ORIGINAL ARTICLE

Relationship between Stress Levels and Endolymphatic Space Volume in Meniere's Disease

Running Title: Stress, endolymphatic hydrops and Meniere's disease

ABSTRACT

Objectives:
Since the first report by Hallpike and Yamakawa in 1938, many more patients with Meniere's disease (MD) with endolymphatic hydrops (EHs) have been described. Mental/physical stress and a subsequent increase in the release of the anti-diuretic hormone (ADH) supposedly triggers MD. In the present study, to assess the relationship between stress and EHs, we conducted a series of stress-related questionnaires as well as a 3D endolymphatic space (ELS) analysis in patients with unilateral MD.

Methods:
We enrolled 76 patients with unilateral MD (uMD) as the active group and 75 patients with unilateral benign paroxysmal positional vertigo (uBPPV) as the control group; both underwent examinations between June 2014 and November 2019. All patients underwent 3-T magnetic resonance imaging (MRI) 4 h after intravenous gadolinium injection. We used the total fluid space (TFS), ELS, and ELS rate (ELS/TFS×100), which is the percentage of the volume of the ELS relative to that of the TFS, for a precise evaluation of the ELS and EHs in MD. Stress was evaluated using the Self-Rating Depression Scale (SDS), the psychological Stress Response Scale (SRS), and the modified Dizziness Handicap Inventory (mDHI). Stress scores and blood ADH levels were compared across patient groups.

Results:
In patients with uMD, ELS rates significantly correlated with SRS scores on both the affected and the healthy side and with mDHI scores on the affected side, while the SDS and ADH showed no significant correlation with the ELS rates. Correlations were much stronger in the group with severe SDS and one with low ADH levels.

Conclusions:
The present results indicate that stress may be involved in EHs development in uMD, not only in the ipsilateral but also the contralateral ear. They also suggest that patients with neuropsychiatric tendencies may develop EHs and MD in response to a stressful lifestyle.

Key Words: Meniere's disease; endolymphatic hydrops volume; depression; stress; vasopressin; 3D inner ear MRI

Abbreviations:

ADH: stress related anti-diuretic hormone; uBPPV: unilateral benign paroxysmal positional vertigo; mDHI: modified dizziness handicap inventory; EHs: endolymphatic hydrops; ELS: endolymphatic space; Gd: gadolinium; uMD: unilateral Meniere's disease; SCCs: semicircular canals; SDS: self-rating depression scale; SRS: stress response scale-18; TFS: total fluid space.

1. Introduction

In modern societies, the development of sicknesses including Meniere's disease (MD) is well known to be induced by insufficient adaptation to various types of stress experienced in daily life. The prevalence of MD is 10–20 per 100000 population (1), and its symptoms are commonly characterized by episodic rotatory vertigo, fluctuating sensorineural hearing loss, and persistent tinnitus due to inner ear pathology. Inner ear endolymphatic hydrops (EHs) was first reported as MD oto-pathology through simultaneous temporal bone studies from Osaka (2) and London (3) in 1938. It has since been proposed that the underlying mechanism could be a disorder of the inner ear water metabolism caused by stress-related molecules (4-10).

Elucidating the relationship between stress and MD with EHs may promote the development of another psychotherapeutic strategy to overcome MD. One of the epoch-making neuro-otologic findings in the 21st century was the visualization of the endolymphatic space (ELS) using 3-T MRI with intravenous gadolinium (Gd) injection, reported by Naganawa's group at Nagoya University in 2007 (11); this was followed by the grading of EHs on inner ear MRI following a conventional method in 2009 (12). Additionally, xxxx's group at xxxx were the first in the world, in 2016, to evaluate ELS quantitatively using 3D analysis (13,14). In the present study, to assess the significant relationship between stress and EHs, we conducted a series of stress-related questionnaires as well as a 3D analysis of ELS in patients with unilateral MD (uMD).

2. Materials and methods

2-1. Ethics approval

The present study was approved by our institutional ethics committee (certificate number: 0889) and registered with the UMIN Administration (certificate number: 000018399). All patients agreed to participate in the study patients and signed an informed consent form prepared in accordance with the Declaration of Helsinki.

2-2. Patients

We enrolled 76 patients with uMD as the active group and 75 patients with unilateral benign paroxysmal positional vertigo (uBPPV) as the control group who had agreed to undergo examinations between June 2014 and November 2019. Patients were diagnosed according to the criteria defined in the international guidelines for both diseases (15,16). There were no significant differences in backgrounds between the patients in the two disease groups (age: 56.4±14.3, male/female: 34/42 in MD and age: 60.3±14.3, male/female: 22/53 in BPPV).

2-3. Inner ear MRI

2-3-1. Imaging processes

Naganawa et al. demonstrated the usefulness of MRI performed 4 h after intravenous Gd injection for imaging EHs (11). Thus, in the present study, MRI measurements were acquired 4 h after intravenous administration of a single dose (0.2 mL/kg or 0.1 mmol/kg body weight) of Gd-diethylenetriaminepentaacetic acid dimethylamide (Magnescope; Guerbet, Tokyo, Japan). A 3-T MRI unit (MAGNETOM Verio, Siemens, Erlangen, Germany) with a 32-channel array head coil was used. Special sequences proposed by Naganawa et al., which reveal the endolymphatic and perilymphatic fluids, were adopted.

Heavily T2-weighted (hT2W) MR cisternography was used to obtain an anatomical total lymph fluid reference. hT2W 3D fluid-attenuated inversion recovery sequences with an inversion time of 2250 ms yielded positive perilymph images (PPIs), whereas hT2W 3D inversion recovery sequences with an inversion time of 2050 ms yielded positive endolymph images (PEIs). A hybrid of the reversed image of the positive endolymph signal and the negative image of the positive perilymph signal was obtained by subtracting PEI from PPI.

2-3-2. Volumetric measurements

We used a previously described method for measuring the volume of the total fluid space (TFS) and the endolymphatic space (ELS) (13) and a recently described method for the precise evaluation of the ELS or EH in MD (14). Briefly, the ELS area was first identified on our workstation (Virtual Place; AZE, Ltd., Tokyo, Japan). In this protocol, the ELS voxels show negative signal values and the perilymph space voxels show positive signal values. The PPIs and PEIs were transferred, and the PEIs were subtracted from the PPIs using the fusion program included in the software of our workstation. The borderline between the gray and green areas of the color bar in the subtracted image was considered the zero value. After activation of the SPACE sequence image and the "PPI–PEI" image on our workstation, components of the inner ear were identified on the SPACE sequence image by the border between the inner ear and the peripheral side of the acoustic nerve, between the end of the cochlea and the vestibule, between the three ampullae of the semicircular canals (SCCs) and the vestibule, and between the distal side of the common crus and the vestibule, using anatomical drawings. The volume of the TFS was acquired by automatically counting

voxels on the workstation. The ELS volume was then measured by counting the voxels of the negative signals on the "PPI–PEI" image. Finally, the percentage of the volume of the ELS relative to that of the TFS was calculated and defined as the ELS percentage. These measurements were performed three times, and the average values were used in the present study.

2-4. Depression and stress questionnaires

The questionnaires included the Self-Rating Depression Scale (SDS) (17) and the Stress Response Scale-18 (SRS-18) (18). Patients with SDS scores >40 (possible range: 20–80) were classified as having depression. The SDS consists of ten positively and ten negatively worded items that inquire about symptoms of depression. These scores were used to define two main categories: no significant severe depression (≤55 points) and significant severe depression (≥56 points). The SDS has been translated into Japanese and its validity has been confirmed.

The SRS-18 consists of 18 items that inquire about stressful feelings stemming from a stressful lifestyle. These scores were used to define two main categories: no having significant stress (0–20 points) and significant stress (21-54 points). In this study, we evaluated the scores using standardized scores calculated from the total scores (0-100). The SRS-18 has been published in Japanese and embodies a new concept of psychological measurement.

2-5. Dizziness handicap questionnaires

Validated clinical metrics such as the Dizziness Handicap Inventory (DHI) by Jacobson and Newman (19) are considered the most appropriate method to analyze

subjective dizziness handicap data. The "modified Dizziness Handicap Inventory" (mDHI) in this paper was derived from the DHI" and has been used for the evaluation of everyday handicap due to dizziness in Japanese patients since 1995. It is composed of 14 principal questions and introduced in English (20). The answers to all principal questions are scored from 1 to 5 (severe handicap = 5, significant handicap = 4, moderate handicap = 3, slight handicap = 2, and no handicap = 1) based on apparent symptoms. The score of each factor (F1–F5) is then calculated as the sum of the scores of the three principal questions. Principal questions 1, 5, and 9 are related to factor 1 (F1) = disturbance of social activity due to dizziness; 2, 6, and 10 are related to factor 2 (F2) = body motion precipitating dizziness (head and sight); 3, 7, and 11 are related to factor 3 (F3) = limitation of physical activity (body movement); 4, 8, and 12 are related to factor 4 (F4) = emotional disturbance due to dizziness; and 1, 12, and 13 are related to factor 5 (F5) = disturbance of interpersonal communications due to dizziness.

2-6. Blood tests

Blood samples were collected between 8:00 am and 10:00 am during vertigo remission to minimize the effects of circadian variation. Blood for the stress-related anti-diuretic hormone (ADH) assay was transferred into an ethylene-diamine-tetraacetic acid tube, centrifuged at 4 °C, and the separated plasma was stored at −80 °C. ADH levels were analyzed using a radioimmunoassay. At our hospital, an ADH ≥2.8 pg/mL is considered positive (5,6).

2-7. Statistical analysis

Chi-square tests and the Mann–Whitney test were used to compare the two groups. Spearman's correlation and Wilcoxon's test were performed to examine statistical correlations between the various scores and the ELS rates. Correlation strength was determined to compare the two groups using one-way analysis of variance (ANOVA). Statistical significance was set at $p<0.05$, using the Statistical Package for the Social Sciences (SPSS) version 24.0 (Chicago, IL, USA).

3. Results

The TFS and ELS rates for all parts of the inner ear in the MD and the BPPV group are shown in Table 1.

In the MD group (Table 1A), the TFS and ELS rates of each region of the inner ear were significantly higher on the affected side than on the healthy side. In the BPPV group (Table 1B), there was no statistically significant difference in TFS or ELS rates between the bilateral sides.

The relationships between ELS rates derived from inner ear MR images and stress levels determined through the questionnaires/hormones are shown in Table 2.

In the MD group (Table 2A), correlations between SDS scores and ELS rates showed no statistical significance ($p>0.05$) on either side. The correlation coefficients between SRS total scores and ELS rates on the affected side were 0.23 ($p=0.04$) in the cochlea and 0.23 ($p=0.04$) in the SCCs; on the healthy side, the coefficients were 0.23 ($p=0.04$) in the whole inner ear and 0.23 ($p=0.04$) in the cochlea, indicating significance. Furthermore, the correlation coefficients between SRS depression-anxiety scores and ELS rates on the affected side were 0.24 ($p=0.04$) in the whole inner ear, 0.24 ($p=0.04$) in the cochlea, and 0.24 ($p=0.04$) in the SCCs; on the healthy side, they were 0.28

(p=0.02) in the whole inner ear, 0.30 (p=0.01) in the cochlea, 0.25 (p=0.03) in the vestibule, and 0.23 (p=0.04) in the SCCs, likewise indicating significance. The correlation coefficients between mDHI scores and vestibular ELS rates on the affected side were also significant, at 0.26 (p=0.02) in F1, 0.27 (p=0.02) in F2, 0.30 (p=0.01) in F4, and 0.27 (p=0.02) in F5. Correlations between blood ADH levels and ELS rates showed no statistical significance ($p > 0.05$) on either side.

In the BPPV group (Table 2B), correlations between stress questionnaire scores/hormones and ELS rates in any part of the inner ear showed no statistical significance ($p>0.05$).

Furthermore, we assessed the correlation strength between the ELS rates of all parts of the inner ear and SRS stress scores (Table 3A), for one group with severe mental illness and one non-severe illness group, based on a cut-off SDS score of 56 (severe: n=8, non-severe: n=67). The correlation coefficients between the SRS helplessness scores and the whole inner ear ELS rates (affected: p=0.04; healthy: p=0.0001) as well as the cochlear ELS rates (affected: p=0.01; healthy: p=0.00003) on both sides were significantly higher in the severely ill than in the non-severely ill group (Figure 1). On the other hand, there were no significant stress and ELS rates interactions between BPPV subgroups according to SDS scores (data not shown).

In addition, we assessed the correlation strength between the ELS rates of all parts of the inner ear and the mDHI (Table 3B), for two groups with high and low ADH levels based on a cut-off blood level of 2.8 (high: n=24, low: n=52). Correlations between factors 1 (p=0.04), 4 (p=0.02), and 5 (p=0.04) of the mDHI and the whole inner ear ELS rate on the affected side were also significantly stronger in the low than in the high ADH group (Figure 2). On the other hand, there were no significant

dizziness handicaps and ELS rates interactions between BPPV subgroups according to ADH levels (data not shown).

4. Discussion

In the present study, uMD ELS rates were significantly correlated with SRS scores in the bilateral inner ear and the mDHI factor in the affected inner ear. This suggests that EHs is significantly correlated with stress levels in uMD, on both the affected and the healthy side, and that stress may cause EHs and symptom expression not only in unilateral but also in bilateral MD. The relationship between stress and MD has been reported in several epidemiological studies, and our intriguing results corroborate these earlier ones (21–23). Moreover, the fact that the volume of the endolymphatic cavity, especially in the affected vestibule, interferes with daily life due to dizziness supports a prior report on temporal bone pathology that demonstrated that edema of uMD occurs more frequently in the affected vestibule (24). Early diagnosis and treatment at the stage of increased EHs are important for rapid symptomatic improvement (15).

BPPV is a non-EH disease, and we found no correlation between ELS rates and other factors in this study. Therefore, not every individual will develop EHs and then MD, if subjected to high levels of stress. We suppose that the SRS scores and mDHI factors significantly correlated with the ELS rates, because the MD group had some characteristics that the BPPV group did not have. Previous reports have shown that the neuropsychiatric complication rate of MD is significantly higher in bilateral than in unilateral cases, and that it is clearly higher than that of other dizziness hearing loss disorders, including BPPV (25-27). Although we found no significant correlation

between SDS scores and ELS rates (assessed with Pearson's correlation coefficient) in the present study, when the MD group was divided into two subgroups (those with severe and those with non-severe illness), stress levels were more strongly correlated with the whole inner ear and cochlear ELS rates in the severe group than in the non-severe group, both on the affected and on the healthy side. That is, the severe group was more likely to develop EHs due to stress than the non-severe group. Several reports of increased stress sensitivity due to neuropsychiatric disorders (28,29) as well as the present results point to a neuropsychiatric mechanism underlying the development of EHs and MD; they also suggest that EHs may occur when individuals are exposed to high levels of stress (33). Further genetic investigations might be needed to elucidate the different mechanisms in stress-sensitive inner ear between MD and the others.

High blood levels of ADH, a hormone that causes water retention in tissues in association with stress, have been reported in MD cases with EHs (5,6). Although we observed no significant correlation between blood ADH levels and inner ear ELS rates in the present study, ADH levels tended to be lower and ELS rates tended to increase. We therefore conducted a sub-analysis by dividing patients into two groups according to blood ADH levels: a group with high levels (above 2.8) and one with low levels (below 2.8). The correlations between stress scores and total inner ear ELS rates, mDHI scores, total inner ear ELS rates, mDHI scores, and vestibular ELS rates were also significantly stronger on the affected side in the low-stress group than in the high-stress group. In other words, the low ADH group was more likely to develop EHs due to stress than the high ADH group and was more likely to experience disruption in their lives due to dizziness. Previous studies have shown a negative correlation

between blood ADH levels and inner ear V2 receptor levels (6,7), suggesting that cases with blood ADH levels in the normal range and increased inner ear V2 receptor levels may develop EHs and MD when subjected to significant stress.

There are several limitations to this study. Blood ADH levels follow a circadian rhythm, and the blood collection should be conducted regularly, during the early morning hours. In this study, blood was collected in the early morning whenever possible; however, it is undeniable that there may have been some variation. Second, the present study was limited to patients who consented to undergo examinations and hospitalization. A bias in the refractoriness of the patients' vertigo symptoms, their temperament, and their personality may thus have occurred.

The results of this study will help to prevent the development of MD and treat the disease. Cases with stress-sensitive neuropsychiatric tendencies have been shown to involve unilateral and bilateral EHs formation and possible MD development. Therefore, we believe controlling neuropsychiatric disorders and reducing stress can prevent EHs formation and MD onset. Cognitive-behavioral therapy, developed by Beck et al. in the 1970s as a psychotherapeutic treatment for depression, has been shown to be effective in treating anxiety, stress-related, and other psychiatric disorders, as well as in preventing relapse (31). Furthermore, the indications for this treatment have been expanded to include problems such as coping with everyday stress (32). Psychological support through cognitive-behavioral therapy may prevent EHs and MD onset if stress and anxiety are reduced. Suppressing blood ADH and inner ear V2 receptor levels could also be important for the development of new treatments for MD. Indeed, there are a number of reports indicating that suppressing blood ADH levels through fluid intake, tympanic tubes, dark sleep, and even

endolymphatic sac surgery has a significant impact on improving therapeutic outcomes (33,34). The potential of this approach for stress hormone management is promising, as it is a step forward from less feasible stress relief therapies that require a long-term course of treatment and can be indexed by realistic and easy-to-understand biomarkers.

5. Conclusion

We studied the correlation between ELS rates derived from inner ear MR images and stress levels determined through questionnaires/hormones in uMD. We found that stress scores were significantly correlated with ELS rates on both the affected and the healthy side, and that dizziness scores correlated with those, but only on the affected side; depression scores or stress hormone ADH levels were not significantly correlated. In a group of patients with uMD with severe SDS, there was a much stronger correlation between stress scores SRS and ELS rates on both the affected and the healthy side. In uMD patients with low ADH levels, there was a much stronger correlation between mDHI-defined dizziness handicap and ELS rates only on the affected side. In the control group of patients with uBPPV, no significant correlation was found between ELS rates derived from inner ear MR images and stress levels determined through questionnaires/hormones.

The present results indicate that stress may be involved in EHs development in uMD, not only in the ipsilateral but also the contralateral ear. They also suggest that patients with neuropsychiatric tendencies may develop EHs and then MD in response to a stressful lifestyle.

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Conflicts of Interest

The authors have no conflicts of interest related to the present study to declare.

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Tables

Table I: TFS and ELS rates for all parts of the inner ear

A: In the unilateral MD group, the TFS and ELS rates in each region of the inner ear were significantly higher on the affected than on the healthy side.

B: In the unilateral BPPV group, there was no statistically significant difference in TFS or ELS rates between the two sides.

Values are expressed as the mean number $\pm$S.D. of ELS rates.

*: $p<0.05$; *** $p<0.0005$.

BPPV, benign paroxysmal positional vertigo; ELS, endolymphatic space; MD, Meniere's disease; SCCs, semicircular canals; TFS, total fluid space.

Table II: Relationships between ELS rates derived from inner ear MR images and stress levels determined through questionnaires/hormones

A: In the MD group, correlations between SDS and ELS rates showed no statistical significance ($p>0.05$) on either side. The correlation coefficients between SRS total scores and ELS rates on the affected side were 0.23 ($p=0.04$) in the cochlea and 0.23 ($p=0.04$) in the SCCs; on the healthy side they were 0.23 ($p=0.04$) in the whole inner ear and 0.23 ($p=0.04$) in the cochlea, indicating a significant correlation. The correlation coefficients between SRS depression-anxiety scores and ELS rates on the affected side were 0.24 ($p=0.04$) in the whole inner ear, 0.24 ($p=0.04$) in the cochlea, and 0.24 ($p=0.04$) in the SCCs; on the healthy side they were 0.28 ($p=0.02$) in the whole inner ear, 0.30 ($p=0.01$) in the cochlea, 0.25 ($p=0.03$) in the vestibule, and 0.23 ($p=0.04$) in the SCCs, likewise indicating a significant difference. The correlation coefficients between mDHI scores and vestibular ELS rates on the affected side were also significant: 0.26 ($p=0.02$) in F1, 0.27 ($p=0.02$) in F2, 0.30 ($p=0.01$) in F4, and 0.27 ($p=0.02$) in F5. Correlations between blood ADH levels and ELS rates showed no statistical significance ($p>0.05$) on either side.

B: In the BPPV group, the correlations between stress questionnaires scores/hormone levels and ELS rates in any part of the inner ear showed no statistical significance ($p>0.05$).

*: $p<0.05$.

ADH, stress-related anti-diuretic hormone; BPPV, benign paroxysmal positional vertigo; mDHI, modified Dizziness Handicap Inventory; ELS, endolymphatic space; MD, Meniere's disease; SCCs, semicircular canals; SDS, Self-Rating Depression Scale; SRS, Stress Response Scale-18.

Table IIIA: Strong correlations between ELS rates of all parts of the inner ear and stress scores under severe mental distress

Correlation strength between the ELS rates of all parts of the inner ear and SRS stress scores was assessed for two subgroups, one with severe (n=8) and one with non-severe illness (n=67), based on a SDS cut-off score of 56.

*: $p<0.05$; ** $p<0.005$, *** $p<0.0005$.

ELS, endolymphatic space; SCCs, semicircular canals; SDS, Self-Rating Depression Scale; SRS, Stress Response Scale-18.

Table IIIB: Strong correlations between ELS rates of all parts of the inner ear and dizziness handicap in patients with low ADH blood levels

Correlation strength between the ELS rates of all parts of the inner ear and dizziness handicap was assessed for two subgroups, one with high (n=24) and one with low ADH levels (n=52), based on a cut-off blood level of 2.8.

*: $p<0.05$.

ADH, stress-related anti-diuretic hormone; mDHI, modified Dizziness Handicap Inventory; ELS, endolymphatic space; SCCs, semicircular canals.

Figure Legends

Figure 1: Strong correlations between ELS rates in the inner ear and stress scores under severe mental distress

Correlations between SRS helplessness scores and whole inner ear ELS rates (A affected: p=0.04; C healthy: p=0.0001) and cochlear ELS rates (B affected: p=0.01; D healthy: p=0.00003) were significantly stronger (on both sides) in the severe SDS group than in the non-severe group (see Table 3).

ELS, endolymphatic space; SDS, Self-Rating Depression Scale; SRS, Stress Response Scale-18.

Figure 2: Strong correlations between ELS rates in the inner ear and dizziness handicap in patients with low ADH levels

Correlations between factors 1 (p=0.04), 4 (p=0.02), and 5 (p=0.04) of the mDHI and the whole inner ear ELS rates on the affected side were significantly stronger in the low ADH than in the high ADH group (see Table 4).

ADH, stress-related anti-diuretic hormone; mDHI, modified Dizziness Handicap Inventory; ELS, endolymphatic space.

Figure

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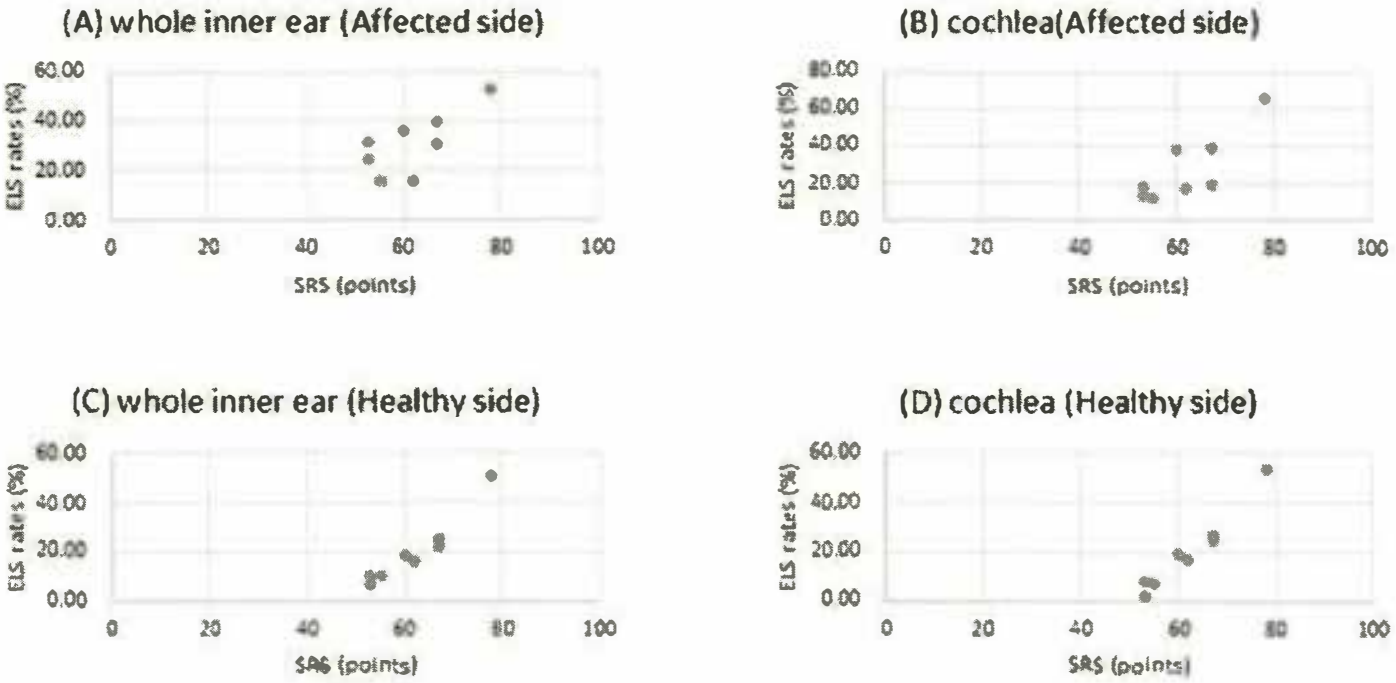

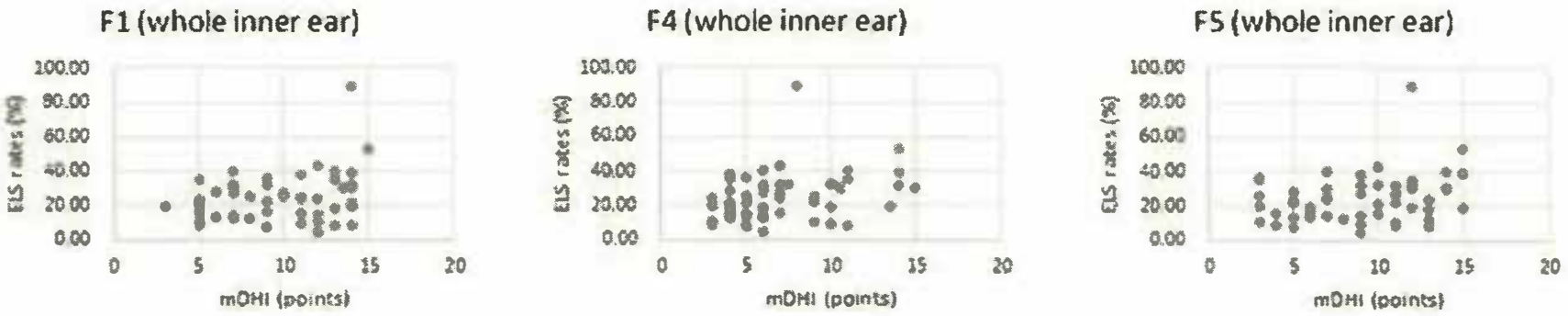

supplemental data 1

	MD (Healthy side)	BPPV (Affected side)		p value
	mean ± SD	mean ± SD		
whole	0.29±0.03	0.29±0.04	[ml]	0.52
	18.8±14.7	15.1±10.1	[%]	0.09
cochlea	0.11±0.02	0.10±0.02	[ml]	0.12
	16.7±15.9	12.5±12.0	[%]	0.09
vestibule	0.07±0.01	0.07±0.01	[ml]	0.11
	21.8±17.2	17.7±11.8	[%]	0.10
SCCs	0.11±0.02	0.12±0.02	[ml]	0.27
	19.1±14.2	16.0±10.7	[%]	0.15

supplemental data 2

		Affected side				Healthy side			
		whole	cochlea	vestibule	SCCs	whole	cochlea	vestibule	SCCs
SRS (SDS≥56)	Depression-Anxiety	-0.05 p=0.89	-0.23 p=0.53	-0.31 p=0.38	-0.43 p=0.22	-0.54 p=0.11	-0.54 p=0.11	-0.44 p=0.21	-0.12 p=0.74
	Irritability-Anger	-0.40 p=0.25	-0.12 p=0.74	-0.56 p=0.09	-0.11 p=0.76	-0.38 p=0.28	-0.27 p=0.44	-0.24 p=0.51	-0.07 p=0.84
	Helplessness	-0.45 p=0.19	-0.46 p=0.19	-0.58 p=0.08	-0.06 p=0.86	-0.77 p=0.009*	-0.65 p=0.04*	-0.61 p=0.06	-0.17 p=0.64
	Total	-0.31 p=0.39	-0.19 p=0.59	-0.52 p=0.12	0.20 p=0.58	-0.59 p=0.07	-0.45 p=0.19	-0.44 p=0.20	-0.02 p=0.95
SRS (SDS<56)	Depression-Anxiety	-0.12 p=0.38	-0.14 p=0.29	-0.09 p=0.51	-0.07 p=0.58	0.01 p=0.96	-0.03 p=0.85	-0.01 p=0.93	-0.03 p=0.82
	Irritability-Anger	-0.12 p=0.36	-0.14 p=0.30	-0.12 p=0.39	-0.06 p=0.65	-0.02 p=0.90	-0.14 p=0.31	0.01 p=0.91	-0.05 p=0.69
	Helplessness	-0.09 p=0.50	-0.10 p=0.45	-0.11 p=0.43	-0.05 p=0.70	-0.03 p=0.82	-0.08 p=0.55	0.03 p=0.81	-0.04 p=0.76
	Total	-0.12 p=0.35	-0.15 p=0.28	-0.11 p=0.42	-0.07 p=0.60	-0.02 p=0.87	-0.09 p=0.48	-0.02 p=0.90	0.005 p=0.97

Table-I
(A)

	Affected side	Healthy side		p value
	mean ± SD	mean ± SD		
whole	0.29±0.03	0.29±0.03	[ml]	0.81
	24.3±13.9	18.8±14.7	[%]	0.019*
cochlea	0.11±0.02	0.11±0.16	[ml]	0.87
	22.3±16.4	16.7±15.9	[%]	0.026*
vestibule	0.07±0.01	0.07±0.01	[ml]	0.76
	34.8±21.7	21.8±17.2	[%]	0.000079***
SCCs	0.11±0.02	0.11±0.02	[ml]	0.76
	20.0±15.2	19.1±14.2	[%]	0.69

Table-I
(B)

	Affected side	Healthy side		p value
	mean ± SD	mean ± SD		
whole	0.29±0.04	0.29±0.04	[ml]	0.93
	15.1±10.1	14.8±11.1	[%]	0.86
cochlea	0.10±0.02	0.10±0.02	[ml]	0.92
	12.5±12.0	13.1±12.7	[%]	0.79
vestibule	0.07±0.01	0.07±0.06	[ml]	0.33
	17.7±11.8	16.8±11.9	[%]	0.67
SCCs	0.12±0.02	0.13±0.12	[ml]	0.31
	16.0±10.7	16.2±12.4	[%]	0.91

Table-II
(A)

		Affected side				Healthy side			
		whole	cochlea	vestibule	SCCs	whole	cochlea	vestibule	SCCs
SDS		0.19 p=0.10	0.18 p=0.13	0.11 p=0.34	0.20 p=0.09	0.18 p=0.13	0.17 p=0.14	0.12 p=0.31	0.16 p=0.16
SRS	Depression-Anxiety	0.24 p=0.04*	0.24 p=0.04*	0.13 p=0.25	0.24 p=0.04*	0.28 p=0.02*	0.30 p=0.01*	0.25 p=0.03*	0.23 p=0.04*
	Irritability-Anger	0.15 p=0.19	0.14 p=0.23	0.05 p=0.70	0.20 p=0.09	0.17 p=0.15	0.15 p=0.20	0.12 p=0.29	0.17 p=0.14
	Helplessness	0.20 p=0.09	0.21 p=0.07	0.13 p=0.26	0.16 p=0.18	0.15 p=0.21	0.15 p=0.20	0.10 p=0.40	0.15 p=0.21
	Total	0.22 p=0.05	0.23 p=0.04*	0.11 p=0.34	0.23 p=0.04*	0.23 p=0.04*	0.23 p=0.04*	0.18 p=0.12	0.21 p=0.07
mDHI	F 1	0.15 p=0.20	0.10 p=0.40	0.26 p=0.02*	0.08 p=0.50	-0.02 p=0.88	-0.05 p=0.68	-0.03 p=0.83	0.04 p=0.76
	F2	0.17 p=0.15	0.08 p=0.50	0.27 p=0.02*	0.14 p=0.25	0.01 p=0.91	0.03 p=0.77	0.04 p=0.73	-0.01 p=0.95
	F3	0.15 p=0.20	0.05 p=0.64	0.22 p=0.06	0.16 p=0.18	0.04 p=0.76	0.02 p=0.85	0.56 p=0.64	0.04 p=0.71

	F4	0.22 p=0.06	0.19 p=0.10	**0.30** **p=0.01***	0.09 p=0.44	0.09 p=0.46	0.10 p=0.39	0.11 p=0.33	0.05 p=0.67
	F5	0.18 p=0.12	0.16 p=0.17	**0.27** **p=0.02***	0.08 p=0.52	0.06 p=0.62	0.05 p=0.70	0.11 p=0.34	0.05 p=0.66
ADH		-0.09 p=0.44	-0.04 p=0.71	-0.13 p=0.25	-0.06 p=0.61	-0.06 p=0.59	-0.03 p=0.81	-0.11 p=0.32	-0.06 p=0.61

Table-II
(B)

		Affected side				Healthy side			
		whole	cochlea	vestibule	SCCs	whole	cochlea	vestibule	SCCs
SDS		-0.06 p=0.63	-0.10 p=0.41	-0.05 p=0.70	-0.02 p=0.90	-0.05 p=0.71	-0.03 p=0.79	-0.10 p=0.42	0.10 p=0.40
SRS	Depression-Anxiety	-0.01 p=0.42	-0.17 p=0.16	-0.10 p=0.41	-0.01 p=0.93	-0.03 p=0.82	-0.04 p=0.72	-0.06 p=0.64	0.07 p=0.55
	Irritability-Anger	-0.13 p=0.28	-0.16 p=0.19	-0.19 p=0.12	-0.03 p=0.79	-0.05 p=0.67	-0.12 p=0.33	-0.04 p=0.77	0.08 p=0.52
	Helplessness	-0.01 p=0.42	-0.15 p=0.22	-0.14 p=0.25	-0.02 p=0.90	-0.07 p=0.57	-0.09 p=0.46	-0.04 p=0.74	0.02 p=0.88
	Total	-0.01 p=0.35	-0.17 p=0.16	-0.14 p=0.26	-0.01 p=0.91	-0.06 p=0.65	-0.08 p=0.50	-0.04 p=0.72	0.06 p=0.61
mDHI	F 1	0.02 p=0.84	0.02 p=0.89	-0.03 p=0.79	0.04 p=0.74	0.02 p=0.87	-0.03 p=0.83	0.04 p=0.73	0.06 p=0.64
	F2	0.10 p=0.41	0.11 p=0.39	0.05 p=0.70	0.10 p=0.41	0.04 p=0.72	0.005 p=0.97	0.06 p=0.66	0.59 p=0.63
	F3	-0.003 p=0.98	0.06 p=0.64	-0.01 p=0.92	-0.06 p=0.64	-0.10 p=0.44	0.001 p=0.93	-0.16 p=0.18	-0.04 p=0.74

	F4	-0.02 p=0.90	-0.05 p=0.66	-0.10 p=0.41	0.07 p=0.55	-0.02 p=0.86	-0.44 p=0.72	-0.12 p=0.31	0.06 p=0.64
	F5	-0.003 p=0.98	0.002 p=0.99	-0.06 p=0.61	0.02 p=0.87	-0.03 p=0.78	-0.07 p=0.57	-0.03 p=0.80	0.01 p=0.91
ADH		-0.18 p=0.15	-0.22 p=0.07	-0.17 p=0.17	-0.07 p=0.59	-0.09 p=0.48	-0.08 p=0.52	-0.08 p=0.53	-0.10 p=0.43

Table-III

A

		Affected side				Healthy side			
		whole	cochlea	vestibule	SCCs	whole	cochlea	vestibule	SCCs
SRS (SDS≥56)	Depression-Anxiety	0.48 p=0.21	0.58 p=0.12	0.17 p=0.67	0.10 p=0.80	0.65 p=0.08	0.76 P=0.03*	0.53 p=0.17	0.50 p=0.20
	Irritability-Anger	0.004 p=0.99	0.08 p=0.85	-0.39 p=0.33	0.25 p=0.54	0.38 p=0.34	0.33 p=0.42	0.20 p=0.63	0.47 p=0.22
	Helplessness	0.73 P=0.04*	0.82 P=0.01*	-0.05 p=0.90	0.58 p=0.12	0.96 P=0.0001***	0.98 P=0.00003***	0.87 P=0.004**	0.88 P=0.04*
	Total	0.46 p=0.24	0.55 p=0.15	-0.12 p=0.76	0.38 p=0.34	0.78 P=0.02*	0.79 P=0.02*	0.61 p=0.10	0.79 P=0.04*
SRS (SDS<56)	Depression-Anxiety	0.14 p=0.22	0.15 p=0.22	0.02 p=0.85	0.21 p=0.07	0.25 P=0.03*	0.23 p=0.06	0.26 P=0.03*	0.22 p=0.07
	Irritability-Anger	0.10 p=0.40	0.10 p=0.40	0.01 p=0.90	0.14 p=0.24	0.14 p=0.23	0.10 p=0.43	0.14 p=0.25	0.15 p=0.21
	Helplessness	0.10 p=0.43	0.11 p=0.38	0.08 p=0.53	0.07 p=0.55	0.07 p=0.56	0.05 p=0.71	0.05 p=0.68	0.09 p=0.48
	Total	0.12 p=0.29	0.14 p=0.26	0.04 p=0.77	0.16 p=0.18	0.18 p=0.13	0.13 p=0.26	0.17 p=0.16	0.18 p=0.13

B

		Affected side				Healthy side			
		whole	cochlea	vestibule	SCCs	whole	cochlea	vestibule	SCCs
mDHI (ADH≤2.8)	F1	0.29 p=0.04*	0.26 p=0.06	0.29 p=0.04*	0.22 p=0.11	0.09 p=0.51	-0.23 p=0.27	0.16 p=0.26	0.15 p=0.28
	F2	0.17 p=0.21	0.11 p=0.41	0.24 p=0.08	0.14 p=0.29	0.01 p=0.92	0.02 p=0.92	0.09 p=0.54	-0.03 p=0.82
	F3	0.18 p=0.18	0.08 p=0.55	0.24 p=0.09	0.19 p=0.18	0.03 p=0.84	0.03 p=0.87	0.09 p=0.52	0.02 p=0.90
	F4	0.32 p=0.02*	0.30 p=0.03*	0.34 p=0.02*	0.17 p=0.21	0.14 p=0.32	-0.03 p=0.88	0.19 p=0.17	0.06 p=0.66
	F5	0.29 p=0.04*	0.28 p=0.04*	0.28 p=0.04*	0.19 p=0.16	0.17 p=0.22	-0.17 p=0.43	0.24 p=0.08	0.15 p=0.28
mDHI (ADH>2.8)	F1	-0.27 p=0.20	-0.38 p=0.07	0.13 p=0.52	-0.31 p=0.14	-0.24 p=0.26	0.05 p=0.74	-0.22 p=0.29	-0.23 p=0.27
	F2	0.14 p=0.51	-0.01 p=0.04*	0.30 p=0.15	0.12 p=0.57	-0.03 p=0.87	0.05 p=0.70	-0.04 p=0.86	0.08 p=0.72
	F3	0.03 p=0.88	-0.03 p=0.87	0.12 p=0.55	0.07 p=0.74	0.06 p=0.77	0.02 p=0.88	-0.005 p=0.98	0.12 p=0.56
	F4	-0.04 p=0.86	-0.06 p=0.77	0.19 p=0.38	-0.10 p=0.65	0.001 p=0.99	0.18 p=0.19	-0.005 p=0.98	0.03 p=0.87
	F5	-0.10 p=0.63	-0.15 p=0.46	0.22 p=0.31	-0.21 p=0.34	-0.14 p=0.51	-0.16 p=0.23	-0.10 p=0.64	-0.16 p=0.45