The Journal of International Advanced Otology

J Int Adv Otol 2017; 13(3): 379-84 • DOI: 10.5152/iao.2017.4311

Original Article

Ear Fullness as a Symptom of Endolymphatic Hydrops in non-Ménière's Patient

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Cite this article as: Maheau M, Alhabib SF, Landry SP, Nader ME, Champoux F, Saliba I. Ear fullness as a Symptom of Endolymphatic Hydrops in non-Ménière's Patient. J Int Adv Otol 2017; 13: 379-84.

OBJECTIVE: 1) To determine if unexplained ear fullness might be a symptom of endolymphatic hydrops (EH) by using Electrocochleography (ECochG) SP/AP area and amplitude ratios. 2) To assess if individuals with unexplained ear fullness without vertigo differ significantly from individuals with ear fullness due to Ménière's disease (MD).

MATERIALS and METHODS: In a case-control study in our tertiary care center, we evaluated 62 ears across 49 patients, including 18 normal healthy ears across 12 control patients, 26 ears with unexplained ear fullness across 20 patients (6 had bilateral symptoms of ear fullness), and 18 ears with definite MD across 17 patients (1 bilateral disease). Outcome measures were SP/AP amplitude and area ratio, hearing threshold, and air-bone gap.

RESULTS: The analysis of auditory thresholds revealed a significant group effect for air conduction [$F(2,50)=49.627$; $p<0.001$] and for bone conduction [$F(2,50)=45.625$; $p<0.001$]. We observed significant differences between MD (36.36±4.87) and control patients (19.85±2.55) ($p=0.015$) for amplitude ratio. Moreover, significant differences were noted between MD (5.32±1.06) and controls (1.36±0.07) ($p=0.035$) and between ear fullness (5.16±1.17) and controls ($p=0.026$) for the area ratio parameter. No significant correlation was observed between SP/AP area or amplitude ratios and air-bone gap at any of the tested frequencies. The amplitude ratio was not significantly different between the ear fullness and control groups ($p=0.406$). The area and amplitude ratios did not reveal significant differences between MD and ear fullness ($p=1.00$).

CONCLUSION: EH can be present even in the absence of vertigo and when patients report unexplained ear fullness. This study, to our knowledge, is the first to possibly allow early identification of cochlear EH in patients suffering from ear fullness without vertigo.

KEYWORDS: Ménière disease, electrocochleography, ear fullness, hydrops, eustachian tube dysfunction, ECoG

INTRODUCTION

Ear fullness is often associated with a possible Eustachian tube dysfunction. This pathology can be identified by pneumo-otoscopy and tympanometry. However, further investigation is warranted when these tests are within normal limits and complaints of ear fullness are still present. Ear fullness is also one of the main symptoms of Ménière's disease (MD). The diagnosis of MD is divided into four different categories based on the presence and severity of four different symptoms - fluctuating hearing loss, episodic vertigo, tinnitus, and ear fullness [1, 2]. The presence of vertigo for more than twenty minutes needs to be identified, based on the actual diagnostic criteria, in order to diagnose MD [2]. More specifically, a patient who is experiencing unexplained ear fullness without reporting vertigo cannot be diagnosed as MD. This situation can sometimes leave patients complaining of ear fullness symptoms without both proper diagnosis and effective treatment.

Endolymphatic hydrops (EH) is thought to be the pathophysiological mechanism associated with MD [3-5]. EH is commonly described as a dysfunction of fluid homeostasis in the inner ear that induces distension within the endolymphatic duct [6]. Electrocochleography (ECochG), a measure of electrical activity from the cochlea and the auditory nerve, is considered to be the only objective electrophysio-

This study was presented at the 123rd Congress of the French Society of ORL HNS, 7-10 October 2016, Paris, France

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Submitted: 20.07.2017 **Revision received:** 25.11.2017 **Accepted:** 28.11.2017

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logical tool able to measure EH [7-9]. This electrophysiological procedure is composed of three auditory evoked potential parameters - Cochlear Microphonic (CM), Summating Potential (SP), and Action Potential (AP) [10,11]. CM is thought to originate from the outer hair cells and is polarity dependent [12, 13]. CM is thus cancelled when using alternating polarity. The SP is generated by the inner hair cells [9, 14], and the AP is generated from the auditory nerve cells (N1) [12].

ECochG analysis for the identification of EH has long been based only on the ratio between SP and AP amplitudes. An increased SP amplitude ratio is typically interpreted as possible EH. Elevation of the SP/AP amplitude ratio has been shown to have high specificity (90%), but poor sensitivity (55% to 65%), for the identification of EH [14]. Over the past few years, efforts have been made toward the improvement of ECochG sensitivity. It has been demonstrated that the use of the SP/AP area ratio when combined with the SP/AP amplitude ratio significantly increases ECochG's sensitivity (92%) without affecting its specificity, which remains as high as 84% [14].

Yen et al. [15] found a correlation between reduction of ear fullness and endolymphatic sac surgery, which has been suggested to have a possible relation between ear fullness and EH. Based on this, we hypothesize that individuals with unexplained ear fullness have significantly higher SP/AP area ratio and SP/AP amplitude ratio compared to healthy individuals. Verification of this hypothesis would indicate that the key symptom in EH diagnosis would be ear fullness with or without the presence of vertigo. Our second hypothesis is that individuals with unexplained ear fullness without vertigo and individuals with MD do not show significant differences for SP/AP area and amplitude ratios. Verification of this hypothesis would suggest that EH is the underlying pathophysiology of these two groups.

The main objective of this study was to determine if unexplained ear fullness might be a symptom of EH by using ECochG SP/AP area and amplitude ratios. The second objective was to determine if individuals with unexplained ear fullness without vertigo differ significantly from individuals with ear fullness due to MD.

MATERIALS and METHODS

Patients

Patients with definite MD or unexplained ear fullness were followed in our tertiary care center between 2014 and 2015. We evaluated 62 ears across 49 patients, including 18 normal healthy ears across 12 control patients, 26 ears with unexplained ear fullness across 20 patients (6 had bilateral symptoms of ear fullness), and 18 ears with definite MD across 17 patients (1 patient received bilateral diagnosis of definite MD).

The inclusion criteria for all three groups were no history of surgery in the tested ear, normal tympanogram, no unexplained air-bone gap (ABG) on audiogram, and hearing thresholds of 60 dBHL or lower for each frequency from 500 Hz to 8000 Hz. This last inclusion criterion is based on the studies of Ferraro et al. [14] where ECochG was performed using a tympanic electrode.

The control group presented normal hearing thresholds, did not report any history of vertigo, ear fullness, tinnitus, or fluctuation in hearing. We excluded six ears within the normal healthy control group because of unilateral middle ear problems and technical issues.

Patients with ear fullness were presented with intermittent or constant ear fullness in one or both ears. Patients with a previous history of vertigo were excluded.

The study was approved by the institutional research ethics board and followed the standards of our institutional ethics committee. Verbal informed consent was obtained from patients.

Procedure and Equipment

Every participant underwent otoscopic examination under a microscopic vision, a hearing test (Itera II, Otometrics, USA), tympanometry, acoustic reflexes evaluation (Otoflex, Otometrics, USA), and ECochG recording (Smart EP, IHS, USA) using tympanic electrodes (Lilly TM Wick, Intelligent Hearing System, USA). We selected tympanic electrodes to maximize the auditory potential amplitudes. Moreover, because they are less invasive then intra-tympanic electrodes they allowed the evaluation to be performed in a clinical setting.

Stimulus and Recording Parameters

The electrode setup and the recording parameters that we used in this study were based upon the study reported by Ferraro [16]. The ground electrode was placed on the forehead (Fz), the active electrode was placed on the eardrum, and the reference electrode was placed on the contralateral mastoid. We used insert earphones delivering a broadband click with an alternating polarity at 90 dBnHL to evoke the SP and AP components. The stimulus rate was 7.1 clicks/s, and we used 512 repetitions per trial. We obtained three repeatable trials and added the tracing before labeling the curve.

SP/AP Amplitude Ratio and SP/AP Area Ratio Calculation

The SP/AP amplitude ratio and SP/AP area ratio were based on Ferraro [16]. The SP and the AP amplitudes were measured from the waveform peak and compared to the pre-stimulus baseline (Figure 1). The

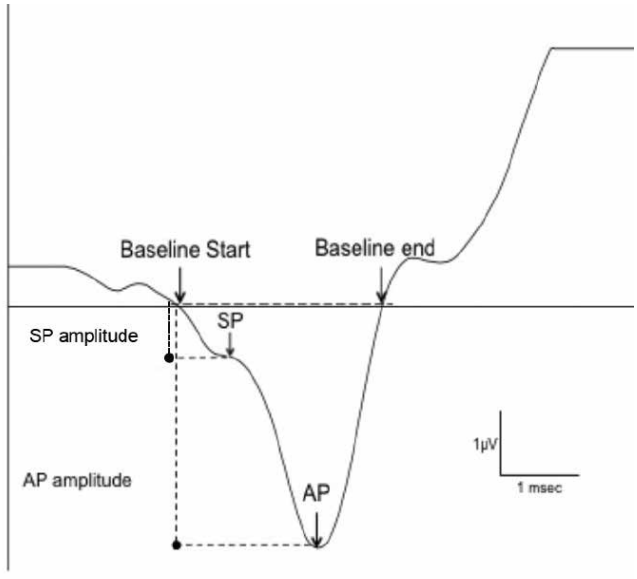

Figure 1. Calculation of the SP/AP amplitude. The SP amplitude is measured as the area under the curve from baseline to the peak of the SP waveform. The AP amplitude is measured from baseline to the peak of the AP waveform

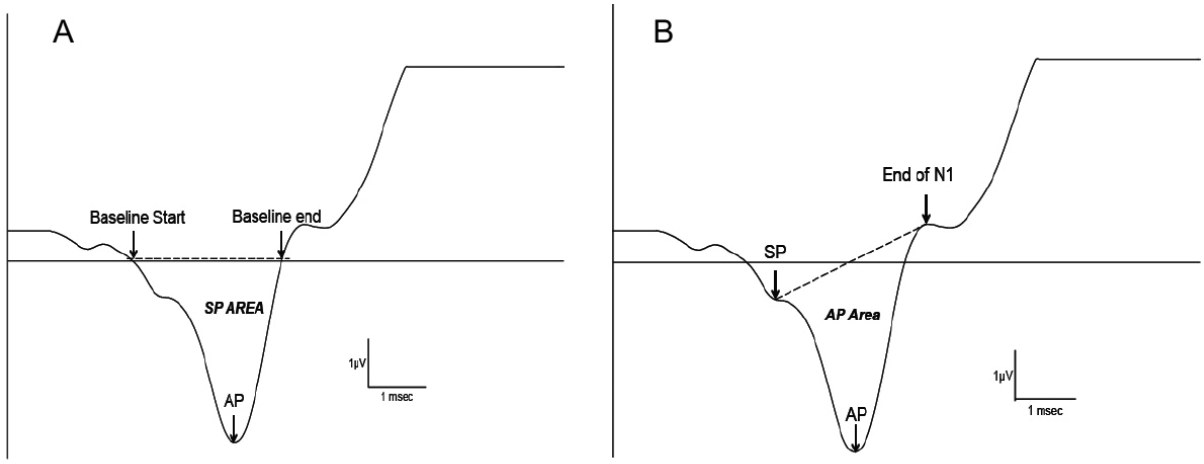

Figure 2. a-b. Calculation of the SP/AP area. (a) The SP area under the curve is defined as the area between where the baseline starts and where the baseline ends. (b) The AP area under the curve is defined as the area between the SP peak and the end of N1

SP area was defined as the area under the curve from the beginning of SP to the next point on the curve where the amplitude returned to baseline [14]. The AP area was defined as the area under the curve from the beginning of AP to the end of AP [14] (Figure 2). The SP/AP amplitude ratio was calculated using the SMART EP version software. However, we performed our area measurements using a special software routine from Nicolet (IHS, USA) designed to measure the area under a curve defined by a straight line connecting two cursors placed at selected points on the ECochG waveform. Therefore, the SP/AP area ratio was calculated using the SMART EP beta version software (IHS, USA).

Statistical Analysis

First, we analyzed auditory thresholds for the three groups using both air conduction and bone conduction. For air conduction, we evaluated frequencies between 250 Hz and 8000 Hz, and for bone conduction the frequencies were between 250 Hz and 4000 Hz. We averaged the auditory thresholds for each frequency. To determine if any significant differences were observed between groups for hearing thresholds, a repeated measure ANOVA using three groups (controls, ear fullness, and MD) for the six air conduction frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz) was performed. To identify differences between groups for bone conduction thresholds, a repeated measure ANOVA using three groups (controls, ear fullness, and MD) for the five bone conduction frequencies (250, 500, 1000, 2000, and 4000 Hz) was performed.

To test our main hypothesis, a one-way ANOVA between the three groups (controls, ear fullness, and MD) and two parameters (SP/AP amplitude ratio and area ratio) was performed to assess if significant differences were present. A bivariate correlation between ABG and SP/AP area ratio and SP/AP amplitude ratio was performed in order to assess possible relations between these variables.

Post-hoc analysis using Bonferroni correction for the multiple comparisons was performed where appropriate to adjust the level of significance. All statistical calculations were carried out using Statistical Package for Social Sciences for Windows version 22.0 (IBM Corp.; Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

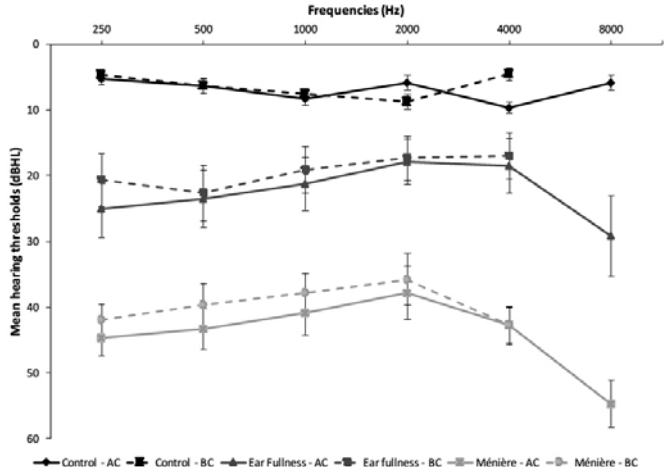

Figure 3. Mean of the air conduction hearing thresholds (solid lines) and bone conduction hearing thresholds (dash lines) of the different groups. Black lines represent the control group, dark gray represents the ear fullness group, and light gray represents the MD group

RESULTS

The analysis of auditory thresholds revealed a significant group effect for air conduction [$F(2.50)=49.627$; $p<0.001$] and for bone conduction [$F(2.50)=45.625$; $p<0.001$]. The mean air conduction hearing thresholds and bone conduction hearing thresholds for the frequencies tested are shown in Figure 3, and none of the subjects presented a significant (more than 10 dB) ABG for any frequency.

We analyzed possible correlations between mean ABG for each frequency tested (250, 500, 1000, 2000, and 4000 Hz) and the SP/AP amplitude and area ratios. The mean ABG was calculated as the mean of the air threshold minus the bone threshold at each frequency. From this analysis, no significant correlation was observed between the SP/AP area ratio and 250 Hz ($r=-0.026$; $p=0.863$), 500 Hz ($r=0.055$; $p=0.709$), 1000 Hz ($r=0.269$; $p=0.064$), 2000 Hz ($r=0.251$; $p=0.085$), or 4000 Hz ($r=-0.199$; $p=0.171$). Also, no significant correlation was observed between the SP/AP amplitude ratio and 250 Hz ($r=0.190$; $p=0.195$), 500 Hz ($r=0,178$; $p=0.225$), 1000 Hz ($r=0.128$; $p=0.385$), 2000 Hz ($r=-0.246$; $p=0.092$), or 4000Hz ($r=-0.132$; $p=0.368$).

A repeated measure ANOVA using three groups (controls, ear fullness, and MD) for the five ABG frequencies (250, 500, 1000, 2000, and 4000 Hz) failed to show any significant difference between groups [F(2,50)=2.353; p=0.106].

When analyzing the SP/AP amplitude ratio, significant differences [F(2,59)=4.594; p=0.014] between groups were observed. The mean and standard error of the SP/AP amplitude ratios were 19.85 (±2.55), 27.71 (±3.43), and 36.36 (±4.87) for the control, ear fullness, and MD groups, respectively (Figure 4). Post-hoc analysis revealed significant differences between MD and controls (p=0.015). However, no significant difference was observed between the MD and ear fullness groups (p=0.303) or between controls and the ear fullness group (p=0.406).

When analyzing the SP/AP area ratio, significant differences [F(2,59)=4.282; p=0.018] between groups were observed. The mean and standard error of the SP/AP area ratio were 1.36 (±0.07), 5.16 (±1.17), and 5.32 (±1.06) for the control, ear fullness, and MD groups, respectively (Figure 5). Post-hoc analysis revealed significant differences between MD and controls (p=0.035) and between ear fullness and controls (p=0.026) for the SP/AP area ratio parameters (figure 5). However, no significant differences between the ear fullness and MD groups (p=1.00) were found.

A significant correlation (r=0.337; p=0.015) was observed between the SP/AP amplitude ratio and mean hearing thresholds of all eight frequencies but not between the SP/AP area ratio (r=0.259; p=0.066) and mean hearing thresholds of the eight frequencies (Figure 6).

DISCUSSION

Frequently, patients experiencing ear fullness without vertigo are mainly diagnosed with Eustachian tube dysfunction. The patients are treated by nasal steroids and often receive a transtympanic tube in an attempt to equilibrate middle ear pressure. For some patients, this treatment either produces no results or worsens the condition, especially after a pressure equalizing tube insertion.

Based on the results of our study, when a patient experiences ear fullness that is unexplained by middle ear pathology, and with no improvement with the use of nasal steroids and multiple Valsalva maneuvers, we believe that this might be an indicator of EH present only at the cochlear level, therefore inducing auditory symptoms and ear fullness. However, at this stage, the hydrops is probably not significant enough in the vestibule because no vertigo is reported by these patients. We were able to demonstrate that at this stage EH would be missed by using only the SP/AP amplitude ratio. We suggest that these patients should be evaluated with ECochG using SP/AP area ratio analysis to determine if EH is present even in the absence of vestibular symptoms.

Even though the mean ABG is clinically larger in MD patients than in EH patients, and is larger than in healthy controls, the absence of a significant correlation between the mean ABG and the SP/AP area or amplitude ratios suggests that the observed results of SP/AP amplitude and area ratio are not influenced by any observed ABG, and this reinforces the possible link between our results and hydrops.

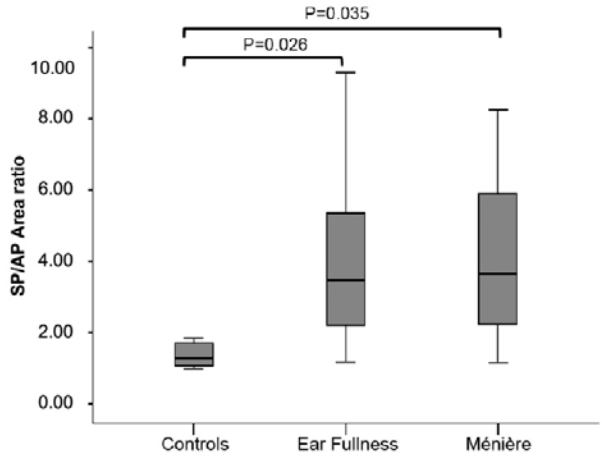

Figure 5. The SP/AP area ratio between groups. To obtain the SP/AP area ratio, we divided the SP area by the AP area

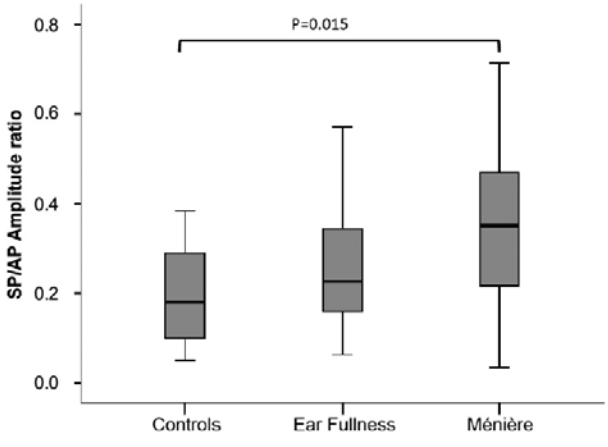

Figure 4. The SP/AP amplitude ratio between groups. To obtain the SP/AP value, we divided the SP amplitude by the AP amplitude and multiplied that by 100

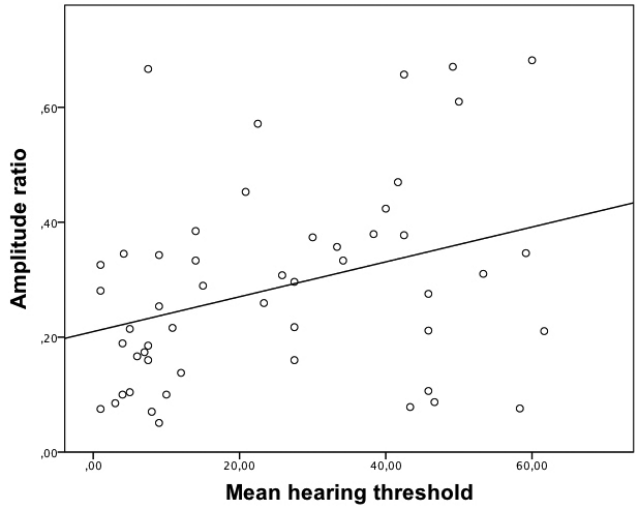

Figure 6. Correlation between the SP/AP amplitude ratio and the mean hearing thresholds of eight frequencies

As shown in Figures 4 and 5, the area ratio and amplitude ratio values were similar for the ear fullness and MD groups. This could mean that both pathologies share a common cochlear pathophysiology (hydrops) and that this could be detected in its early stages by using the SP/AP area ratio. This study, to our knowledge, is the first electrophysiological test to possibly allow early identification of cochlear EH.

It is known that using intratympanic electrodes to record ECochG provides a larger SP and AP amplitude. However, we showed that using tympanic electrodes is sufficient to identify possible hydrops in non-MD patients. This is of importance because this procedure is less invasive and can be performed in a normal clinical setting. However, hearing threshold should be 60 dB or better for each frequency from 500 Hz to 8000 Hz.

Although these results are interesting, some caution is required because other pathologies such as superior canal dehiscence (SCD) might explain the observed symptoms [17]. However, this is not very likely because the reported symptoms and the audiometric results observed in our patients are very different from the cochlear-vestibular SCD symptoms. Moreover, when SCD is suspected, a high-resolution CT scan and a vestibular evoked myogenic potential examination were performed to rule out this suspicion. Finally, our ear fullness group differed significantly in hearing thresholds compared to our control group. The presence of sensorineural hearing loss in the subject population but not in the control population could lead to test results that bias in favor of abnormal ECochG findings in the patient population. The absence of correlation between SP/AP area ratio ($r=0.259$; $p=0.066$) and mean hearing thresholds of the tested frequencies supports the our results that the SP/AP area ratio is not related to the difference in hearing thresholds, but probably more to hydrops. Following the ear fullness group over time will be of interest in order to determine how this pathophysiology will evolve and to observe if it might be the precursor of MD. Moreover, observing the effects of treatments for MD on ECochG parameters could help us to identify which of these are the most effective in reducing EH.

In addition, no statistical difference was found between the ABG of the MD group and the other two groups or between the ear fullness group and the control group. However, this ABG could be explained by cochlear conductive hearing loss due to the hydrops. Conductive hearing loss is sometimes detected in MD, which is apparently not indicative of middle ear pathology. High incidence of conductive involvement in MD patients who have had a recent episode of vertigo might indicate a distortion of the vibratory movement of the stapes [18].

The MD and ear fullness groups had a larger within-group variability for SP/AP amplitude and SP/AP area ratios compared to the control group. We believe that the variability within the MD group could be in part due to the fact that patients were not at the same stage of hydrops when we tested them. Moreover, an MD diagnosis is given based on the symptoms expressed by the patients. The key symptoms are ear fullness, tinnitus, hearing loss confirmed by a hearing test, and vertigo for more than twenty minutes [1, 19].

The variability within the ear fullness group might be explained by the severity of the subjective ear fullness sensation at the moment of the evaluation. In fact, some patients could be experiencing severe ear fullness symptoms while others could be experiencing mild ear fullness. It would be of interest to correlate the level of ear fullness sensation and the ECochG parameters.

CONCLUSION

These results are the first to show that unexplained ear fullness might be an early sign of cochlear EH and that using the SP/AP area ratio is necessary to identify EH, especially in non-MD patients. However, before drawing definitive conclusions, it would be necessary to 1) follow these patients over time in order to determine how many might develop definitive MD and 2) to replicate these data in an affiliated center.

Ethics Committee Approval: Ethics committee approval was obtained for this study from the Institutional Ethics Committee.

Informed Consent: Verbal informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.M., F.C., I.S.; Design - M.M., F.C., I.S.; Supervision - I.S.; Resource - M.M., S.F.A., I.S.; Materials - M.M., S.F.A., I.S.; Data Collection and/or Processing - M.M., S.F.A., S.P.L.; Analysis and/or Interpretation - M.M., S.P.L., M.E.N., I.S.; Literature Search - M.M., S.F.A., S.P.L., M.E.N.; Writing - M.M., I.S.; Critical Reviews - M.M., S.F.A., S.P.L., M.E.N., F.C., I.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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