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Presence of endolymphatic hydrops on listening difficulties in patients with normal hearing level

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ABSTRACT

Background: Listening difficulties (LiD) present difficulties in listening and paying attention to spoken information despite normal pure tone audiometry. Endolymphatic hydrops (EH) is a common inner ear condition associated with Ménière's disease but may also be present in the asymptomatic ear.

Objectives: Using magnetic resonance imaging, we investigated EH in patients with LiD and assessed whether the severity of EH was related to the results of auditory processing tests (APTs).

Materials and Methods: 111 patients with no abnormalities on pure tone audiometry, but displaying difficulties in listening, underwent evaluation through APTs and questionnaires. Upon obtaining informed consent, the inner ears of 20 consenting patients were evaluated utilizing a 3-Tesla magnetic resonance imaging.

Results: A higher percentage of patients diagnosed with LiD by APTs had significant EH in the cochlea and vestibule than in previously reported control cases. The percentage of correct answers in the speech-in-noise test was significantly lower in patients with than in those without significant EH.

Conclusion and significance: In this study, significant EH of the cochlea was associated with poor listening to noise. The presence of EH affects the functioning of the auditory processing system, even in ears that test normally on standard audiometric tests.

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Listening difficulties; magnetic resonance imaging; endolymphatic hydrops

Introduction

The symptoms of auditory processing disorder (APD) include difficulty in listening in daily life despite normal hearing test results; APDs are considered to be a form of central auditory dysfunction. Listening difficulties (LiD) indicated a deficit in recognizing sounds or understanding speech, which has been used as an umbrella term [1]. Symptoms commonly noted by people with LiD include frequent mishearing, inability to hear in noisy environments, forgetting what is said orally, inability to hear fast speech or soft voices, and inability to pay attention to long conversations or to understand auditory information. In a patient with these symptoms but normal hearing, a LiD should be suspected.

The diagnosis and treatment of LiD vary between countries. In general, the diagnosis depends on the results of several auditory processing tests (APTs) and electrophysiological procedures, and questionnaires are often added to provide further information. Moore [2] reported that the symptoms of LiD can also affect cognitive ability, for example, attention and memory. In Japan, Obuchi and Kaga [3] developed a questionnaire to assess listening difficulties in adults with LiD based on the Speech, Spatial, and Qualities of Hearing Scale (SSQ-12) [4] and added a psychological domain, and this later questionnaire was used widely.

Mismatch negativity and P300 are known as event-related potentials associated with hearing. Mismatch negativity is a negative potential detected at a latency of 100–200 ms after a sound stimulus [5]. P300 is a positive wave that is recognized at a latency of about 300 ms after a sound stimulus. Event-related potentials are considered to reflect higher-order functions and are used to assess the effects of treatments for psychological, physiological, psychiatric, and neurological disorders. Mismatch negativity is expected to be applied to the study of auditory memory, such as attention testing for infants who cannot understand tasks, and for the temporal integration of auditory information. P300 is considered useful as an objective method for evaluating attention function in people with attention deficit hyperactivity disorder in terms of temporal changes and treatment effects and as an objective method to evaluate APD. P300 is also expected to be a neurophysiological biomarker for the objective assessment of APD.

Recently developed neuroimaging techniques can image the structure and function of the nervous system directly or indirectly. Technological advances and a better

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understanding of the anatomical and physiological aspects have been used to develop imaging techniques to evaluate and diagnose various disorders. Imaging studies of LiD have focused mainly on auditory processing pathways and brain function. Positron emission tomography, functional MRI, electroencephalography, and magnetoencephalography have been used to evaluate LiD. Currently, speech–language pathologists use only clinical tests to diagnose hearing impairment and determine reverse language dominance, and there is no evidence from imaging or electrophysiological tests. Both electrophysiological testing and imaging testing are more objective measures of evaluation and are needed for an appropriate clinical diagnosis of LiD. Imaging techniques are now recommended for the proper diagnosis of LiD, and these imaging studies target primarily brain function. However, no reports of imaging studies have focused on the inner ear as a peripheral sensory organ. Yoshida et al. [6] have reported the presence of endolymphatic hydrops (EH) in the cochlea and vestibule in patients with Ménière's disease, tinnitus, fluctuating hearing loss, or vertigo, and in healthy ears. Considering that EH may affect listening but that patients with LiD do not complain of the cochlea–vestibular symptoms other than listening difficulties, we investigated the distribution of EH in patients with LiD.

Methods

Patients

Among 111 patients who visited our department with symptoms of listening difficulties from 2019 to 2022, twenty patients who underwent 3-Tesla magnetic resonance imaging (MRI) were included in the present study. All patients had a normal hearing but complained of listening difficulties encountered during everyday life. Their mean age was 20.1 years; fourteen were women and six were men. All the patients had no previous hearing loss or vertigo attacks related to EH, intellectual disability, history of neurological disorder, head trauma, or severe mental disorder or surgery. Informed consent has been obtained from all individuals included in this study.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethics Review

The study was approved by the Ethics Review Committee of Nagoya University School of Medicine, Nagoya, Japan (No. 2022–0339).

Auditory processing tests

Before the APTs, the average pure tone threshold was determined in all patients using an audiometer (AA-78, RION Co Ltd, Kokubunji, Japan) as the mean threshold at six frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz). The computer program of the Japanese APT battery was developed by Obuchi and Harashima as reported by Fujimoto et al. [7] and ran on a laptop personal computer. A headphone delivered the sound stimuli for the APTs, and the audiometer was connected to the laptop computer in a soundproof room. Each patient responded to the test sound at the 40 dB sensation level. We diagnosed LiD if any APT item was less than two standard deviations below the mean for healthy subjects [8].

Dichotic listening test

In the dichotic listening test (DLT), different speech stimuli were presented simultaneously to the right and left ears, and the patient was asked to focus on only one ear and to respond to what he or she heard only on the side to which attention was directed. The stimuli used in this test were monosyllables (30 trials) and sentences (10 trials), all in Japanese. The test sound sentences were set to be short, no more than 10 mora. For sentences, the laterality index of the percentage of correct responses was calculated using the formula (right ear − left ear)/(right ear + left ear) × 100. A positive value indicates right ear dominance. Most right-handed people typically show a right ear advantage, which indicates left-hemispheric language dominance when verbal auditory stimuli are presented.

Speech-in-noise test

The stimuli for the speech-in-noise test (SINT) comprised 36 words and speech-spectrum noises presented equally to both ears. In this test, the words and noises were presented simultaneously and randomly, and the patients were asked to repeat the words they heard. The signal-to-noise ratio (SNR) is defined as the difference between the signal sound pressure level and the background noise sound pressure level, and the SNR was increased in 5 dB steps to −15, −10, −5, 0, 5, and 10 dB. The reception threshold was determined as the SNR at which 50% correct performance was achieved. The SNR was varied randomly in each trial without an adaptive procedure.

Auditory attention test

The auditory attention test (AAT) is an attention test that uses auditory stimuli. Single-digit numbers (1, 2, 3, 4, 5, and 9) are presented randomly, and the interstimulus interval is set at 800, 1500, and 3000 ms. The patient is asked to press a button and respond when 9 appears after 1. Twenty target test words were used, and the total number of presented words was 100. The number of correct responses to the test words, number of errors, and reaction times for correct and incorrect responses were analyzed.

Questionnaire

The questionnaire on listening difficulty for adults with suspected APD proposed by Obuchi and Kaga [3] was used. This questionnaire includes a shortened version of the SSQ-12 [4] with four additional items in the psychological domain to assess psychological and social reactions to hearing difficulties. The questionnaire included 16 items and was administered to adults with APD. All items are presented in Appendix 1. The questionnaire assesses four domains of the quality of hearing: Speech, Spatial, Quality, and Psychological. Each item was scored from 0 to 10, where 0 indicates "not at all" and 10 indicates "perfect." All patients in this study completed this questionnaire by rating their responses on a 10-point scale. The score for each item and the total score were calculated and compared between groups. The questionnaire cutoff score indicating APD is 109 (maximum 160; sensitivity: 93.9%, specificity: 82.9%). The area under the receiver operating characteristic curve representing the questionnaire scores is 0.95 [3].

MRI

MRI was performed using a 3-Tesla scanner (MAGNETOM Skyra; Siemens, Erlangen, Germany) equipped with a receive-only, 32-channel, phased-array coil. MRI was performed after intravenous administration of a standard dose of gadolinium hydrate (gadobutrol 0.1 mmol/kg; Gadovist; Bayer AG, Leverkusen, Germany). All patients underwent heavily T2-weighted (hT2W) MR cisternography (MRC) for anatomical reference of the fluid space and hT2W three-dimensional (3-D) fluid-attenuated inversion recovery MRI (3D-FLAIR) for evaluation of labyrinthine fluid alterations in 7 min. The inversion time was 2250 ms after the MRC images were obtained using a variable flip angle 3-D turbo spin-echo technique and sampling perfection with application-optimized contrasts using different flip angle evolutions, and the repetition time was 9000 ms.

The presence of EH was investigated using a hybrid of a reversed image of the positive endolymph signal and native image of the positive perilymph signal, a hybrid of the reversed image of MRC, positive perilymph signal by hT2W 3D-FLAIR, and 3-D-real inversion recovery (IR) sequences. The detailed parameters of 3-D-real IR have been reported previously [9,10]. A radiologist with >20 years of experience who was blinded to the clinical symptoms classified the degree of EH in the cochlea and vestibule into one of three groups: none, mild, or significant, according to previously described criteria [10]. Within the vestibule, the ratio of the area of the endolymphatic space to that of the total vestibular fluid space was used to grade the degree of EH. The total vestibular fluid space was the sum of the endolymphatic and perilymphatic spaces. Patients with no EH in the vestibule had a ratio of 1:3 or less, those with mild EH had ratios between 1:3 and 1:2, and those with significant EH had a ratio greater than 1:2. Patients categorized as having no EH in the cochlea displayed no displacement of Reissner's membrane. Patients with mild EH demonstrated displacement of Reissner's membrane, however, the area of the endolymphatic space did not exceed the area of the scala vestibuli. In patients with significant cochlear EH, the area of the endolymphatic space exceeded the area of the scala vestibuli. If the EH grade was different between the basal and upper turns of the cochlea, we used the higher grade to score the EH. The presence of EH observed in nine patients in the present study was compared with that in control subjects without hearing disturbances, as reported earlier [6].

Statistical analyses

IBM SPSS Statistics software (version 28, IBM Corp., Armonk, NY, USA) was used for statistical analyses. The significance level was set at 5%. The *t*-test or Fisher's exact test was used for comparisons.

Results

The patients' characteristics are shown in Table 1. EH in the cochlea was classified as significant in fourteen ears, mild hydrops in nine ears, and no EH in the other seventeen ears. Five patients had significant EH in both cochleae. EH in the vestibule was classified as significant in six ears, mild hydrops was found in five ears, and no EH was found in the other 29 ears. Patient 2 and 7 showed significant EH in both the right and left cochleae and vestibules. The DLT laterality index showed negative values in a few cases but did not show any particular association with the distribution of EH. Comorbidities included one patient each with depression, autism spectrum disorder and attention deficit hyperactivity disorder, but none of these were associated with EH. Figure 1 shows sample images of the cases included in this study. In this study, patients with significant EH in at least one cochlea were defined as having EH.

EH in the cochlea and vestibule was significantly more common in patients with LiD than in the control values ($p < 0.01$) reported previously [6] (Figure 2). All the cases in the cited reference used for comparison do not have auditory vestibular symptoms, including hearing difficulties; both MRI imaging and evaluation were performed under the same conditions.

In the DLT, the percentages of correct responses for monosyllables and sentences did not differ between patients with and without significant EH (Figure 3(a,b)). In patient 3, significant EH was found only in the right ear, and the laterality index was left predominant (Table 1). Patient 5 showed significant EH in the cochlea only in the right ear, but the DLT result was poor in both ears and did not differ between the right and left ears.

In the SINT, the percentages of correct answers for SNRs of +5 and 0 were significantly worse in patients with than in those without significant EH in the cochlea ($p < 0.05$) (Figure 4). In the AAT, the severity of EH was not significantly related to the correct response rate (Figure 5). There

Table 1. Characteristics of the patients.

No.	Age	Gender	Mean hearing level (dB) R/L	Endolymphatic hydrops: Cochlea R/L	Endolymphatic hydrops: Vestibule R / L	Dichotic listening test: laterality index*	Listening difficulty checklist score[a]	Pre-existing disability or illness
1	18	F	20.0/23.3	Significant/significant	None/none	23.1	73	none
2	30	F	6.7/8.3	Significant/significant	Significant/significant	0	113	none
3	18	F	15.0/10.0	Significant/none	None/none	−33.3	36	none
4	14	F	10.0/11.7	Significant/none	Mild/none	11.1	78	none
5	18	F	3.3/3.3	Significant/none	Mild/none	0	88	none
6	13	M	10.0/8.3	Mild/significant	Mild/mild	5.9	79	none
7	13	F	6.7/6.7	Significant/significant	Significant/significant	11.1	66	Autism spectrum disorder
8	15	F	18.3/18.3	Significant/significant	None/mild	−17.7	77	none
9	23	F	13.3/13.3	Significant/significant	None/none	0	67	none
10	20	M	8.3/8.3	None/none	None/none	23.1	49	none
11	12	F	5.0/5.0	Mild/mild	None/none	0	88	none
12	25	M	11.7/10.0	Mild/none	None/none	0	43	depression
13	35	M	8.3/10.0	None/none	None/none	12.5	61	Attention deficit hyperactivity disorder
14	34	F	11.7/15.0	Mild/mild	None/none	0	59	none
15	17	F	6.7/8.3	None/none	Significant/significant	33.3	30	none
16	18	M	10.0/8.3	None/none	None/none	17.6	63	none
17	19	F	6.7/8.3	None/mild	None/none	−11.1	68	none
18	13	M	5.0/6.7	None/mild	None/none	5.9	57	Autism spectrum disorder
19	33	F	8.3/8.3	None/mild	None/none	−23.1	107	none
20	14	F	10.0/8.3	None/none	None/none	5.3	80	None

*The laterality index of the percentage of correct responses was calculated using the formula (right ear − left ear)/(right ear + left ear) × 100. A positive value indicates right ear dominance.
[a]Questionnaire to assess listening difficulties in adults with APD.[2.]

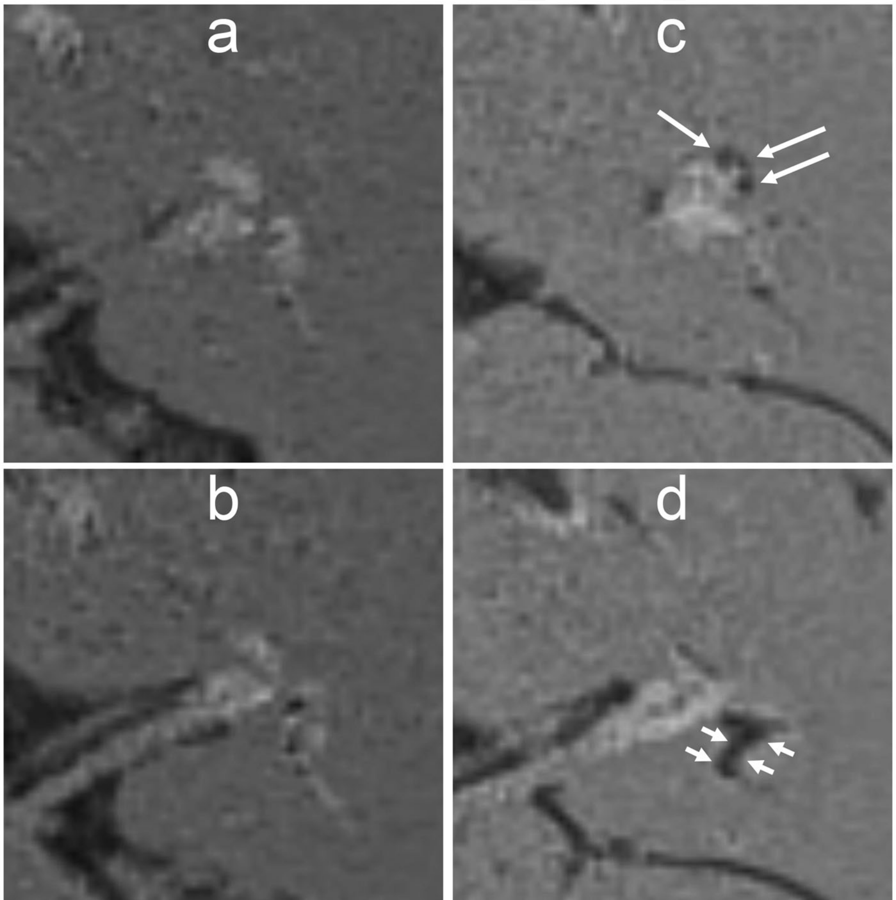

Figure 1. Sample HYDROPS images of EH from a case with LiD (axial plane). Images are used to detect EH. No EH was shown on the left (a, b). EH is seen as black areas surrounded by gadolinium-filled perilymphatic spaces, as depicted on the right side (c, d). The cochlea (c, arrows) and the vestibule (d, short arrows) show significant EH. EH: endolymphatic hydrops; LiD: listening difficulty; HYDROPS: hybrid of a reversed image of positive endolymph signal and native image of positive perilymph signal

was no significant difference on the Listening Difficulty Checklist of the questionnaire between patients with and without significant EH (Figure 6). The mean score on the questionnaire on listening difficulty for adults was 69.1. All but one patient had a total score of <109.

Discussion

We identified the presence of EH in patients with normal hearing and suspected LiD based on symptoms such as listening difficulties and APT results. EH is a hallmark of Ménière's disease and can now be visualized using MRI [11]. Ménière's disease is a disorder in which excessive endolymph accumulates in the inner ear and damages ganglion cells. In most cases, the clinical symptoms of Ménière's disease appear after significant endolymph accumulation. However, some patients have symptoms early in the development of EH, although the reason for this variation in symptoms is unknown [12]. MRI often identifies EH in the affected ear of people with Ménière's disease and sometimes in the asymptomatic ear or the ear contralateral to that affected by Ménière's disease [13]. A previous study using control ears reported significant EH in the cochlea in 4 of 42 ears and mild EH in 12 ears. On the other hand, 37/52 (71.2%) of the patients with definite Ménière's disease had significant EH in the cochlea [6]. A temporal bone study also reported a higher frequency of EH in the apical turn of the cochlea in asymptomatic ears [14].

Although the patients included in this study reported listening difficulties, none was affected by cochlear vestibular symptoms that would raise the suspicion of Ménière's disease. No association between EH and age has been reported to date, but there are many reports of EH and hearing loss, vertigo, duration of disease, and vestibular electrophysiological responses. Even though our patients were relatively

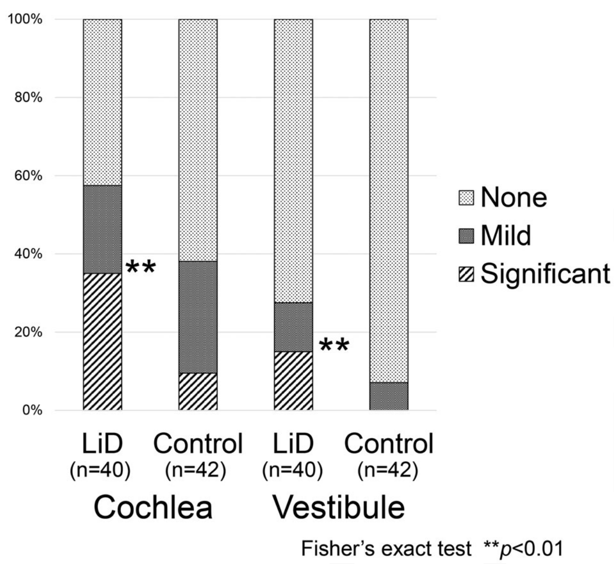

Figure 2. Comparison of the distribution of endolymphatic hydrops in previously reported control patients and patients with listening difficulty (LiD) in this study.

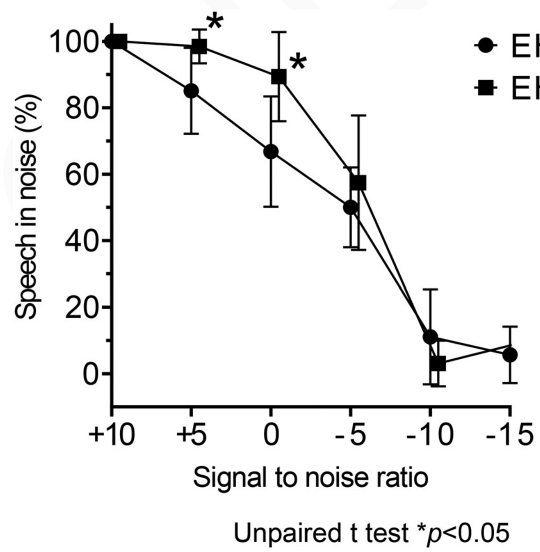

Figure 4. Comparison of mean percentage of correct answers at different signal-to-noise ratios of speech in the speech-in-noise test in patients with and without significant endolymphatic hydrops in the cochlea. EH + refers to significant EH in the cochlea and EH– to none or mild EH. Symbols indicate the mean and thin bars indicate the standard deviation.

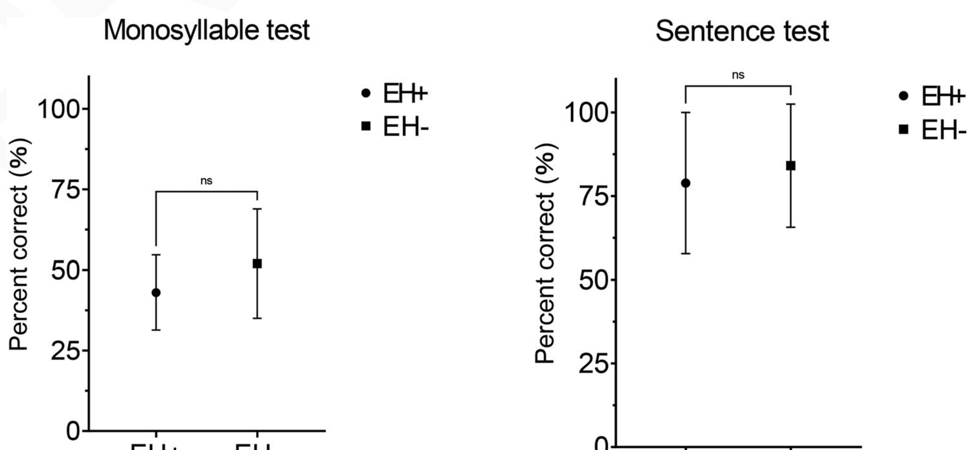

Figure 3. Comparison of the mean percentage of correct answers on the dichotic listening test according to the presence of significant endolymphatic hydrops in the cochlea. The results for the right and left ears are included. EH + refers to significant EH in the cochlea and EH– to none or mild EH. Symbols indicate the mean and thin bars indicate the standard deviation. Left (a): Monosyllable test results; Right (b): sentence test results.

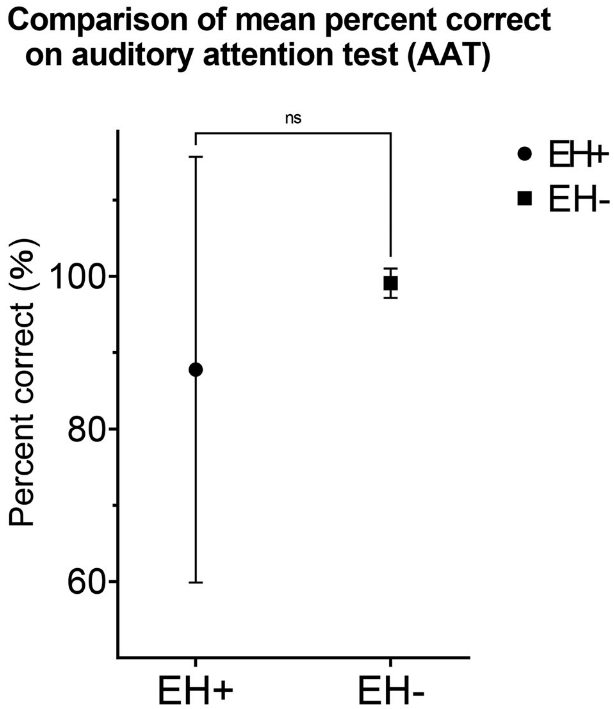

Figure 5. Comparison of mean percentage correct answers on the auditory attention test in patients with and without significant endolymphatic hydrops in the cochlea. EH + refers to significant EH in the cochlea and EH– to none or mild EH. Symbols indicate the mean and thin bars indicate the standard deviation.

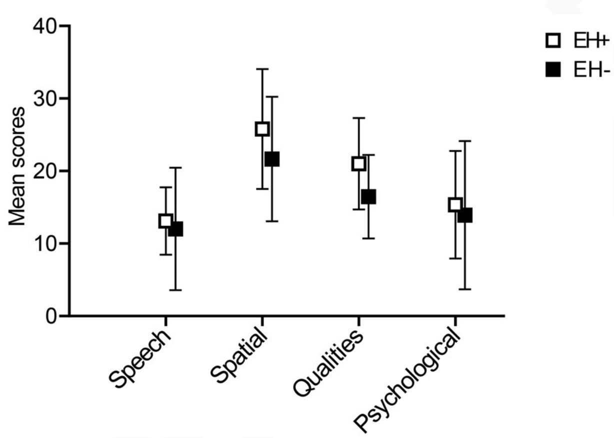

Figure 6. Comparison of mean scores for each domain of the questionnaire according to the presence or absence of significant endolymphatic hydrops in the cochlea. EH + refers to significant EH in the cochlea and EH– to none or mild EH. Symbols indicate the mean and thin bars indicate the standard deviation.

young and were therefore expected to have a short disease duration, the high frequency of EH suggests its involvement in the LiD symptoms.

The gap in speech discrimination performance between quiet and noisy environments has been reported. Differences of ≥40% in speech discrimination scores between tests performed in quiet and in white noise occur in <1% of normal ears but in 8% of ears with noise trauma, 48% of ears with Ménière's disease, 62% of ears with subsequently surgically confirmed eighth nerve tumors, 14% of ears of patients with multiple sclerosis [15], and 42% of ears contralateral to the lesion in patients with temporal lobe disorder [16].

Moderate noise exposure levels were previously thought to cause only temporary threshold changes. However, the synaptic connections between inner ear hair cells and cochlear nerve fibres are immediately and irreversibly lost [17]. This phenomenon is referred to as hidden hearing loss because conventional hearing tests do not detect it. Although some studies suggest that cochlear synaptopathy is not common in humans, others report that it contributes to various hearing abnormalities, including difficulty hearing in noise, tinnitus, and hearing hyperacusis. An animal study reported EH and decreased synaptic ribbons in the basal to the middle rotation of the cochlea were observed in mice exposed to noise at 100 dB for 2 h [18]. Patients with multiple sclerosis have been found to have deficits in aspects of central auditory processing, including temporal resolution, auditory patterns, the memory of auditory tasks, and difficulty with speech discrimination in noisy environments, because of the involvement of the central nervous system [15]. One study found a dissociation between pure tone audiometry and speech recognition in patients with Ménière's disease. In the patients with Ménière's disease, speech recognition was significantly worse than the change in pure tone audiometry 108 months after the initial hearing test [19].

Because patients with LiD also show a gap in speech discrimination between quiet and noisy environments, it is presumed that changes in auditory processing in the inner ear and central auditory cortex are present, as described above. In some audiology tests such as DLT, the right ear advantage is expected to be related to left hemisphere dominance [20]; however, the current study included four patients whose results did not fit this pattern. Regardless of whether the hearing impairment is the result of dysfunction of outer hair cells, inner hair cells, or synapses of the auditory nerve if peripheral loss adversely affects any of these abilities, more central auditory processes that depend on normal spectral or temporal resolution should also be affected [1]. An evaluation of travelling wave velocity derived from the auditory brainstem was conducted on asymptomatic ears with unilateral Ménière's disease to determine the presence of endolymphatic hydrops. 27% of the participants showed indications of endolymphatic hydrops. The group affected by endolymphatic hydrops exhibited a velocity significantly surpassing that of the normal controls, particularly at a frequency of 5.7 kHz. The postulation is that an augmentation in pressure within the scala media will result in increased basilar membrane stiffness and, thus, a heightened speed of the travelling wave. Our findings suggest that the presence of EH may be one factor that is associated with LiD without hearing loss.

The limitations of this study include the small sample size, lack of a control group, and possible selection bias. Because patient fatigue can influence the test results, the patients in this study were allowed sufficient rest to be able to complete the test. The data contained in this report are preliminary and have not been previously reported or confirmed. Therefore, future comparative studies with larger groups of patients and controls are needed.

Conclusions

LiD is considered mainly a problem of the auditory processing pathway in the central nervous system, but few imaging studies of the peripheral auditory organs have been conducted. This study found a high incidence of EH in patients with LiD and that this seemed to contribute to their listening difficulties. Further research is needed to clarify the impact of EH on LiDs.

Disclosure statement

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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