The Correlation Between Symptoms of Definite Meniere’s Disease and Endolymphatic Hydrops Visualized by Magnetic Resonance Imaging

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Objective/Hypothesis: This study aimed at investigating the correlation between a battery of diagnostic symptoms of definite Meniere’s disease (MD) and the degree of endolymphatic hydrops (EH) in the inner ear.

Study Design: Prospective study.

Methods: Fifty-four patients diagnosed with unilateral definite MD were enrolled in the study. The hearing levels of all patients at the low, middle, and high frequencies were evaluated. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) and three-dimensional real inversion recovery (3D-real IR) magnetic resonance imaging (MRI) were performed 24 hours after bilateral intratympanic injection of gadolinium to assess the presence and grading of EH.

Results: Various degrees of EH were observed in the vestibule and/or each turn of the cochlea in the affected ears of all patients. The duration of MD disease and low-tone and middle-tone hearing thresholds were proportional to the extent of EH in the vestibule and cochlear. However, no significant correlation was demonstrated between EH and other aspects of symptoms such as high-tone hearing loss, tinnitus, and aural fullness. Of all subjects, 16.7% exhibited bilateral EH on MRI exam who were diagnosed with unilateral MD based on diagnostic criteria.

Conclusions: EH in the inner ear of MD patients exhibits a progressive deteriorative trend over time. Low-tone and middle-tone hearing thresholds can indirectly reflect the severity of EH in the cochlea. EH may not be the primary cause of tinnitus and aural fullness in patients with MD. Patients diagnosed with unilateral MD should maintain long-term regular follow-ups for the possibility of developing bilateral EH.

Key Words: Meniere’s disease, endolymphatic hydrops, symptom, magnetic resonance imaging.

Level of Evidence: 4

INTRODUCTION

Meniere’s disease (MD), whose pathological basis is thought to be endolymphatic hydrops (EH),¹ ² is a refractory inner ear disorder characterized by spontaneous attacks of vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. MD is primarily diagnosed on the basis of the criteria established by the American Academy of Otolaryngology–Head and Neck Surgery (1995) accompanied by various examinations, such as pure-tone audiometry (PTA), caloric test, electrocochleography, and vestibular-evoked myogenic potential (VEMP). The guideline states that certain MD is defined by histopathological confirmation; therefore, clinicians primarily rely on the clinic symptoms to diagnose definite, probable, or possible MD.³

Nakashima et al.⁴ reported the first visualization of EH in patients suffering from MD by utilizing three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) 24 hours after intratympanic gadolinium (Gd) administration. Two years later, a three-stage standard grading of EH in the vestibule and cochlea was put forward after intratympanic Gd injection using 3D-FLAIR MRI and three-dimensional real inversion recovery (3D-real IR) MRI.⁵ Both 3D-FLAIR MRI and 3D-real IR MRI have their own advantages and disadvantages, and the two modalities are complimentary to each other. 3D-real IR MRI aids in differentiating the endolymphatic space, perilymphatic space, and surrounding bone separately and is generally thought to obtain a better image of the endolymphatic extension after intratympanic Gd injection. However, when the Gd concentration is insufficient in the perilymph, it is more difficult to visualize the enhanced signal of Gd in 3D-real IR MRI than in 3D-FLAIR MRI.⁶ ⁷ Both images were applied to determinate the boundary and grading of EH in MD patients.

The images of the endolymphatic and perilymphatic space not only provide a better understanding of EH inside the inner ear, but pave the way to investigate the
correlation between clinical symptoms of MD and EH. In the present study, we attempted to explore the correlation between the degree of EH evaluated using 3D-FLAIR MRI and 3D-real IR MRI after intratympanic Gd injection and specific clinical characteristics of definite MD, including the duration of the disease, and the symptoms such as vertigo, hearing loss, tinnitus, and aural fullness.

MATERIALS AND METHODS

Patients

Fifty-four patients (45 males and 9 females; age range, 23–74 years; median age, 52 years; duration of MD, 2 months–20 years; median duration, 2 years) were included in the study conducted in the Department of Otology and Skull Base Surgery of the Eye, Ear, Nose & Throat Hospital, Fudan University between July 2013 and December 2014. All patients were clinically diagnosed with unilateral definite MD according to the criteria of the 1995 American Academy of Otolaryngology–Head and Neck Surgery guidelines.

The detailed criteria used to enroll patients were as follows: unilateral disease, two or more definitive episodes of vertigo with hearing loss, tinnitus, aural fullness, and no history of middle ear or neurological disorders. All individuals complained of hearing loss in the affected ear. With the exception of one patient, patients (98.1%) suffered from tinnitus in their affected ear. Tinnitus associated with vertigo (tinnitus occurred or deteriorated before vertigo attack) was present in 23 patients (43.4%). In the other 30 patients (56.6%), tinnitus was not associated with vertigo. Approximately 65% (n = 35) of patients referred to the clinical characteristic of aural fullness and 35% (n = 19) denied aural fullness in the affected ear.

The study obtained permission from the medical ethics committee of the Eye, Ear, Nose and Throat Hospital, and all the patients signed informed consent.

PTA Thresholds

PTA thresholds were tested at all frequencies (0.125–8 kHz). In addition, the hearing levels at the low (125–250 Hz), middle (500–2,000 Hz), and high (4–8 kHz) frequencies were also evaluated. With regard to the affected ear, all patients showed various degrees of sensorineural hearing loss, and the average hearing thresholds at low frequencies, middle frequencies, and high frequencies were 59.6 ± 16.6 dB (range, 20 dB–80 dB), 60.0 ± 14.7 dB (range, 28 dB–88 dB) and 67.9 ± 17.2 dB (range, 33 dB–110 dB), respectively. The hearing thresholds in the contralateral ears were in the normal limitation.

Intratympanic Gd Injection and MRI

All patients were subjected to bilateral intratympanic injection of Gd using a 22-gauge spinal needle and a 1-mL syringe. About 0.3 to 0.5 mL Gd was injected through the tympanic membrane to fill each tympanic cavity under otoendoscopy while in a seated position. Gd was diluted eight-fold with saline (v/v 1:7). The patients remained in the seated position for 30 minutes without speaking or swallowing.

MRI was performed 24 hours after bilateral intratympanic Gd injection with a 3T unit (Vereis; Siemens Healthcare GmbH, Erlangen, Germany) using a 32-channel phased array receive-only coil. T2-space, 3D-FLAIR, and 3D-real IR sequences MRI were applied for the image collection. The parameters for 3D-FLAIR sequence were as follows: voxel size = 0.7 mm * 0.7 mm * 0.6 mm, scan time = 6 min, repetition time (TR) = 6,000 ms, echo time (TE) = 387 ms, inversion time (TI) = 2,100 ms, slice thickness = 0.60 mm, echo train length (ETL) = 173, field of view (FOV) = 220 mm * 220 mm, and matrix size 1,701 * 810. The parameters for 3D-real IR sequence were as follows: voxel size = 0.4 mm * 0.4 mm * 0.8 mm, scan time = 14 min, TR = 9,000 ms, TE = 181 ms, TI = 1,730 ms, slice thickness = 0.80 mm, FOV = 160 mm * 160 mm, and matrix size 3,300 * 918.

Imaging Evaluation

Gd rapidly permeates into the perilymph of the inner ear through the oval window and round window after intratympanic administration. When EH presents, the endolymph fluid must occupy the area of perilymph fluid confined to the bony labyrinth. Therefore, endolymphatic space is enlarged and visible as a negative signal dilating to the contrast-enhanced signal of perilymph space. The evaluation of EH was mainly focused on the vestibule and all turns of the cochlea in this study. The degrees of EH in the vestibule and cochlea were classified into three stage gradings: none, mild, and significant (Table I). All images were judged by a radiologist with expertise in this field who was blinded to the diagnosis of all individuals. Furthermore, the ratio of the area of the endolymphatic space to the vestibular space was calculated to represent the degree of EH in the vestibule using Adobe Photoshop CS5 (Adobe Systems, Inc., San Jose, CA).

Statistical Analysis

The data were analyzed with SPSS 16.0 (IBM, Armonk, NY). The Pearson correlation, Spearman correlation, two independent samples t test, and Mann-Whitney test were used to analyze the data. The level of significance was set at P < .05.

RESULTS

EH was observed in the affected inner ear of all patients 24 hours after bilateral intratympanic Gd injection. T2-space sequence MRI was successfully applied to exclude other middle ear and neurological disorders. 3D-FLAIR and 3D-real-IR sequences MRI were complementary determining the degree of EH in the vestibule and all turns of the cochlea on the affected side. Figures 1, 2, and 3 present various extents of vestibular and cochlear EH in the affected ear in patients with MD. Figure 4 presents the specific percentage of different...
gradings of EH in the vestibule and cochlea in the affected ears. Less than one-third area ratio of the endolymphatic space to the vestibular space and mild hydrops in all turns of the cochlea were evaluated in four individuals. Three of 54 patients exhibited a mild negative signal of endolymphatic space in the vestibule and normal perilymphatic enhancement in all turns of the cochlea. Mild or severe grade EH was involved in both the vestibule and cochlea in addition to the above-mentioned seven patients. The ratio of area of the endolymphatic space to the vestibular space ranged from 12.1% to 81.7% (median, 60.3%). Approximately 91.7% (22 patients) of 24 patients suffering from MD lasting more than 2 years exhibited a greater enlargement of negative signal in the vestibule. An unpredicted EH was observed in nine patients (16.7%) revealing EH in the cochlea and/or vestibule of the contralateral ears. Among these patients, nine individuals exhibited mild EH in the cochlea, although it was normal in the vestibule, and one individual had mild EH in both the cochlea and vestibule. A set of bilateral images of EH is presented in Figure 5.

Fig. 1. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (a) and three-dimensional real inversion recovery (3D-real IR) magnetic resonance imaging (MRI) (b, c) exam employed 24 hours after bilateral intratympanic gadolinium (Gd) injection in a 74-year-old male patient with left Meniere’s disease. (a) 3D-FLAIR MRI reveals Gd entering the bilateral perilymphatic space. Endolymphatic hydrops was identified in the left ear. (b) Black arrow indicates mild endolymphatic space in all turns of the cochlea in the left ear. (c) Dotted lines mark the endolymphatic space, and solid lines mark the perilymphatic space in the vestibule. The area ratio of the endolymphatic space to the vestibular space is 44.9% (i.e., mild hydrops in the vestibule).

Fig. 2. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (a) and three-dimensional real inversion recovery (3D-real IR) magnetic resonance imaging (MRI) (b) exam employed 24 hours after bilateral intratympanic gadolinium (Gd) injection in a 30-year-old male patient with right Meniere’s disease. (a) 3D-FLAIR MRI reveals Gd entering the bilateral perilymphatic space in the inner ear. The right ear exhibits signs of endolymphatic hydrops. (b) Black arrow indicates mild endolymphatic space in all turns of the cochlea in the right ear. The area ratio of the endolymphatic space (dotted lines) to the vestibular space (solid lines) is 63.2% (i.e., significant hydrops in the vestibule).

Fig. 3. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (a) and three-dimensional real inversion recovery (3D-real IR) magnetic resonance imaging (MRI) (b) exam employed 24 hours after bilateral intratympanic gadolinium (Gd) injection in a 52-year-old male patient with right Meniere’s disease. (a) 3D-FLAIR MRI reveals Gd entering the bilateral perilymphatic space. The right ear has signs of endolymphatic hydrops. (b) Black arrow indicates significant endolymphatic space in all turns of the cochlea. The area ratio of the endolymphatic space (dotted lines) to the vestibular space (solid lines) is 66.5% (i.e., significant hydrops in the vestibule).
Spearman correlation analysis revealed a significant correlation between the duration and degree of EH in the vestibule by assessing the area ratio of the endolymphatic space to the vestibular space. Meanwhile, the duration was also significantly correlated with the extension of EH in each turn of the cochlea. PTA thresholds in the affected side at low and middle frequencies were significantly correlated with the extent of EH in all turns of the cochlea. However, there was no significant correlation detected with the vestibule using the Pearson correlation test. The average hearing threshold at high frequency had no significant relationship with EH in the vestibule and all turns of cochlea. Table II reveals the specific statistical data in the study, which indicate the correlation of duration and hearing impairment with EH. When considering tinnitus associated with vertigo or not, no significant difference was detected in the degree of EH in the vestibule and cochlea between these two groups (Table III). Meanwhile, there was no significant difference in the extent of EH in the vestibule and cochlea between affected ears with fullness and those without fullness (Table III).

**DISCUSSION**

It was mainly based on clinical characteristics without histopathological evidence to make the diagnosis for patients with MD while patients were alive. Now, with advanced MRI imaging, it is possible to reveal the boundaries of endolymphatic and perilymphatic spaces inside the inner ear following intratympanic Gd injection. Besides intratympanic Gd injection, delayed intravenous contrast-enhanced 3D-FLAIR MRI of inner ear is another option to visualize the endolymphatic hydrops in the inner ear. It allows the visualization of the bilateral endolymphatic spaces simultaneously without invading tympanic membranes. However, the contrast effect of intravenous administration usually shows less intense than intratympanic application. As for intratympanic Gd injection, no side effect has been reported so far. All individuals in this study were precisely evaluated and exhibited varying degrees of EH in the affected ears by 3D-FLAIR and 3D-real-IR sequences MRI 24 hours after bilateral intratympanic Gd injection. Fifty-four patients suffering from definite MD were included. In this study, a close relationship was detected between specific symptoms of MD and the degree of EH, which may be of value in predicting the severity of EH in specific locations of the inner ear.

We identified a positive correlation between the duration of MD and the expansion of endolymphatic fluid in the vestibule and cochlea. The result indicates MD patients were suffering from deterioration of EH with disease progression. Our results are consistent with Fiorino et al.’s studies. In addition, the present study revealed that the vast majority of patients after their second year of the disease suffered severe EH in the vestibule. Based on this result, clinicians can preliminarily speculate on whether the extent of EH is greater than half of the vestibular fluid space. MD is presumed to be a self-healing disease. Perez-Garrigues

![Fig. 4. Endolymphatic hydrops classified as none (0), mild (1), or significant (2) grading in the vestibule and cochlea of affected ears. Vest = vestibule; CAT = cochlear apical turn; CMT = cochlear middle turn.](image)

**Laryngoscope 00: Month 2015 Wu et al.: Correlation of Symptoms of MD and EH by MRI**

**Fig. 5. Three-dimensional real inversion recovery magnetic resonance imaging (a–c) exam employed 24 hours after bilateral intratympanic injection in a 30-year-old male patient diagnosed with left Meniere’s disease. (a, b) In the affected ear, the endolymphatic space in all turns of the cochlea is clearly visible as mild hydrops marked by a long black arrow. The area ratio of the endolymphatic space (dotted lines) to the vestibular space (solid lines) is 28.7% (i.e., no hydrops in the vestibule). (c) The short black arrow indicates mild endolymphatic hydrops of the cochlea in the contralateral ear.**
et al.\textsuperscript{14} reported that the frequency of vertigo attack diminished until 9 to 20 years, and that most patients would reach a steady state without vertigo when 510 patients with MD were retrospectively reviewed. Meanwhile, recent studies suggest that the hypofunction of the vestibule occurs primarily in the first 5 to 10 years.\textsuperscript{15,16} VEMP is widely used to examine otolith function. A significant association between the degree of EH and VEMP has been established.\textsuperscript{17} Therefore, a dynamic correlation between vestibular function, the degree of EH, and the time course of the disease can be studied by combining advanced MRI imaging and VEMP with the increasing number of patients. Nonetheless, EH in the semicircular canals was not included in this study because, to the best of our knowledge, a reliable and acceptable grade standard of EH in the semicircular canals has not been established. A more reliable relationship between EH and MD duration would be indicated by a long-term repeated MRI follow-up. However, this study is restricted by both patients’ compliance and ethics issues.

Hearing impairment is believed to occur mainly within the first 5 to 10 years of MD disease and then to settle at a mean level of approximately 50 to 60 dB.\textsuperscript{15} The hearing loss at low and middle frequencies was associated with the extent of negative signal area in all turns of the cochlea. In addition, the correlation index in Table II indicated that EH in the apical turn of the cochlea was more correlated with low-tone hearing loss. The finding is compatible with the traveling wave theory that low-frequency hearing is transmitted to the cochlea apex along the basilar membrane. It is well established that the lesion in patients with MD starts from the cochlear apex and spreads to the basal turn, the saccule, utricle, and ampullae as the disease progresses.\textsuperscript{18} In this study, it also indicated that the EH was present from the apical turn to the basal turn according to the probability of EH occurring in the cochlea. However, whether EH initiates from the apical turn of the cochlea or the vestibule or both simultaneously could not be clarified by this study, because the expansion of endolymphatic space solely appearing in the cochlea or the vestibule can be observed in some patients. The reason why high-tone hearing loss did not exhibit a close relationship with EH in the cochlea may be associated with age-related high-tone hearing loss. The peak incidence of MD is 40 to 60 years of age.\textsuperscript{19} The median age for patients to visit doctors was 52 years old in this study. A recent study suggested that a peak curve characterizing the affected ears represented an upward sloping curve after subtracting the normal ear hearing threshold.\textsuperscript{20} To provide a reliable way to examine the correlation between the degree of EH and the high frequency of hearing loss, it may be helpful to exclude the impact of age-related high-tone hearing loss by considering the hearing threshold of unaffected ears.

Tinnitus is a common symptom in MD patients. As reported by Hererra et al.\textsuperscript{21}, tinnitus was the initial presentation in 67\% of cases and the most troublesome symptom in more than half of MD patients. A previous study taking advantage of 3D-FLAIR and 3D-real IR MRI 4 hours after intravenous Gd administration emphasized that patients with fluctuating tinnitus were more likely to exhibit EH than patients with stable tinnitus.\textsuperscript{22} In the present study, we also focused on the correlation between tinnitus and the degree of EH. Tinnitus was present in 98\% of individuals in this study. Therefore, definite MD patients were subdivided into two groups: group A, tinnitus associated with vertigo (tinnitus occurred or deteriorated before vertigo attack); and group B, tinnitus not associated with vertigo attack (stable or irregular tinnitus). The extension of the endolymphatic space did not differ significantly between the above-mentioned two groups either in the vestibule or in the cochlea. Aural fullness, another complaint from many definite MD patients, was reported by 65\% of all subjects in the present study. Aural fullness may be associated with EH via sensory trigeminal fibers.\textsuperscript{23} However, there was no correlation between ear fullness and the degree of EH in either the vestibule or cochlea in this study. The correlation between these two troublesome symptoms (tinnitus and aural fullness) and the

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**Table II.**

Correlation Between Endolymphatic Hydrops and the Duration of Disease as Well as Correlation Between Endolymphatic Hydrops and the Level of Hearing Loss in the Cochlea and Vestibule.

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<th>Cochlea (Mann-Whitney Test)</th>
<th>Vestibule (Two Independent Samples t Test)</th>
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<tbody>
<tr>
<td></td>
<td>Apical</td>
<td>Middle</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>0.422</td>
<td>0.01</td>
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<tr>
<td>Low-tone hearing loss</td>
<td>0.479</td>
<td>0.000</td>
</tr>
<tr>
<td>Middle-tone hearing loss</td>
<td>0.422</td>
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<tr>
<td>High-tone hearing loss</td>
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<td></td>
<td>0.074</td>
<td>0.596</td>
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**Table III.**

Correlation Between Endolymphatic Hydrops and Tinnitus (Associated With Vertigo or Without) and Aural Fullness (Suffering From or Not).

<table>
<thead>
<tr>
<th></th>
<th>Cochlea (Mann-Whitney Test)</th>
<th>Vestibule (Two Independent Samples t Test)</th>
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<tbody>
<tr>
<td></td>
<td>Apical</td>
<td>Middle</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0.524</td>
<td>0.230</td>
</tr>
<tr>
<td>Aural fullness</td>
<td>0.257</td>
<td>0.340</td>
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</table>
pathology of MD is uncertain, and further study with large samples should be conducted. MRI exam identified mild EH in the cochlea of the contralateral ears in nine subjects in the present study. Thus, EH may present in the asymptomatic contralateral ear of unilateral MD patients. Therefore, clinical history alone may not provide a comprehensive and reliable assessment of bilateral MD. Human temporal bone histological studies have also emphasized this viewpoint and have reported a 14% risk of progressing to bilateral MD, which was similar to the 16.7% bilateral MD identified in this study. Morita et al. noted also a history of progression from unilateral to bilateral MD to 21 years after the initial onset. Therefore, regular follow-ups should be considered by clinicians and patients. Although the purpose of bilateral intratympanic Gd injection is to exclude the potential of bilateral EH or identify the responsible ear for vertigo attack in cases of bilateral hearing loss, administration on the asymptomatic contralateral ear may raise concerns about the potential risk on the inner ear. In our study, we observed no adverse effects such as hearing deterioration or vertigo in all patients. The study focusing on the hearing function of healthy volunteers reveals no adverse effects 1 month after intratympanic Gd injection. Meanwhile, no deterioration in auditory function is reported after an average of 19 months postinjection in 17 patients. However, systematic studies with long-term follow-up in a larger scale should still be carried out to confirm the safety of intratympanic Gd injection.

CONCLUSION
Advanced MRI technology provides an accurate examination to visualize endolymphatic spaces in patients with MD. A gradual expansion of the endolymphatic space in the inner ear over time indicates that MD is a progressive disease. Hearing impairment of low and middle frequencies can indirectly reflect the severity of EH in each turn of the cochlea. EH, the pathological basis of MD, may not be the primary cause of tinnitus and aural fullness in patients with MD. Bilateral EH based on the MRI exam in unilateral MD patients indicated that EH could appear in the asymptomatic ear. Therefore, long-term regular follow-up is indispensable for individuals with unilateral MD.

BIBLIOGRAPHY