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OTOLOGY

Clinical manifestations of hydropic ear disease (Menière's)

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Abstract

Introduction Hydropic ear disease, initially described by and named after Prosper Menière, is one of the most frequent vertigo disorders and one of the most frequent inner ear disorders. It is the syndrome of endolymphatic hydrops which until 2007 could be diagnostically confirmed only by post-mortem histology. In the past, various attempts to formulate clinical diagnostic criteria have been undertaken but were hampered by the inability to ascertain the diagnosis in living patients. With the milestone achievement of endolymphatic hydrops imaging, today the pathology can be ascertained. In this study, we have performed a detailed analysis of the clinical features of hydropic ear disease for the first time by examining a large cohort of patients with morphologically confirmed endolymphatic hydrops using a detailed physician-administered neurotologic face-to-face interview.

Results During a hydropic vertigo attack, the patients report nausea, vomiting, sweating, urge to defecate, urge to urinate, phosphenes, headache, photophobia, phonophobia and even transient loss of consciousness. A third of the patients does not experience auditory symptoms during the vertigo attacks. Vertigo attacks last less than 20 min in more than one-fourth of the patients. Audiometric hearing loss has its greatest diagnostic value at the frequencies of 1 kHz and below. Cochleovestibular symptom onset simultaneity is associated with a high frequency of drop-attacks. Migraine and autoimmune disorders are not associated with hydropic ear disease.

Conclusion This study marks the beginning of the clinical characterization of hydropic ear disease. The findings have important implications for the future formulation of clinical diagnostic criteria.

Keywords Hydropic ear disease · Endolymphatic hydrops · Diagnostic criteria · Menière's disease · Vertigo · Dizziness · Hearing loss · Tinnitus

Introduction

Traditionally, hydropic ear disease has been the great mimicker among the otological diagnoses. Prosper Menière initially described this clinical entity in 1861, and his great achievement was to recognize that vertigo can originate from the inner ear, and does not—as the dogma of his time dictated—invariably result from cerebral disturbances such as apoplectiform or epileptic disorders [1]. The disease named after him is easily diagnosed when the typical symptom triad of low-frequency hearing loss, tinnitus/aural pressure and rotatory vertigo with nystagmus appears repeatedly and simultaneously. However, many variations in the clinical presentations are frequently encountered in clinical practice and render the diagnosis more difficult. This has led to a multitude of different terms being used in the literature for this disease, such as Menière's syndrome, cochlear Menière's disease, vestibular Menière's disease, forme fruste, fluctuating low-frequency hearing loss, and monosymptomatic Menière's disease. Likewise, the definition and classification proposals for this disease have differed over time, sometimes including the non-classical variations/subtypes and sometimes not [2–8]. The discovery of endolymphatic hydrops in temporal bone studies by Cairns

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and Hallpike and by Yamakawa in 1938 as the pathological hallmark of the disease has enabled the certain diagnosis by post-mortem examinations [6, 9, 10]. But, for living patients, indirect measures of Endolymphatic Hydrops (ELH) such as electrocochleography and osmotic loading audiometry (Klockhoff test) have been used clinically for many decades [11–13] to add objective diagnostic information to the history-based subjective clinical information. Nevertheless, many authors have regarded the diagnosis as a diagnosis of exclusion and our understanding of hydropic ear disease is hitherto based on clinical studies in patient populations which were defined predominantly according to a small set of subjective clinical features and thus often suffer from diagnostic uncertainty.

The most important diagnostic milestone achievement since 1938 was the visualization of ELH in living patients using clinical MR imaging in 2007 [14], shortly after the first human in vivo visualization of the endolymphatic space [15]. With the capability of positively confirming ELH at hand, the diagnosis is no longer a diagnosis of exclusion. This paved the way for the development of the concept of hydropic ear disease as the first comprehensive classification system for this disorder which includes the atypical as well as the typical forms and the primary as well as the secondary forms [8, 16–19].

Today we have the unique opportunity to positively study the clinical picture of HED. In this study, we aim to present for the first time a detailed description of the clinical manifestations of patients with hydropic ear disease (HED) to promote the future formulation of diagnostic criteria.

Methods

Patients

Between 2012 and 2016, 249 consecutive patients presenting to our neurotology clinic and suspected of hydropic ear disease were included in this study. Fluctuating audiovestibular symptoms were the predominant reason to suspect hydropic ear disease and the diagnosis was ascertained by inner ear MRI. Any signs of neurological disorders (e.g. central ocular motor lesions) prompted referral to a neurology specialist. Furthermore, alternative intracranial pathologies were ruled out by diffusion-weighted (to rule out cerebral ischemia) and T1-weighted contrast-enhanced cranial MRI (to rule out cerebellopontine angle neoplasm). We did intentionally not apply diagnostic criteria based only on vaguely defined symptoms and audiometry [7, 8], because this would contradict the logical cohesiveness of this study. The aim of this study is to "positively" describe the clinical features of patients with certain HED. Patients with additional clearly defined alternative diagnoses being the more likely explanation for their fluctuating audiovestibular symptoms were excluded. Examples are otosclerosis, cholesteatoma or other inflammatory middle ear diseases, BPPV, vestibular schwannoma, and multiple sclerosis. Vestibular migraine (migrainous vertigo) was not such an exclusion, because this term represents a vaguely defined concept [20] and hitherto lacks a specific underlying pathology. Furthermore, it would be an impossible task to "rule out" migrainous vertigo since it lacks a positively identifying diagnostic marker and the currently used diagnostic criteria show an overlap with the symptoms of Menière's Disease (while both diagnoses are being viewed as exclusion diagnoses by those criteria!). Nevertheless, migraine and symptoms suggestive of migraine may co-exist in patients with hydropic ear disease and these symptoms were examined in a detailed manner in the present study. The study was approved by the local ethics committee, and informed consent was obtained from the patients.

We did not label the individual patients as suffering from "unilateral" or "bilateral" disease. The distinction between these two entities is difficult and most authors base it on the contralateral audiometric hearing loss. Based on the current state of evidence, it seems likely that primary hydropic ear disease is generally a bilateral phenomenon, and initially manifests itself most frequently on one side, and later in the disease course also on the contralateral side [21]. It was not the aim of this study to analyse the difference between unilateral and bilateral hearing loss, but to provide a general description of hydropic ear disease.

Inner ear MRI

In addition to conventional cranial MRI for the exclusion of alternative diagnoses, inner ear MRI was performed, as previously described [19, 22, 23]: a T2-weighted MR cisternography sequence, a fluid-attenuated inversion recovery (FLAIR) sequence and a real reconstruction inversion recovery (Real-IR) sequence. The contrast agent was a single intravenous dose of gadobutrol or a 1:8 diluted intratympanic injection of gadopentetate dimeglumine and the MR scanners used were 3T units manufactured by Siemens and General Electrics.

The definition of ELH was based on the criteria proposed by Nakashima et al. [24] and on the normative values obtained in healthy controls [25–29]. Images of the inner ear were analysed in all three planes (axial, coronal, and sagittal) and in the Stenvers and Pöschl planes, to avoid a false-positive diagnosis of vestibular ELH which in our experience may occur when the examiner analyses only one single axial image. Images were analysed by two examiners with more than 10 years' experience with endolymphatic hydrops imaging independently, blinded to clinical information, and any discrepancy was resolved by discussion.

During image analysis, our strategy was to "err on the safe side", i.e. in cases with impaired image quality (e.g. motion artefacts) rendering the evaluation of the endolymph space dimensions difficult, we preferred not to diagnose endolymphatic hydrops.

When the contrast agent was applied intratympanically, the "index" ear was chosen for this. The index ear was defined (in descending order of priority) by the following lateralizing signs: vertigo-associated auditory symptoms, fluctuating auditory symptoms (even independently from vertigo), greater hearing loss, earlier onset of hearing loss, and greater caloric canal paresis.

Reporting of symptoms

The clinical symptoms were documented using the custom-designed questionnaire "Neurotologic interview conducted by clinician" (NOTICC). This instrument includes closed and open questions and single-choice and multiple-choice questions. The symptoms are recorded by the clinician (ENT attending or resident) and not self-recorded by the patient. The wording of the questions was pre-determined. This was designed so to maximize standardization of data-gathering from the patient history, and at the same time give the patient enough room to express what bothers him during the open questions. The NOTICC questionnaire was further designed to capture in the most comprehensive way the manifold features of the audiovestibular symptoms in patients suspected of hydropic ear disease, and at the same time record additional symptoms (e.g. headache and aura-like symptoms) which may cause diagnostic confusion, especially in clinical situations where specific audiovestibular testing or inner ear imaging may not be available. It also included questions aiming at the disease duration, co-morbidities and use of medications.

In the German language, the term "Schwindel" is the term most commonly used in the context of vertigo/dizziness and other vestibular complaints. It should be kept in mind that this term encompasses not only the meaning of a rotatory sensation (i.e. "vertigo" in its strict sense), but also sensations more accurately described as dizziness and also lightheadedness/drowsiness. We, therefore, have translated the German term "Schwindel" with the English combined term "vertigo/dizziness", and have added several descriptive terms to assess the quality of this sensation as precisely as possible. These descriptive terms were not mutually exclusive, and a patient could use several terms to describe his vertigo/dizziness sensation. Also, these qualitatively descriptive terms were assessed separately from the temporal characteristics of vertigo/dizziness, i.e. the question whether it appears as attacks (paroxysmal or episodic) or is present continuously.

For the sake of brevity, in this article, the term "vertigo" is also used, but always in the broader sense of "vertigo/dizziness", unless it is specifically termed "rotatory vertigo".

Audiometry

As the only audiovestibular function test, audiometric criteria for hydropic ear disease have been formulated in detail by the AAO-HNS in 1995 [6] and have since been widely used in controlled clinical trials [30]. We accordingly analysed air conduction pure tone thresholds at 0.125/0.25/0.5/1/2/3/4/6/8 kHz. Patients who presented a significant air–bone gap not attributable to HED, i.e. middle ear related conductive hearing loss, were excluded, e.g. patients with otosclerosis or other middle ear disorders.

Data analysis

This study represents the first detailed report of clinical features in a large cohort of patients with certain hydropic ear disease. Therefore, we chose to perform a hypothesis-free and exploratory data analysis and representation in summarized form. We did not perform statistical testing of hypotheses since this would require pre-determined specific hypotheses.

Results

Basic epidemiologic data

The study population consisted of 249 patients with a mean age of 55.0 years and a median age of 56.0 years. The gender distribution was balanced, with 125 patients being females (50.2%) and 124 patients being males (49.8%). Mean age at diagnosis was 47 years and the mean age of symptom onset in our population was 44 years.

We defined the disease duration according to the first appearance of vertigo or hearing loss. The median hearing loss disease duration was 72 months and the median vertigo disease duration was 39 months. The median combined audiovestibular disease duration (i.e. time since both vertigo AND hearing loss have appeared) was 30 months, and the median single audiovestibular disease duration (i.e. time since either hearing loss OR vertigo has appeared) was 96 months.

The median cochleovestibular delay (i.e. the difference between the hearing loss disease duration and the vertigo disease duration) was 9 months, i.e. in most cases hearing loss preceded vertigo during the disease evolution.

Vertigo/dizziness

The cardinal feature of balance-related complaints in hydropic ear disease is their paroxysmal occurrence, i.e. vertigo/dizziness attacks. This feature was present in 97.6% of the patients. 12% of the patients had both paroxysmal and continuous vertigo, but the sole presence of continuous vertigo is infrequent (1.2%). A large proportion, 85.5% of the patients, suffered exclusively from vertigo attacks, and 1.2% had no vertigo at all (Fig. 1a).

Concerning the quality of the vertigo/dizziness, a rotatory sensation is the predominant feature in hydropic ear disease, described by 81.1% of the patients. Since, in our experience, it is difficult for most patients to decide whether the patient herself feels to be rotating or whether the environment feels to be rotating, we did not ask for this distinction (as it is proposed by the Barany Society description of vestibular symptoms [31]). A to-and-fro (rocking) sensation (as if on a boat) is also a very frequent feature and present in 46.6%. Drowsiness/lightheadedness is also a relatively frequent vertigo sensation, reported by 32.5% of the patients, as is the feeling of a moving environment (irrespective of this being rotatory or linear), present in 30.2% of the patients. An elevator-like sensation and visual loss, however, are relatively rare, with 6.0% and 6.4%, respectively. We also assessed three features of postural instability as components of the vertigo sensation: gait instability, propensity to fall and drop-attacks. Decreasing in frequency with their increasing severity, these were present in 39.8%, 24.2% and 13.5%, respectively (Fig. 1b).

In the subgroup of patients with drop-attacks ($n = 14$), all patients had rotatory vertigo attacks. Furthermore, all qualitative vertigo features were more frequent, with the sensation of a moving environment, gait instability and propensity to fall being present in more than 80% of the patients, respectively (Fig. 1c, d).

In the subgroup of patients with a vertigo disease duration (i.e. time since first onset of vertigo) of 12 months or less ($n = 58$), continuous vertigo was relatively rare (8.6%), and a rotatory sensation (67.2%) as well as drop-attacks (6.9%) were less frequent (Fig. 1e, f).

In the subgroup of patients with a vertigo disease duration (i.e. time since the first onset of vertigo) of 7 years or more ($n = 64$), surprisingly, rotatory vertigo is even more frequent (92.2%) whereas continuous vertigo does not occur more frequently. Lightheadedness/drowsiness and a to-and-fro sensation are largely unchanged, but drop-attacks occur more frequently (20%) (Fig. 1g, h).

In the subgroup of patients with cochleovestibular onset simultaneity (i.e. cochleovestibular delay < 1 month; $n = 49$), gait instability and propensity to fall was more frequent (49% and 26.7%, respectively). Surprisingly, drop-attacks were more than twice as frequent (29.4%) compared to the overall patient population (Fig. 1i).

In the subgroup of patients with a cochleovestibular delay of 60 months or more ($n = 66$), the frequencies of vertigo attacks and continuous vertigo are largely unchanged. To-and-fro sensation (36.4%), lightheadedness/drowsiness (22.7%), visual loss (3.0%) and the sensation of a moving environment (22.2%) occurred less frequently (Fig. 1j).

In an open question, we asked the patients to describe their vertigo in their own words. This self-reported vertigo description was analysed and the contents were allocated to the categories listed in Table 1. Regarding the vertigo/dizziness quality, as expected, more than half of the patients reported rotatory vertigo. Drowsiness/lightheadedness was also frequently reported (22.3%). A relatively large proportion of patients (28.4%) reported to have different types of vertigo, and about 7% told us that the vertigo quality had changed over time. Surprisingly, aural symptoms were spontaneously brought forward only by 6.1% of the patients. Almost every fifth patient described postural instability. About 7% did not mention vertigo at all in response to the question, or they stated that vertigo is not a problem.

The duration of the vertigo attacks was assessed in two different ways: (1) interval question: the patients were offered a selection of duration intervals and had to choose one of those intervals: less than 10 s, between 10 s and 5 min, between 5 min and 20 min, between 20 min and 24 h, between 24 and 28 h, longer than 48 h. However, this was not a forced choice, since the patients were given the opportunity to declare "cannot decide". (2) Open question: in a different approach, the patients were asked, "How long does your vertigo attack usually last?"

Interval question results The most frequent vertigo duration was 20 min–4 h. Surprisingly, only about 70% of patients chose an interval between 20 min and 24 h. A relatively large proportion of patients (20.8%) had vertigo attacks lasting less than 20 min (Fig. 2a).

Open question results The mean vertigo attack duration was 163 min (i.e. 2 h and 43 min), and the median vertigo attack duration was 75 min. The distribution of the individual vertigo attack duration along the interval categories overall corresponded well to the attack duration determined by the alternative method. Here, the proportion of patients with attacks shorter than 20 min was even higher, namely 27.4% (Fig. 2b).

Vertigo-associated symptoms

The detailed assessment of simultaneous symptoms (i.e. occurring within 60 min before vertigo onset or after vertigo ending) associated with the vertigo attacks revealed that among the auditory symptoms, tinnitus and aural pressure occur more frequently (in more than half of the patients)

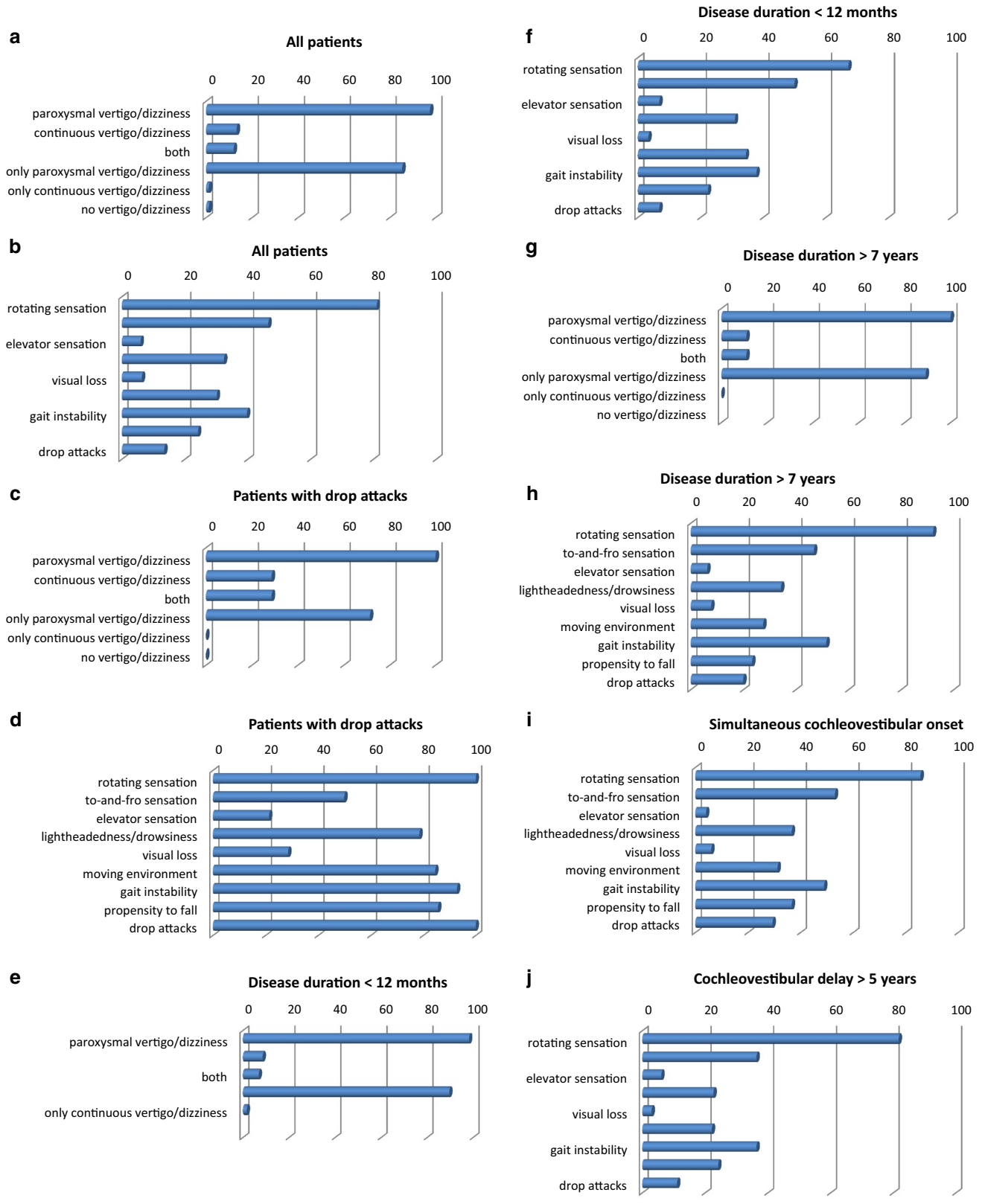

Fig. 1 Characteristics (in % prevalence) of vestibular symptoms in patients with hydropic ear disease (**a**, **b**) and in subgroups of patients with drop attacks (**c**, **d**), disease duration of less than 12 months (**e**, **f**), disease duration of more than 7 years (**g**, **h**), simultaneous onset of cochlear and vestibular symptoms (i) and cochleovestibular symptom onset delay of more than 5 years (**j**)

Table 1 Prevalence (in %) of self-reported complaints in response to the question "Please describe your vertigo in your own words" in patients with hydropic ear disease

	Self-reported description of vertigo/dizziness	Percent
Vertigo quality	Rotatory vertigo/environment is rotating	51.4
	Environment is moving (but NOT rotating)	23
	Self-movement	4.1
	Drowsiness (lightheadedness, "weird" feeling)	22.3
	Like drunken	3.4
	Different types of vertigo	28.4
	Vertigo quality has changed over time	6.8
	Change from rotatory vertigo to dizziness	6.1
Cochlear symptoms	Aural symptoms	6.1
	Aural symptoms simultaneously with vertigo	5.4
Onset	Triggered by position change/movement	7.4
	Sudden onset of vertigo	11.5
Functional consequences	Postural instability (difficulty walking/standing, falls)	18.2
	Necessity to withdraw or stop moving	4.7
	Loss of consciousness	2
	Fear	4.1
	Vegetative symptoms	12.8
Severity	Only mentions level of discomfort, e.g. "terrible", without describing the quality of vertigo	6.1
	Level of discomfort, e.g. "terrible"	8.8
	Does NOT mention vertigo/vertigo is NOT the problem	6.8

than hearing loss (in 35.5%). A surprisingly high proportion of patients, 34%, have no vertigo-associated auditory symptom. On the other hand, 24.3% of the patients display the full-blown typical clinical picture of a vertigo attack with associated hearing loss, tinnitus and aural pressure (Fig. 3a).

Nausea (89.7%) and vomiting (76.4%) were by far the most typical accompanying symptoms, followed by profuse sweating (56.8%). Urge to defecate, urge to urinate, hypesthesia and paresthesia are also surprisingly common (between 10 and 14%). Transient loss of consciousness, witnessed by a third person, occurred in 7.2%. These episodes of witnessed loss of consciousness were shortlived: they had a median duration of 1 min.

Furthermore, symptoms which are often considered to be typical for migraine, such as headache, phosphenes ("seeing stars"), photophobia and phonophobia, occur with a relatively high frequency (between 19 and 29%) (Fig. 3b).

Subjective hearing loss

Hearing loss was reported by 95.2% of the patients. Subjective hearing loss was right sided in 31.6%, left sided in 40.5% and bilateral in 27.8%. The hearing loss was reported to be associated with other audiovestibular symptoms in 39.5% and these were most frequently vertigo and tinnitus (59.8% and 56.5%, respectively) and less frequently aural pressure (32.6%). Current hearing loss fluctuations were reported by 43.6%, and initial hearing loss fluctuations (i.e. at the time of the first appearance of hearing loss) were reported by an almost equal proportion (45.3%) of the patients. 30.7% were hearing aid users.

Audiometric hearing loss

Pure tone audiometry revealed three characteristics of hydropic ear disease: (1) in the low-frequency region (0.125–1 kHz), the difference in median hearing levels between the index ear and the contralateral ear is most pronounced and has a flat course. (2) In the mid-to-high-frequency range (2 kHz and above) this difference is smaller and the hearing levels increase in parallel with increasing frequency, i.e. they have a diagonal course which likely reflects age-related hearing loss in the contralateral ear. The greatest difference, and hence greatest diagnostic value, is observed at 0.250/0.500/1 kHz, with a difference in medians of at least 40 dB. (3) Within the low-frequency region, the contralateral hearing levels are worst at the lowest frequencies (0.125–0.250 kHz), which corresponds well to the (delayed) onset of low-frequency hearing loss typical for hydropic ear disease evolving in the contralateral ear during the course of the disease. Figure 4a depicts the median pure tone thresholds for the index ear (ME) and the contralateral ear (CE).

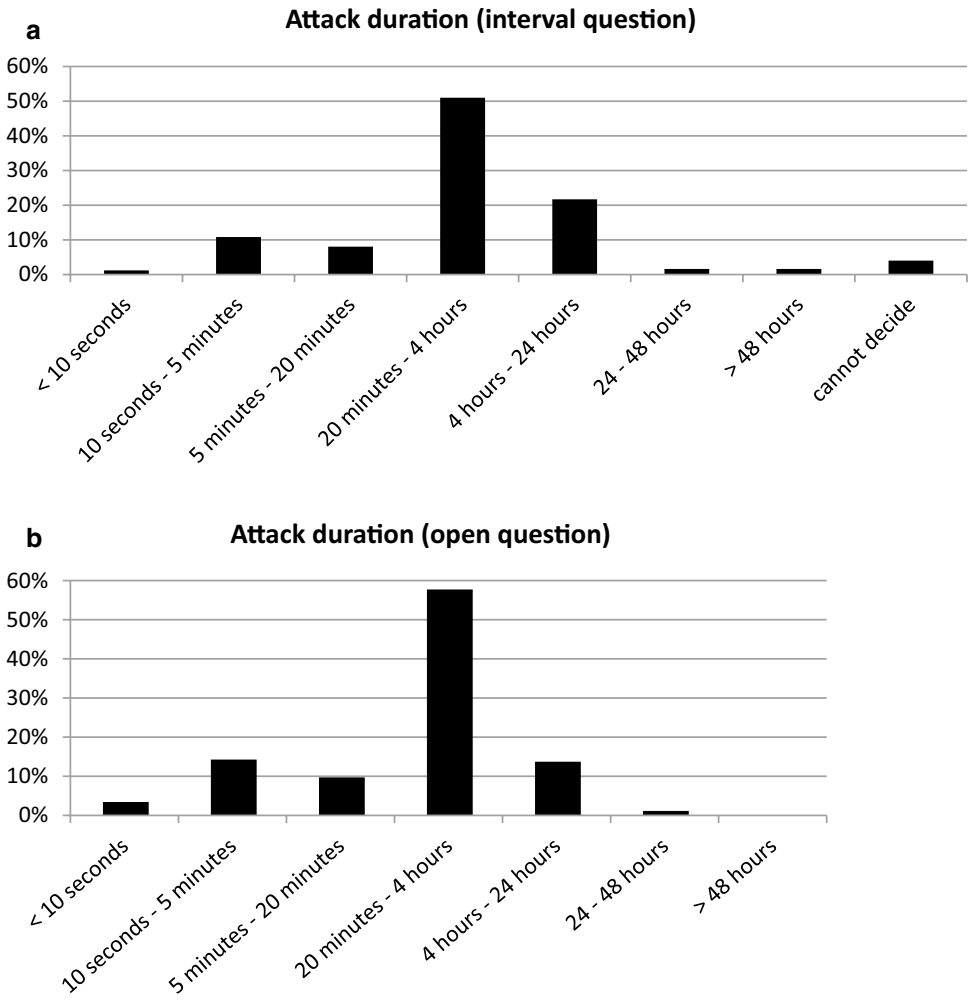

Fig. 2 Duration of vertigo attacks in patients with hydropic ear disease, as assessed by offering fixed intervals (**a**) and by an open question (**b**)

Tinnitus

We distinguish between two types of tinnitus: vertigo-associated tinnitus is defined by an intensification or change or exclusive appearance during or within 1 h before or after the vertigo. It is, therefore, distinguished from vertigo-independent tinnitus which does not have any of these features.

Vertigo-associated tinnitus was present in 48% of the patients, and among those it was more frequently unilateral than bilateral. It affected the low-frequency region about twice more frequently than the high frequency or the combined low/high-frequency regions. On the other hand, the criterion "low-frequency tinnitus" is not a reliable diagnostic feature of hydropic ear disease, since about half of the patients do not describe their tinnitus as being of a low frequency. Surprisingly, the vertigo-associated tinnitus type was permanently present in about two-thirds of the patients (Fig. 4b).

Vertigo-independent tinnitus was even more frequent than vertigo-associated tinnitus and occurred in 57.2% of the patients. It showed the features of unilaterality, low frequency and intermittent appearance less frequently than vertigo-associated tinnitus (Fig. 4c).

Headache

Headache is a very frequent symptom in patients with hydropic ear disease, as 43.5% of the patients reported having headache. The duration was several hours in the large majority of the patients, and it never lasted only seconds. The headache was most frequently (61.6%) bilateral and more often left sided than right sided (Fig. 5a). Concerning the quality of the headache sensation, a pressure/tightness sensation was by far the most frequent (72.7%), whereas pulsating, stabbing and radiating features were markedly less common. Burning pain was rare, and sharp shooting pain (such as in typical trigeminal neuralgia) never occurred (Fig. 5b). The location of the headache was most frequently bifrontal/bandlike and occipital/nuchal, followed by hemifrontal, hemicranial and temporal, whereas holocephalic, retroorbital and facial pain locations were relatively rare (Fig. 5c). More than half of the patients (55.4%) reported

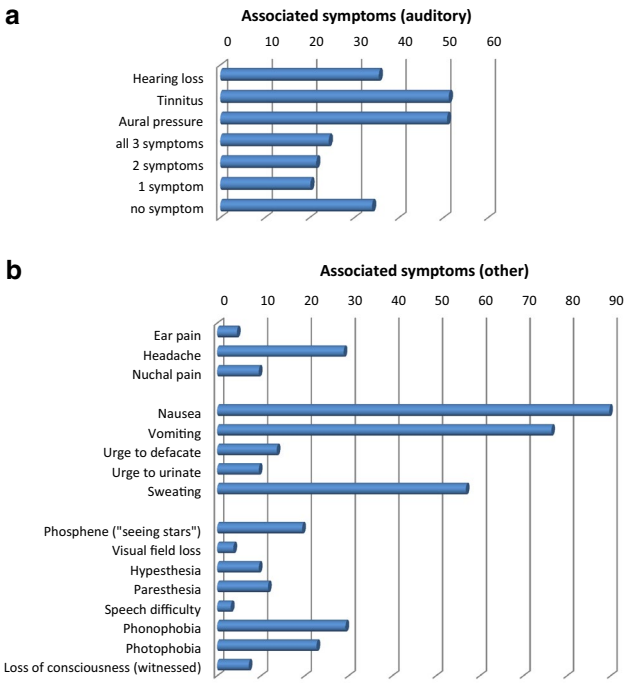

Fig. 3 Frequency of symptoms (in %) associated with vertigo attacks in patients with hydropic ear disease. **a** Auditory symptoms, **b** other associated symptoms

that their headache appeared in association with their vertigo episodes.

Co-morbidities

Patients were asked about the presence of any other medical conditions. Among these, we specifically asked every patient whether she/he was suffering from migraine. The diagnoses were grouped according to the organ system involved, and cancer was regarded as a separate category. Cardiovascular diseases were by far the most frequent and reported by about 40% of the patients, followed by endocrine, neurologic, autoimmune and gastrointestinal disorders (in the range of 14–19%). The remaining organ systems were affected less frequently (Fig. 5d).

Among the specific diagnoses, hypertension was by far the most frequent. Figure 5e depicts the frequencies of diagnoses that affected more than five patients, i.e. had a prevalence of more than 2%. The prevalence of migraine was 7.2%. Therefore, a putative epidemiological association between hydropic ear disease and migraine cannot be supported from these data. Among the autoimmune disorders, asthma was by far the most common and was reported by 6.4% of all patients. Hypothyroidism and gastritis were relatively frequent diagnoses. For a complete list of all diagnoses, see Appendix 1 in ESM.

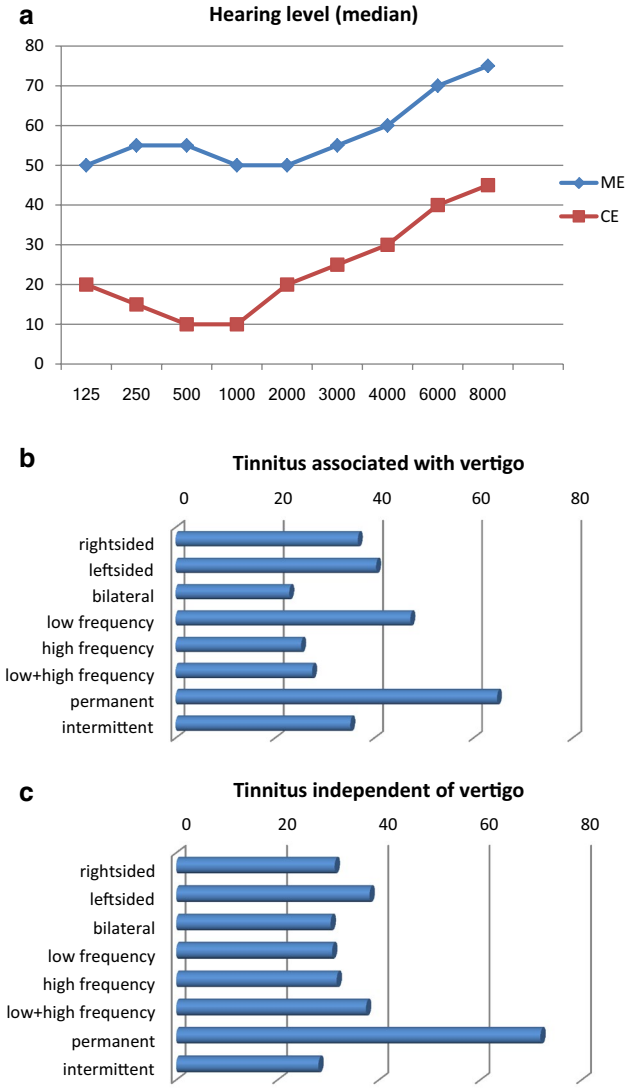

Fig. 4 **a** Median pure tone audiometric hearing levels across frequencies for the index ear (ME) and the contralateral ear (CE) in patients with hydropic ear disease. **b** characteristics (in % prevalence) of vertigo-associated tinnitus. **c** characteristics (in % prevalence) of vertigo-independent tinnitus

Use of medication

The regularly used drugs were documented and classified according to the ATC system. The most frequently used drugs (i.e. used by more than 9% of the patients) were—in descending order—antivertigo preparations, antihypertensive drugs, hormones (mostly thyroxine), anticoagulants (mostly acetylsalicylic acid), lipid-lowering drugs, proton pump inhibitors and anti-depressants. For a complete list of medications, see Appendix 2 in ESM.

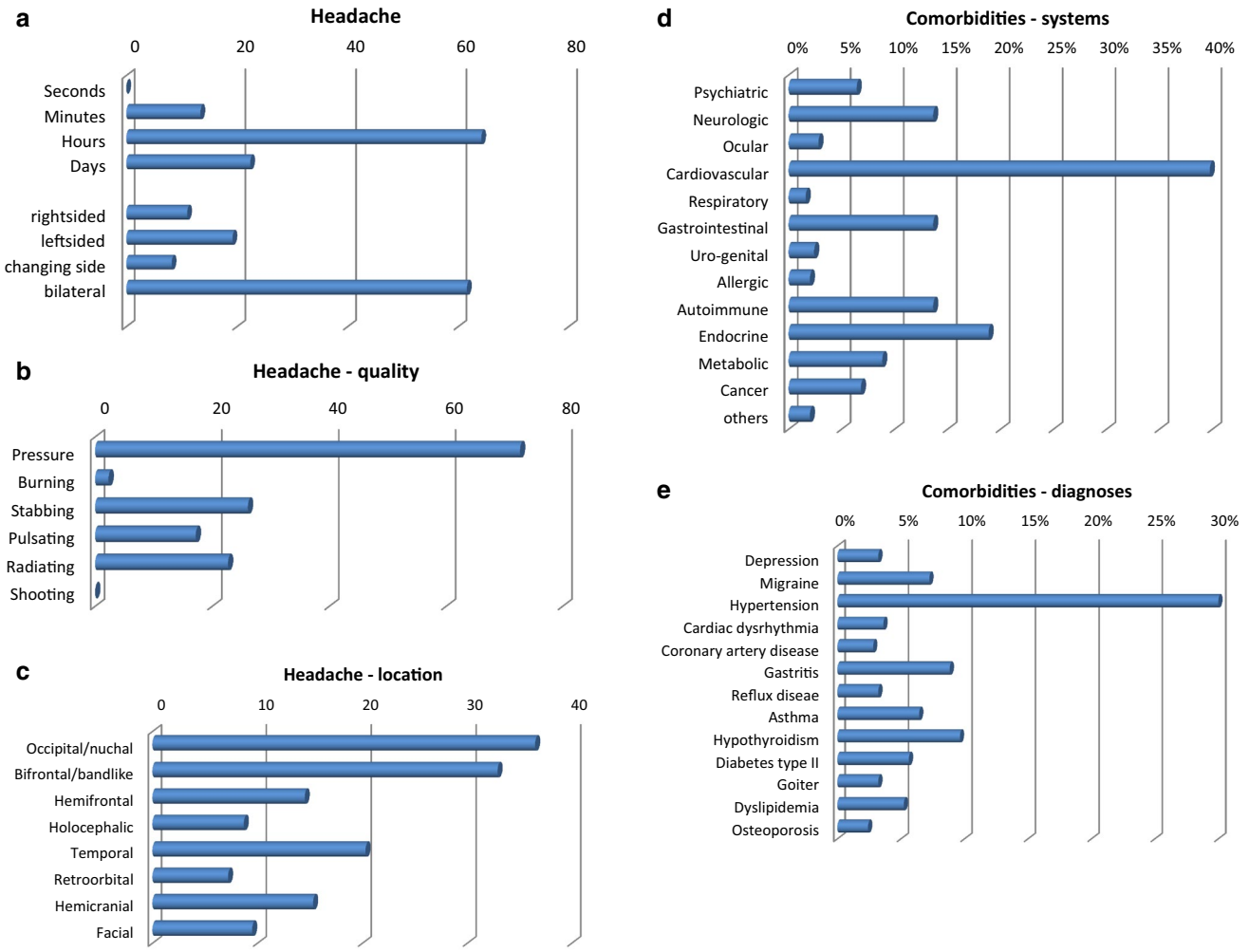

Fig. 5 Duration, sidedness (**a**), location (**b**), quality (**c**) of headache reported by patients with hydropic ear disease (in % prevalence). Comorbidities grouped accordin to organ systems (**d**) and comorbid diagnoses with a prevalence of at least 2% in patients with hydropic ear disease (in % prevalence)

Family history

We asked all patients about any family members of the first or second degree suffering from Menière's disease, migraine or early-onset sensorineural hearing loss (not attributed to otosclerosis or inflammatory middle ear disease or otologic surgery). According to these criteria, a positive family history was found in 22.3% of the patients for migraine, in 4.3% of the patients for Menière's disease and in 12.0% of the patients for hearing loss.

Discussion

This study represents the first detailed characterization of the clinical features of a large population of patients with confirmed endolymphatic hydrops. We propose that the best way to define a disease—especially in the context of inclusion criteria for controlled therapeutic trials—is to consider not only the subjectively reported symptoms, but also the specific organic pathology. In the past, Menière's disease—although defined as the syndrome of endolymphatic hydrops—was frequently considered from the perspective of its typical symptoms only. Diagnostic certainty could only be obtained post-mortem [6]. However, during the last decade, the advent of hydrops imaging has confirmed the presence of endolymphatic hydrops in clinical situations which were hitherto difficult to classify. For example, so-called "cochlear MD" has a very typical clinical picture, with fluctuating low-frequency hearing loss. Although still being recognized as a variant of MD in 1972 [2], it has been excluded from the diagnostic criteria in 1995 due to a lack of diagnostic certainty. Today, however, this diagnostic certainty has been provided by MRI studies, which have

confirmed the presence of ELH in virtually all cases with the typical clinical picture of "cochlear MD" [21, 32]. Another exemplary entity is the group of patients with long-standing severe hearing loss (e.g. due to congenital hearing loss or profound sudden hearing loss), who develop MD-like vertigo attacks but lack the presence of simultaneous auditory symptoms during the attacks. Most likely, this absence of subjective simultaneous auditory symptoms is due to the already "dead" inner ear, and this clinical situation was previously termed "delayed endolymphatic hydrops". Today, inner ear imaging can confirm the presence of endolymphatic hydrops [19] in these patients. Furthermore, there was a confusion in the past about the terms Menière's disease/Menière's syndrome/primary MD/secondary MD/secondary ELH. Patients with lesions affecting the inner ear, such as vestibular schwannoma or endolymphatic sac tumour, can develop typical recurring vertigo attacks due to ELH along the disease course, even in the absence of any tumour progression [18, 33, 34], as has been demonstrated by inner ear imaging. Today, all these variants are classified in the logical conceptual framework of hydropic ear disease, even in settings where MR imaging is not available [8, 17]. Since there is a need for useful clinical criteria characteristic of hydropic ear disease, we set out to explore the clinical features of these patients in a hypothesis-free manner. Our data provide valuable clues as to the relative importance of the numerous diverse features which can be assessed during history-taking and simple functional testing such as audiometry. In the following, some of the most striking results are discussed.

Audiovestibular symptoms

While a rotatory vertigo/dizziness sensation was expectedly the most frequent, we found a high prevalence of to-and-fro movement sensation and also of dizziness in the sense of drowsiness. The overall frequency of drop-attacks (13.5%) corresponds well to previously published cohorts. We also confirmed that the frequency of drop-attacks increases with the disease duration. However, the relative frequency of rotatory vertigo sensation followed the same pattern, and—to our surprise—continuous vertigo (as opposed to vertigo attacks) was not associated with a longer disease duration. This contradicts the traditional belief that during the disease course, the early phase is dominated by rotatory vertigo attacks and the later phase is dominated by more continuous and less rotatory vertigo symptoms, as it has been brought forward under the label of "burning out".

Another peculiar result was the observation that among the patients with simultaneous onset of auditory and vestibular symptoms, the prevalence of drop-attacks was the highest, with about 30%. This prompts the hypothesis that in this subgroup of patients the disease might be of a particularly high severity, and such a correlation would obviously have important implications for the prognosis and the counselling of the patients at the time of diagnosis. Further, hypothesis-driven studies are warranted to explore this phenomenon, which is here described for the first time, to the best of our knowledge.

The analysis of the answers to the open question about the vertigo quality ("please describe your vertigo in your own words") taught us an important lesson: almost 30% of the patients reported to have several types of vertigo. Therefore, this should be kept in mind by the clinician when performing the important and artful task of history-taking in patients with vertigo. Furthermore, only 6.1% of patients spontaneously mentioned accompanying auditory symptoms. This result shows that the clinician should not forget to actively ask about any vertigo-associated auditory symptoms.

A very important observation was made concerning the duration of the vertigo attacks. Since, in routine clinical practice, it is not realistic to obtain a reliable account from the patient detailing the duration of every single vertigo attack experienced hitherto, during the history-taking the clinician has to rely on more general inquiries such as "how long are your vertigo attacks usually lasting?" A striking result of our analysis was that in about one-fourth of the patients (between 21 and 27%), the vertigo attacks lasted only 20 min or less. This has important implications for the formulation of clinical diagnostic criteria, which have been using the cut-off of 20 min in the past [6, 7].

The simultaneous occurrence of auditory symptoms before/during/after the vertigo attacks was traditionally believed to be an important and pathognomonic feature of hydropic ear disease. Our data show, however, that in 34% of the patients this is not the case. Likewise, a previous study has reported the absence of simultaneous auditory symptoms in 38% of patients diagnosed with definite or probable MD [35]. A possible explanation for this observation is based on the following: (1) in the presence of profound hearing loss ("dead ear"), it is well conceivable that during the attacks the endolymph-related pathomechanism of the attack does not lead to a perceptible auditory fluctuation. (2) Patients with such a constellation, in our clinical experience, are frequently misdiagnosed, because the treating physician—although aware of the significant but non-fluctuating hearing loss—does not suspect hydropic ear disease as the cause of the vertigo attacks, but rather follows the clue provided by the possible presence of headaches in the patients and tentatively labels them with the diagnosis of migrainous vertigo.

Loss of consciousness has long been regarded as an exclusion criterion for the diagnosis of hydropic ear disease, and only recently has it been recognized as a real phenomenon occurring in patients with a prevalence as high as 12% [36]. In our population, about 7% of the patients reported a witnessed episode of a loss of consciousness in connection with a vertigo attack. The duration of these episodes was

generally short (about a minute). This observation seems surprising at the first glance, but one should keep in mind that a hydropic vertigo attack is a catastrophic event for the patient, as can be well seen from the high prevalence of associated symptoms such as nausea, vomiting and sweating. In such a state of severe illness it seems conceivable to us that a patient may be non-responsive to his environment for a very short period of time. Furthermore, vestibular sympathetic reflex pathways may be disturbed during an attack and, therefore, cause transient loss of consciousness [36, 37].

Concerning the fluctuating hearing loss, the patients reported subjective fluctuations in hearing equally frequently at the time of presentation and at the time of initial appearance of the hearing loss. This result contradicts the traditional belief that hearing fluctuations were restricted to the early phase of the disease course, and it shows that, although according to clinical experience the audiometric hearing loss appears relatively stable in the later disease stages in most patients, the patients may still suffer from auditory fluctuations.

As it was expected, the audiometric hearing loss showed the greatest differences to the contralateral side in the low-frequency region, i.e. 0.125–1 kHz. We, therefore, recommend using these frequencies for differential diagnostic considerations and not the frequencies of 2 kHz and above.

Tinnitus in hydropic ear disease more often appears independently from vertigo than it does in association with vertigo, and it does not appear as a reliable diagnostic feature.

Headache

80 years ago, Dederding et al. described headaches in 91% of their MD patients [38]. Vice versa, in migraine patients visiting an ENT office, sinus-related symptoms and balance problems (most often lightheadedness) are very frequent complaints occurring in more than 80% of the patients [39]. Headache is a very frequent symptom in patients with hydropic ear disease. It is present in 43.5% of the patients in our study, and most of them report that their headache appears in association with the vertigo attacks. The features of the reported headache, however, are generally not suggestive of migraine (side: bilateral, quality: pressure, location: back of head/neck and bifrontal), and only 7.2% of the population had a migraine diagnosis. The present study, therefore, cannot support a pathophysiologic overlap between hydropic ear disease and migraine. In concordance with our data, a previous study has reported a high frequency of symptoms such as headache and photophobia in patients with definite MD; vertigo attacks were accompanied by photophobia in 46% and by headache in 27% (29% in our study) of the patients [40]. Considering the abovementioned features of the hydropic ear disease attacks and its severe impact on the patient, it appears likely that a symptom such as headache is a diagnostically rather non-specific manifestation of the attack (such as many other attack-associated symptoms, e.g. sweating, urge to defecate, urge to urinate, paresthesia) and possibly linked to an accompanying transient autonomous nervous system derangement (and/or electrolyte disbalance due to anxiety-induced hyperventilation). Likewise, headache is a very frequent symptom of various other conditions, e.g. epilepsy and hypertension [41, 42]. In many acute conditions, headaches are associated with various disorders that lead to acute stress. Therefore, in analogy to headache associated with hypertension, we propose to classify headache associated with hydropic ear disease attacks within the ICHD-3 under 10.7 “Headache attributed to disorders of homeostasis”.

Co-morbidities

Previous reports in the literature are characterized by a considerable variation in results concerning the association of MD with other diagnoses, which is likely due to heterogeneities in the selection of patient populations, diagnostic methods and data analysis methods. Furthermore, previous publications are generally not comparable to the present study, since this is the first time that a population with the certain diagnosis of hydropic ear disease is characterized. Nevertheless, we shall attempt to discuss some of our findings in the context of previous reports.

Migraine

In the present population of patients with hydropic ear disease, a migraine was found in 7.2% of the patients. The general population-based prevalence of migraine is estimated at 13–20% (females) and 7.6–14% (males) [43]. Therefore, the prevalence in the present population of patients with hydropic ear disease is not higher than expected by chance.

In a multi-centre study from Spain on 690 patients with a clinical diagnosis of definite MD [44], migraine was present in about 10% of the patients. Therefore, in their MD population, a diagnosis of migraine was not observed with a higher frequency than described in the general population, which is in line with our results.

In a large population-based study, Gopen et al. [45] analysed interviews from 70,000 individuals and found migraine in 4.5% of MD patients, while the migraine prevalence in the general population was 3.8%. Therefore, the prevalence was not significantly elevated compared to the general population, which is in line with our results.

In an analysis of the UK Biobank database [46], participants with Menière’s disease had double the odds of reporting a broad array of disorders such as rheumatoid arthritis, osteoarthritis, spinal arthritis, chronic fatigue syndrome,

irritable bowel syndrome, gastro-oesophageal reflux disease, migraine, and psoriasis, compared with the overall general practice patient population. All these conditions have previously been associated with autonomic nervous system (ANS) dysfunction, and the authors interpret their data as suggestive of a link between MD and ANS pathology.

In summary, vertigo and headache are both very common symptoms and their co-existence in individual patients has led to the rather loosely defined construct of vestibular migraine [47], which is under debate [20], because its main supporting argument consists in the difference between a 38% prevalence of migraine among a population with vertigo vs a 24% prevalence of migraine in a control group (patients hospitalized on an orthopaedic ward) where a medical student had identified migraine by a semi-structured interview. Our current results, however, in line with previous reports, do not show a specific association of hydropic ear disease with migraine.

Autoimmune disorders

Gazquez et al. [44] reported an association of MD with autoimmune disorders: for rheumatoid arthritis and ankylosing spondylitis, the estimated prevalence in patients with MD was two to three times more common [48], and for systemic lupus erythematosus the prevalence was eight times more frequent [49] compared to estimated prevalences in the general population.

In our present study, asthma was by far the most common autoimmune disorder in the patients with hydropic ear disease, affecting 16 patients. Other autoimmune disorders (numbers of patients in parentheses) encountered in this patient population were autoimmune hypothyroidism (Hashimoto) (4), rheumatoid arthritis (2), atopic eczema (2), idiopathic thrombocytopenic purpura (2), diabetes mellitus type I (1), optic neuritis (1), recurrent uveitis (1), ulcerative colitis (1), ankylosing spondylitis (1), lichen planus (1), and scleroderma (1). Two patients had fibromyalgia, but we do not consider this diagnosis as an autoimmune disorder, due to its vague diagnostic criteria and its considerable overlap with somatoform disorders. Thus, with the exception of asthma, each of the autoimmune diseases occurred in less than five patients. With such low prevalence rates (< 2%), it does not seem very useful to calculate a prevalence number and compare it to reported prevalences in other populations. Furthermore, even if the prevalence of some of these disorders were higher than in the general population, it seems highly unlikely that any such association would play an important pathophysiologic role in a significantly large proportion of patients with hydropic ear disease.

In contrast to Gazquez et al., Tyrrell et al. [46] found an association of MD with rheumatoid arthritis and psoriasis, but not with autoimmune hypothyroidism and other autoimmune diseases. Asthma was not associated with MD in their study. It should be noted, though, that the prevalence rates for asthma may be quite different between the general populations of the UK and Germany. For the former it is estimated at 18%, but for the latter it is estimated at 8% [50]. For the German population, a review of epidemiologic studies found an asthma prevalence between 5 and 9% in most studies [51]. In our German study population, asthma was present in 6.4% of the patients with hydropic ear disease and, therefore, it does not seem to be positively correlated. When pooling all patients with any autoimmune disease together, the prevalence in our patient population was 13.7%. In comparison, the UK control population had a prevalence of 16.8% for autoimmune disorders [46]. Therefore, we cannot identify a positive correlation between hydropic ear disease and autoimmune disorders in our study.

Other disorders

In the present study, 30.5% of the patients suffered from hypertension. Tyrrell et al. [46] found a very similar prevalence (30.8%) in their MD population and they did not find a difference to the general population who had a prevalence of 26.1%. For the general population of Germany [52], the prevalence of hypertension in the age group of 45–64 years is estimated at 35–40% (and in the higher age groups it is markedly higher). Therefore, we cannot find a positive correlation between hydropic ear disease and hypertension in our study cohort.

Hypothyroidism (non-autoimmune) was present in 9.6% of the patients with hydropic ear disease. For Germany, there are no original epidemiologic studies published [53], but a large population-based study in the US found a prevalence of 9.5% [54]. Thus, we cannot find evidence for an association of hydropic ear disease with hypothyroidism.

Strengths and limitations

Strengths The interview which is the main source of the data was prospectively conducted by a certified physician, either an otolaryngology attending or a resident in otolaryngology training in our study. This should ensure a high quality and reliability of the obtained information and represents a significant advantage over numerous other studies using self-report questionnaires or questionnaires obtained by non-physicians or retrospectively collected data. Furthermore, this approach more closely resembles the real-life situation, where a clinician obtains the history from the patient and uses this information as a basis for his differential diagnostic considerations. Also, in contrast to most other reports that we know of, we included questions specifically asking

about the time of the first appearance of the symptoms. This allowed us to achieve a high degree of precision and comparability when it comes to the estimation of the disease duration and the cochleovestibular symptom onset delay. Moreover, the vertigo attack duration was assessed by two different methods in the same patients, and these yielded very similar results, thereby supporting the validity of the obtained data. Most importantly, the present patient population is unique in that it has the highest degree of diagnostic certainty possible, i.e. morphologic confirmation of endolymphatic hydrops, which was established using validated criteria, multiplanar image analysis and comparison with normative data from healthy individuals.

Limitations

On a first glance, the disease duration in this cohort may appear relatively long. However, this may very well be due to our specific assessment of the time of first appearance of the symptoms as the basis for the disease duration calculation (as opposed to the time of diagnosis). Furthermore, the proportion of patients with cochlear hydropic ear disease, i.e. patients without vertigo attacks, may be underrepresented in the study sample. This is likely due to the fact that in this specific subgroup of patients, the MRI morphologic confirmation of endolymphatic hydrops is not always performed, because the therapeutic consequence is not significant in most cases, considering that the primary therapeutic goal of most interventions is the reduction of vertigo attacks. Some bias may also result from the fact that our institution is a tertiary referral centre. However, unlike many other countries, in Germany, every patient can freely choose his doctor (including our tertiary neurotology clinic) at no additional cost and a referral from his general practitioner or otolaryngologist is not required for the presentation at our tertiary neurotology clinic. Indeed, we have frequently performed the initial diagnostic workup in many cases. Therefore, this bias most likely does not have a very strong effect on patient selection.

Conclusion

This study marks the beginning of the clinical characterization of the new concept of hydropic ear disease. Instead of relying on crude diagnostic criteria based on a very limited set of items obtained from subjectively reported symptoms, hydropic ear disease was objectively defined by its pathology. Our detailed clinical analysis of this large cohort of patients with hydropic ear disease revealed that (1) a third of the patients does not experience auditory symptoms during the vertigo attacks; (2) the hydropic vertigo attack is a catastrophic event for the patient and includes the symptoms nausea, vomiting, sweating, urge to defecate, urge to urinate, phosphenes, headache, photophobia, phonophobia and even transient loss of consciousness; (3) vertigo attacks last less than 20 min in about one-fourth of the patients; (4) subjective hearing loss precedes vertigo during the disease course in most patients; (5) audiometric hearing loss has its greatest diagnostic value at the frequencies of 1 kHz and below; (6) migraine and autoimmune disorders are not significantly associated with hydropic ear disease; (7) a positive family history is present in about 4% of the cases. These findings have important implications for the future formulation of diagnostic criteria aiming to enable a diagnosis even in the absence of hydrops imaging.

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Compliance with ethical standards

Conflict of interest All authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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