentala E, Pykkö I, Auramo Y, *et al*. Otoneurological expert system. *Ann Otol Rhinol Laryngol* 1996;105:654–8.
- Stephens D, Pykkö I, Kentala E, *et al*. Positive experiences reported by people with Meniere's disease: a quantitative study. *Acta Otolaryngol* 2010;130:1013–18.
- Levo H, Stephens D, Poe D, *et al*. Use of ICF in assessing the effects of Meniere's disease on life. *Ann Otol Rhinol Laryngol* 2010;119:583–9.
- Yamazaki M, Naganawa S, Kawai H, *et al*. Signal alteration of the cochlear perilymph on 3 different sequences after intratympanic Gd-DTPA administration at 3 tesla: comparison of 3D-FLAIR, 3D-T1-weighted imaging, and 3D-CISS. *Magn Reson Med Sci* 2010;9:65–71.
- Nakashima T, Naganawa S, Pykkö I, *et al*. Grading of endolymphatic hydrops using magnetic resonance imaging. *Acta Otolaryngol Suppl* 2009;560:5–8.
- Vibert D, Caversaccio M, Hausler R. Meniere's disease in the elderly. *Otolaryngol Clin North Am* 2010;43:1041–6.
- Lin MY, Timmer FC, Oriol BS, *et al*. Vestibular evoked myogenic potentials (VEMP) can detect asymptomatic saccular hydrops. *Laryngoscope* 2006;116:987–92.
- Rauch SD. Clinical hints and precipitating factors in patients suffering from Meniere's disease. *Otolaryngol Clin North Am* 2010;43:1011–17.
- Alexander TH, Harris JP. Current epidemiology of Meniere's syndrome. *Otolaryngol Clin North Am* 2010;43:965–70.
- Tuunainen E, Poe D, Jantti P, *et al*. Presbyequilibrium in the oldest olds, a combination of vestibular, oculomotor and postural deficits. *Aging Clin Exp Res* 2011;23:364–71.
- Teranishi M, Naganawa S, Katayama N, *et al*. Image evaluation of endolymphatic space in fluctuating hearing loss without vertigo. *Eur Arch Otorhinolaryngol* 2009;266:1871–7.
- Poe DP, Pykkö I. *Endolymphatic hydrops in patients with superior semicircular canal dehiscence syndrome (abstract)*. Iceland: Barany Society Meeting, 2010.
- Naganawa S, Kawai H, Sone M, *et al*. Endolymphatic hydrops in patients with vestibular schwannoma: visualization by non-contrast-enhanced 3D FLAIR. *Neuroradiology* 2011;53:1009–15.
- Alford BR. Report of subcommittee on equilibrium and its measurement. Meniere's disease: criteria for diagnosis and evaluation of therapy for reporting. *Trans Acad Ophthalmol Otolaryngol* 1972;76:1462–4.
- Liu F, Huang W, Wang Z, *et al*. Non-invasive evaluation of endolymphatic space in healthy volunteers using magnetic resonance imaging. *Acta Otolaryngol* 2011;131:247–57.
- Fiorino F, Pizzini FB, Beltramello A, *et al*. Reliability of magnetic resonance imaging performed after intratympanic administration of gadolinium in the identification of endolymphatic hydrops in patients with Meniere's disease. *Otol Neurotol* 2011;32:472–7.

29. Naganawa S, Sugiura M, Kawamura M, *et al.* Imaging of endolymphatic and perilymphatic fluid at 3T after intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. *AJNR Am J Neuroradiol* 2008;29:724–6.
30. Pyykko I, Zou J, Poe D, *et al.* Magnetic resonance imaging of the inner ear in Meniere's disease. *Otolaryngol Clin North Am* 2010;43:1059–80.
31. Zou J, Li M, Zhang Y, *et al.* Transport augmentation through the blood-inner ear barriers of guinea pigs treated with 3-nitropropionic acid and patients with acute hearing loss, visualized with 3.0 MRI. *Otol Neurotol* 2011;32:204–12.
32. Zhang Y, Zhang W, Johnston AH, *et al.* Improving the visualization of fluorescently tagged nanoparticles and fluorophore-labeled molecular probes by treatment with CuSO₄ to quench autofluorescence in the rat inner ear. *Hear Res* 2010;269:1–11.
33. Tagaya M, Yamazaki M, Teranishi M, *et al.* Endolymphatic hydrops and blood-labyrinth barrier in Meniere's disease. *Acta Otolaryngol* 2011;131:474–9.
34. Zou J, Pyykko I, Bjelke B, *et al.* Communication between the perilymphatic scalae and spiral ligament visualized by in vivo MRI. *Audiol Neurootol* 2005;10:145–52.
35. Naganawa S, Yamazaki M, Kawai H, *et al.* Imaging of Meniere's disease after intravenous administration of single-dose gadodiamide: utility of subtraction images with different inversion time. *Magn Reson Med Sci* 2012;11:213–19.
36. Merchant SN, Adams JC, Nadol JB Jr. Pathophysiology of Meniere's syndrome: are symptoms caused by endolymphatic hydrops? *Otol Neurotol* 2005;26:74–81.
37. Salt AN, Plontke SK. Endolymphatic hydrops: pathophysiology and experimental models. *Otolaryngol Clin North Am* 2010;43:971–83.
38. Nakashima T, Naganawa S, Teranishi M, *et al.* Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Meniere's disease. *Acta Otolaryngol* 2010;130:338–43.
39. Iwase A, Suzuki Y, Araie M, *et al.* The prevalence of primary open-angle glaucoma in Japanese: the Tajimi study. *Ophthalmology* 2004;111:1641–8.
40. Yamamoto T, Iwase A, Araie M, *et al.* The Tajimi study report 2: prevalence of primary angle closure and secondary glaucoma in a Japanese population. *Ophthalmology* 2005;112:1661–9.