The relationship between cochleovestibular function tests and endolymphatic hydrops grading on MRI in patients with Menière’s disease

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Abstract
Purpose In this retrospective study the relationship between cochleovestibular function and a magnetic resonance imaging (MRI-) based classification system of endolymphatic hydrops was investigated.

Methods Seventy-eight patients with unilateral definite Menière’s disease who underwent MRI were included. The parameters of Pure Tone Audiometry (PTA), caloric irrigation test, cervical vestibular evoked myogenic potentials, and video Head Impulse Test were compared between the grades of endolymphatic hydrops (EH) and perilymphatic enhancement (PE) on MRI.

Results The low-frequency PTA was significantly different between cochlear EH grades I and II (p = 0.036; Grade I: mean (Standard Deviation, SD) = 51 decibel Hearing Level (dB HL) (18 dB HL); Grade II: mean (SD) = 60 dB HL (16 dB HL)), and vestibular EH grades 0 and III (p = 0.018; Grade 0: mean (SD) = 43 dB HL (21 dB HL); Grade III: mean = 60 dB HL (10 dB HL)). The ipsilateral caloric sum of ears with vestibular EH grade I (n = 6) was increased with regards to vestibular EH grades 0 (p = 0.001), II (p < 0.001), and III (p < 0.001) (Grade 0: mean (SD) = 24°/s (15°/s); Grade I: mean (SD) = 47°/s (11°/s); Grade II: mean (SD) = 21°/s (13°/s); Grade III: mean (SD) = 16°/s (8°/s)).

Conclusion According to these results we can conclude that only the highest grades of cochlear and vestibular EH seem to be associated with decreased cochleovestibular functioning

Keywords Menière’s disease · Magnetic Resonance Imaging · Endolymphatic Hydrops · Perilymphatic Enhancement · Vestibular function test

Introduction
Menière’s disease is a cochleovestibular disorder associated with endolymphatic hydrops and characterized by a combination of fluctuating auditory and vestibular symptoms [1, 2]. The clinical profiles of patients with Menière’s disease (MD) are variable, leading to overlapping differential diagnostics with other vestibular disorders such as vestibular migraine [3]. To diagnose MD, many diagnostic criteria, tools, and even algorithms have been developed [2, 4–8]. The most recent diagnostic criteria are those formulated by the Classification Committee of the Bárány Society [2] which are based on the nature of the auditory and vestibular symptoms (i.e. symptom type, symptom duration, symptom frequency, and evolution of the symptoms since the onset of the disease) and the exclusion of any other vestibular disorders.

A complementary approach for diagnosing MD is identifying endolymphatic hydrops with magnetic resonance imaging (MRI) of the inner ear [5]. The absence or presence of endolymphatic hydrops is based on gadolinium as a contrast agent which is administered intratympanically
or intravenously [9]. Gadolinium passes through the blood-perilymph barrier and enhances the perilymph, thus resulting in the ‘white’ perilymph on the MR image. The gadolinium-enhanced perilymph delineates the non-enhancing endolymphatic fluid-filled structures, visible as ‘black’ cut-outs. Endolymphatic hydrops is per definition characterized by a distention of the endolymphatic spaces into the perilymphatic spaces [10]. Hence, based on the resulting MRI changes in these black and white structures, cochlear and vestibular endolymphatic hydrops can be detected and graded [5, 8, 11, 12].

In the preceding study of the current research group, an algorithm was developed for diagnosing symptomatic patients, who have a clinical profile that fits the diagnostic criteria for unilateral definite MD, as described by the Classification Committee of the Bárány Society [2]. The algorithm is based on the level of cochlear perilymphatic enhancement (PE) and the grade of vestibular endolymphatic hydrops (EH) on MRI. The combination of both signs gives the best accuracy to confirm MD [8] with a sensitivity of 85% and specificity of 92%. This classification was recently confirmed by a paper from another group [13].

Previously, several research teams have investigated the relationships between imaging-based grading systems and the results of auditory and vestibular tests [14–21]. In literature, positive correlations were reported between auditory test results and cochlear and/or vestibular EH grades [15–18]. The reported outcomes for the caloric test [17–19] and for the cervical and ocular vestibular evoked myogenic potentials [14, 20] are more variable. Further, Kahn et al. [21] concluded that there is no correlation between endolymphatic hydrops in the ampulla of the horizontal semicircular canal and the gain of the video Head Impulse Test.

The newly proposed classification system of Bernaerts et al. [8] has not been investigated yet with regards to possible clinical associations. The current study was therefore designed to define to which extent this classification system is related to cochlear or vestibular dysfunctions, measured through standard, auditory and vestibular tests.

Materials and methods

Patients

Seventy-eight patients were diagnosed with unilateral, definite MD. The diagnosis was based on the clinical diagnostic criteria for MD described by the Classification Committee of the Bárány Society [2]. The patients were referred to the Ear-Nose-Throat department of the Sint-Augustinus Hospital, Antwerp, Belgium between January 2015 and December 2016, and were admitted to our radiology department for MRI evaluation.

A right-sided definite MD was diagnosed in 38 patients; the remaining 40 subjects were diagnosed with left-sided definite MD. The mean age of the 78 subjects, at the time of performing the MRI, was 58.2 years (standard deviation (SD) = 11.9 years; median = 58.5 years; age range: 33.6—83.7 years). In total, 41 males and 37 females were included.

Magnetic resonance imaging (MRI) and imaging analysis

The MRI protocol was described in detail previously [8]. Briefly, the MRI was performed with a 3-T scanner (MAGNETOM Skyra-Fit, Siemens, Erlangen, Germany) using a 32-channel array head coil. The MRI was performed 4 h after a double dose of intravenous gadolinium (Gadovist; Bayer-Schering Pharma, Berlin, Germany) administration (1.0 mmol/mL at a dose of 0.2 mmol/kg) to assure the maximum perilymphatic enhancement. A three-dimensional fluid-attenuated inversion recovery (3D FLAIR) sequence was performed.

Cochlear endolymphatic hydrops (cochlear EH) was evaluated and graded according to the three-grade classification system as described by Baráth et al. [12]. Cochlear EH grade 0 indicates a normal cochlea with preservation of the endo- and perilymphatic spaces, and no signs of endolymphatic hydrops. Cochlear EH grade I indicates that the perilymph of the scala vestibuli is still detectable but that Reissner’s membrane has distended towards the scala vestibuli due to EH in the scala media. In case of a cochlear EH grade II, the endolymph of the scala media completely fills the scala vestibuli, so that only the perilymph of the scala tympani can be seen (Fig. 1a).

Vestibular endolymphatic hydrops (vestibular EH) was interpreted according to the modified four-stage grading system of Bernaerts et al. [8]. According to this modified four-stage grading system, a vestibular EH grade I indicates that the saccule, which is normally the smallest of the two vestibular sacs, is equal or larger than the utricle but not yet confluent with it. A vestibular EH grade II shows a dilatation of the endolymphatic space which fills more than 50% of the vestibule. The utricle and the saccule are thus confluent but a small white border of residual enhancing perilymph is still visible around them. A grade III vestibular EH indicates that the bony vestibule is completely filled with endolymph without any surrounding enhanced perilymphatic space (Fig. 1b).

Furthermore, the amount of cochlear and vestibular perilymphatic enhancement (PE) was compared between the symptomatic ear and the contralateral healthy ear. As a result, three subgroups could be identified: patients with equal PE in both ears, patients with less PE in the
symptomatic ear, and patients with more PE in the symptomatic ear. In the case of grade III vestibular EH, PE could not be evaluated since there is by definition no visible perilymphatic space left.

**Cochleovestibular function tests**

The capability of detecting sound was evaluated through air-conduction pure tone audiometry (PTA). Two PTA averages, expressed in decibel hearing level (dB HL), were calculated: the average of 500, 1000 and 4000 Hz (i.e. ‘PTA’) and the low-frequency average of 125, 250 and 500 Hz (i.e. ‘PTA Low’).

Semicircular canal and otolith function were evaluated through the caloric irrigation test, the video Head Impulse Test, and the cervical vestibular evoked myogenic potential test. During the timeframe of this retrospective study, the ocular vestibular evoked myogenic potential (oVEMP) test was not yet included in the daily clinical practice of the ENT department and, therefore, oVEMP data were not available for interpretation.

The standard four caloric irrigations with cold (30° Celsius) and warm (44° Celsius) water were performed. The parameter ‘unilateral weakness (%)’ was compared between all grades of EH and PE. Due to the healthy contralateral side, it is expected that the responsiveness of the healthy side may influence the unilateral weakness parameter. A side-specific caloric sum was, therefore, composed by adding the results of the bithermal irrigations of each side leading to two new variables: ‘ipsilateral caloric sum (°/s)’ and ‘contralateral caloric sum (°/s)’. In addition, the unilateral weakness was calculated with regard to the MD ear. Jongkees’ Formula was thus adjusted: (((cold water MD ear + warm water MD ear)–(cold water contralateral ear + warm water contralateral ear))/caloric sum)*100. These new values were labeled as ‘side-specific unilateral weakness (%)’. A negative value indicates a unilateral weakness in the symptomatic ear.

The video Head Impulse Test (vHIT) was performed with the DIFRA Headstar® system (DIFRA®, Eupen, Belgium). Only head impulses with a velocity of approximately 200 to 220°/s were accepted. Gain calculations were defined by the regression slope of the head velocity (°/s) in relation to the eye velocity (°/s). Only the data

Fig. 1 a Cropped axial delayed gadolinium-enhanced 3D FLAIR images at midmodiolar level of the cochlea. In the normal cochlea (grade 0), one can recognize the interscalar septum (arrow), the scala tympani and scala vestibuli. The scala media is normally minimally visible. The scala media becomes indirect visible as a nodular black cut-out of the scala vestibuli (arrow) in a cochlear hydrops grade I. In a cochlear hydrops grade II, the scala vestibuli (arrow) is fully obliterated due to the distended cochlear duct, visible as a linear black cut-out. b Cropped axial delayed gadolinium-enhanced 3D FLAIR images at the level of the vestibule. In a normal vestibule, the saccule (small arrowhead) and utricle (large arrowhead) are visibly separately and take less than half of the surface of the vestibule. In a vestibular hydrops grade I, the saccule (small arrowhead), normally the smallest of the two vestibular sacs, has become equal or larger than the utricle (large arrowhead) but is not yet confluent with the utricle. There is a confluence of the saccule and utricle (arrowhead) in a vestibular hydrops grade II, with still a peripheral rim enhancement of the perilymphatic space (arrow). The perilymphatic enhancement is no longer visible (arrowhead) in a vestibular hydrops grade III. (a+b) is adapted from the original publication Bernaerts A, Vanspauwen R, Blaivie C, et al. © The Authors 2019, Neuroradiology 61: 421 (https://doi.org/10.1007/s00234-019-02155-7) distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).
of the horizontal vHIT was included in the database as there was not enough reliable data available on the vertical vHIT. The gain and the absence or presence of overt and/or covert correction saccades were used for interpretation of the result. A ‘normal vHIT’ was characterized by a normal gain (≥ 0.61) and absent (overt/covert) correction saccades. An ‘abnormal vHIT’ was identified by an abnormal gain (< 0.61) and/or present (overt/covert) correction saccades.

The cervical vestibular evoked myogenic potential (cVEMP) test was performed with air- or bone conducted 500 Hz tone bursts of alternating polarity with a 2 ms rise/fall and plateau time (2-2-2 ms) (repetition rate = 5.1 Hz). The electromyographic responses were amplified and band-pass filtered (10–1500 Hz) with a sampling rate of 80 kHz (Neurosoft®, NeurAudio®, Ivanovo, Russia). For air-conducted cVEMP, insert earphones (Tone 3A Insert Earphones, E-A-R Auditory Systems®, Indianapolis, IN, USA) with a maximum sound level of 130 decibel sound pressure level (dB SPL) were used. A B71 bone vibrator (B71 Bone transducer headset, RadioEar®, Middelfart, Denmark) attached to an additional amplifier with a gain of 15 dB (Neurosoft®, NeurAudio®, Ivanovo, Russia), was used for stimulation at the mastoids when an air–bone gap of more than 10 dB was present. The maximum output was 117 dB Force Level (dB FL). Only cVEMP-traces with an average muscle contraction level higher than 100 microvolts (µV) were accepted [22].

**Statistics**

Statistical analysis was performed with IBM® SPSS® Statistics, version 25 (IBM, Armonk, NY, USA). A significance level of 0.05 was used.

In order to evaluate whether cochleovestibular function differed depending on the observed grading on the MR image, the raw data of the left and right inner ear was regrouped into ipsilateral and contralateral variables with respect to the symptomatic ear. The following ipsilateral dependent variables were used for the analyses: PTA (average of 500, 1000, 4000 Hz), PTA Low (average of 125, 250, 500 Hz), cVEMP threshold (decibel sound pressure level, dB SPL), cVEMP corrected amplitude, vHIT gain, and vHIT interpretation. For the caloric irrigation test, the original unilateral weakness parameter (%), the ipsi- and contralateral caloric sum (°/s), and the side-specific unilateral weakness (%) were evaluated.

The Shapiro–Wilk normality test was used for defining whether parametric or non-parametric analyses were warranted. The One-Way Analysis of Variance (ANOVA, parametric) or the Independent-Samples Kruskal–Wallis Test (non-parametric) were performed for comparing the dependent variables (cf. supra) between the grades of vestibular and cochlear EH. Post hoc tests were performed when the observed probability value was less than 0.05. In case a One-Way ANOVA was performed, the Bonferroni post hoc test (equal variances assumed within the subgroups) or the Tamhane’s T2 post hoc test (equal variances not assumed within the subgroups) were selected. In case the non-parametric Independent-Samples Kruskal–Wallis Test was required, the Mann–Whitney U-Test was used for post hoc pairwise analyses. The adjusted p-values (i.e. the observed probability value multiplied by the number of comparisons) were reported in this manuscript.

For the analyses of cochlear and vestibular PE, either the Mann–Whitney U-Test (not-normal distribution) or the Independent Samples T-Test (normal distribution) was used. The sample size of the subgroup of patients with less PE in the symptomatic ear was too small for statistical analysis (n = 3). Therefore, only the results of the patients with bilaterally equal PE and those with more PE in the symptomatic ear were used for evaluation.

The categorical analyses of the variable ‘vHIT interpretation’ (normal or abnormal vHIT) was performed with the Chi Square test for evaluating whether the vHIT was related to the grades of cochlear and vestibular EH or PE.

This study was conducted according to the principles of the Declaration of Helsinki and institutional ethical approval was obtained (GasthuisZusters Antwerpen study number: 161205 RETRO).

**Results**

**Pure tone audiometry**

**Cochlear endolymphatic hydrops**

No statistically significant differences could be found between the cochlear endolymphatic hydrops grades for PTA (Table 1). However, the PTA Low of the patients with a cochlear EH grade II was significantly higher than the PTA Low of the patients with a grade I (Fig. 2a) (p = 0.036; Grade I: mean (SD) = 51 dB HL (18 dB HL); Grade II: mean (SD) = 60 dB HL (16 dB HL)) (Table 1). The time between each test and the MRI was summarized in Table 2.

**Vestibular endolymphatic hydrops**

In comparison to the patients with no vestibular EH in the MD ear (i.e. Grade 0), the PTA was significantly higher for patients with a vestibular EH grade III (p = 0.041; Grade 0: mean (SD) = 44 dB HL (27 dB HL); Grade III: mean (SD) = 60 dB HL (13 dB HL)) (Table 1, Fig. 2b). A similar result was found for PTA Low (p = 0.018; Grade 0: mean
The PTA and PTA Low variables were higher for patients with more cochlear PE in the MD ear than those with equal cochlear PE in both ears (Table 1). However, the difference was statistically not significant. Similar findings were obtained for vestibular perilymphatic enhancement.

### Vestibular assessments

The vestibular test results did not show significant differences for vHIT gain, cVEMP threshold or corrected amplitude, and the original unilateral weakness parameter with regards to the different grades of the EH and PE variables. Categorical analyses of the vHIT test results ("normal vHIT" vs "abnormal vHIT") also did not show significant differences.

Even though no significant differences were found for the original unilateral weakness parameter, the ipsilateral caloric sum and the side-specific unilateral weakness differed significantly between certain grades of cochlear and vestibular endolymphatic hydrops (cf. infra).

### Cochlear endolymphatic hydrops

The ipsilateral caloric sum of the patients with a cochlear EH grade II was significantly lower than the caloric sum of the patients with no cochlear EH ($p = 0.001$; Grade 0: mean (SD) = 33°/s (17°/s); Grade II: mean (SD) = 15°/s (11°/s)) (Fig. 3a; Table 3).

The side-specific unilateral weakness was significantly higher in patients with a cochlear EH grade II than in patients with a grade 0 ($p = 0.006$; Grade 0: mean (SD) = −5% (30%); Grade II: mean (SD) = −24% (32%)) (Fig. 4a; Table 3).

### Vestibular endolymphatic hydrops

Furthermore, patients with a vestibular EH grade I had a significantly higher ipsilateral caloric sum than those with vestibular EH grades 0 ($p = 0.001$), II ($p < 0.001$) and III ($p < 0.001$) (Grade 0: mean (SD) = 24°/s (15°/s); Grade I:

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**Table 1** Descriptive statistics of Pure Tone Audiometry (PTA) of the symptomatic ear

| Variable | Grade 0 ($n = 19$) | Grade I ($n = 30$) | Grade II ($n = 27$) | Grade III ($n = 33$) |
|----------|-------------------|-------------------|-------------------|-------------------|
| PTA (dB HL): Average of 500, 1000, 4000 Hz | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Cochlear endolymphatic hydrops | Grade 0 ($n = 19$) | 48 (26) | 42 (28; 63) | 49 (21) | 49 (28; 68) |
| Vestibular endolymphatic hydrops | Grade 0 ($n = 16$) | 44 (27) | 38 (21; 59) | 53 (20) | 58 (18; 60) |
| Cochlear perilymphatic enhancement | Equal PE ($n = 24$) | 49 (21) | 49 (38; 62) | 58 (18) | 60 (18; 70) |
| Vestibular perilymphatic enhancement | Equal PE ($n = 25$) | 48 (23) | 52 (27; 62) | 53 (25) | 52 (31; 73) |

PTA pure tone audiometry, $n$ number of cases, $dB HL$ decibel hearing level, $SD$ standard deviation, $IQR$ interquartile range, $PE$ perilymphatic enhancement

(SD) = 43 dB HL (21 dB HL); Grade III: mean = 60 dB HL (10 dB HL)) (Table 1; Fig. 2b).
mean (SD) = 47°/s (11°/s); Grade II: mean (SD) = 21°/s (13°/s); Grade III: mean (SD) = 16°/s (8°/s)) (Fig. 3b; Table 3). No further significant differences were found.

Cochlear and vestibular perilymphatic enhancement

No statistically significant differences could be found for cochlear or vestibular PE, expect for the side-specific unilateral weakness parameter (Table 3). The comparison of the side-specific unilateral weakness between patients with ‘equal’ and ‘more’ vestibular PE led to the observation that the patients with more vestibular PE had a higher value for the side-specific unilateral weakness (n = 34; p = 0.046; Equal PE: mean (SD) = –10% (35%); More PE: mean (SD) = –32% (24%)) (Fig. 4b; Table 3).

The data also suggests that the patients with more cochlear PE in the MD ear have a lower ipsilateral caloric sum (mean (SD) = 20°/s (12°/s)) than those with bilaterally equal PE (mean (SD) = 27°/s (16°/s)) (Table 3). The difference was, however, not statistically significant (p = 0.058).
Discussion

The goal of this study was to evaluate possible associations between the recently proposed Bernaerts classification system [8] and cochleovestibular performance. The MRI findings are partially associated with the cochleovestibular test results, but it is unclear how they are related to each other. Low to middle-frequency hearing and caloric responsiveness are significantly decreased in MD-ears with a high grade of cochlear and/or vestibular endolymphatic hydrops. Interestingly, the degree of vestibular EH was not only associated with caloric responsiveness but also with the hearing, and the degree of cochlear EH was associated with hearing (PTA low) and caloric responsiveness. Although these associations are counterintuitive, similar findings have been reported in the literature [15, 18]. Sepahdari et al. [15] (n = 12 MD ears) reported a significant strong correlation between PTA and vestibular EH, which was expressed as the ratio of the size of the vestibular endolymphatic space over the size of the entire endolymphatic space.
vestibule. Cho et al. [18] calculated similar ratios for both cochlear and vestibular EH in 29 MD patients, and obtained comparable results. Although EH is a histologic marker for MD [23], the mechanisms underlying the cochleovestibular associations remain unknown [23, 24]. Recently, Hegemann [25] suggested that overexpression of calcitonin gene-related peptide (CGRP, a strong vasodilator) in the inner ear might be the cause of the symptoms and MRI findings related to MD. However, this hypothesis still needs to be proven and currently it does not provide an answer to why people without MD-like symptoms can also have EH and/or PE on MRI.

The caloric irrigation test was the only vestibular test for which significant changes could be found. Because the caloric test and the vHIT evaluate the same vestibular end-organ, a similar finding could have been expected for the vHIT. However, this was not the case. Literature suggests that a dissociation between the vHIT and the caloric test results in MD patients is not uncommon [26–28]. One explanation for this caloric-vHIT dissociation has been formulated by McGarvie et al. [27]. Their theory suggests that the aberrant caloric performance is caused by the hydropic expansion of the semicircular canal leading to a convective recirculation within the semicircular canal. As a result, the hydrostatic force on the cupula is decreased. Performing a vHIT in the same MD patient might show a normal test result because the vHIT stimulus (i.e. the head impulse or the angular acceleration) is dependent on the radius of the curvature of the semicircular canal which is not affected by the hydropic expansion. Consequently, the vHIT may be normal when no concomitant hair cell damage is present [27]. In addition, the difference in frequency sensitivity of both vestibular tests may also contribute to the discrepancy. This theory suggests that often the low-frequency vestibulo-ocular reflex (VOR; measured with the caloric test) shows signs of deterioration before the high-frequency VOR (measured with the vHIT) [26]. However, in light of the caloric-vHIT dissociation theory of McGarvie et al. [27], the difference in frequency sensitivity might only partially provide an explanation in patients with MD.

The association between the caloric test and MRI findings can only be confirmed partially by findings reported in literature. Jerin et al. [17] found that there is no correlation between the degree of cochlear (n = 175 patients) or vestibular EH (n = 161) and the caloric canal paresis, while Cho

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**Table 3** Descriptive statistics of the ipsilateral caloric sum (°/s) and the side-specific unilateral weakness (%)

|                          | Mean   | SD    | Median | IQR          |
|--------------------------|--------|-------|--------|--------------|
| **Caloric sum (°/s) of the symptomatic ear** |        |       |        |              |
| Cochlear endolymphatic hydrops |        |       |        |              |
| Grade 0 (n = 17)         | 33     | 17    | 26     | [20; 48]     |
| Grade I (n = 29)         | 21     | 11    | 19     | [14; 27]     |
| Grade II (n = 19)        | 15     | 11    | 10     | [8; 19]      |
| Vestibular endolymphatic hydrops |        |       |        |              |
| Grade 0 (n = 14)         | 24     | 15    | 23     | [12; 31]     |
| Grade I (n = 6)          | 47     | 11    | 46     | [39; 55]     |
| Grade II (n = 19)        | 21     | 13    | 21     | [10; 29]     |
| Grade III (n = 26)       | 16     | 8     | 16     | [10; 20]     |
| Cochlear perilymphatic enhancement |        |       |        |              |
| Equal PE (n = 19)        | 27     | 16    | 24     | [15; 35]     |
| More PE than contralateral (n = 43) | 20     | 12    | 18     | [10; 25]     |
| Vestibular perilymphatic enhancement |        |       |        |              |
| Equal PE (n = 21)        | 28     | 16    | 24     | [20; 39]     |
| More PE than contralateral (n = 14) | 22     | 16    | 19     | [7; 38]      |
| **Caloric side-specific unilateral weakness (%)** |        |       |        |              |
| Cochlear endolymphatic hydrops |        |       |        |              |
| Grade 0 (n = 16)         | –5     | 30    | 0      | [–36; 14]    |
| Grade I (n = 29)         | –25    | 26    | –30    | [–45; –8]    |
| Grade II (n = 19)        | –39    | 34    | –38    | [–68; –20]   |
| Vestibular endolymphatic hydrops |        |       |        |              |
| Grade 0 (n = 14)         | –15    | 37    | –24    | [–40; 9]     |
| Grade I (n = 6)          | –2     | 11    | –2     | [–11; 6]     |
| Grade II (n = 18)        | –28    | 30    | –32    | [–50; 2]     |
| Grade III (n = 26)       | –32    | 31    | –39    | [–50; –10]   |
| Cochlear perilymphatic enhancement |        |       |        |              |
| Equal PE (n = 18)        | –16    | 34    | –13    | [–41; 3]     |
| More PE than contralateral (n = 43) | –29    | 30    | –31    | [–50; –10]   |
| Vestibular perilymphatic enhancement |        |       |        |              |
| Equal PE (n = 20)        | –18    | 35    | –1     | [–33; 10]    |
| More PE than contralateral (n = 14) | –32    | 24    | –31    | [–45; –18]   |

*n number of cases, SD standard deviation, IQR interquartile range, PE perilymphatic enhancement, negative value indicates a unilateral weakness towards the diseased ear*
et al. [18] (n = 29) and Choi et al. [19] (n = 16) concluded the opposite. Furthermore, the current study shows that the additional lower grade I vestibular EH [8] possibly allows for identification of more specific vestibular function patterns. It is, however, unclear how the perceived saccular enlargement is related to the increased ipsilateral caloric sum. This trend was not observed for the unilateral weakness variables. It is possible that the responsiveness of the contralateral healthy ear ‘improved’ the unilateral weakness parameter and thus reduced the likelihood of obtaining a statistically significant result.

In addition to the knowledge gap regarding the effect of endolymphatic hydrops on the inner ear functions (or vice versa) [23, 24], the effect of the enhanced perilymph is unknown as well. Moreover, EH and PE can also be detected in patients without MD-like symptoms. Understanding how both MRI findings affect the performance of the inner ear structures (or vice versa) may help provide an explanation for the increased caloric responsiveness during grade I of the vestibular EH. Nonetheless, an important limitation of the present study was the small sample size of the patients within this subgroup (n = 6). In future studies, larger sample sizes should be striven for.

There were no significant differences between EH grades (cochlear nor vestibular) and the other vestibular test parameters (i.e. cVEMP threshold, cVEMP corrected amplitude, vHIT gain, vHIT interpretation), which is consistent with several other studies [18, 20, 21]. Kahn et al. [21], for example, investigated the possible correlations between saccular hydrops and cVEMP, utricular hydrops and oVEMP, and ampullar hydrops and vHIT but no significant correlations (n = 31) were observed. Guo et al. [20] did not find significant changes for the cVEMP threshold in 56 patients with unilateral definite MD, although they did report a significant increase of the interaural cVEMP amplitude ratio with regards to the degree of vestibular EH. In contrast to the approach of the current study, Katayama et al. [14] evaluated the absence of the cVEMP (n = 36 ears) rather than the
changes in its morphology (e.g. reduced amplitude). They concluded that the absence of the cVEMP is significantly associated with the degree of both cochlear and vestibular EH. In the current study, the absence or presence of the cVEMP was not evaluated, only the changes in threshold or corrected amplitude. Due to the retrospective study design, only 500 Hz tone bursts were used for eliciting the cVEMP. However, it has been suggested that the best stimulus frequency for evoking the cVEMP in MD patients shifts to 1000 Hz [29, 30]. Therefore, the inclusion of the cVEMP elicited at 1000 Hz in the analyses might lead to additional associations with the MRI findings.

In the preceding paper [8], cochlear PE and vestibular EH were concluded to be two discriminant parameters in the decision-making process of MD. The current results do indicate a tendency towards the correlation of the PE with cochlear or vestibular function tests, but most were not statistically significant. An important remark is that the subgroups with less PE in the MD ear were excluded from the comparisons due to too small sample sizes (n = 3). Further research is required to fully comprehend the significance and influence of perilymphatic enhancement in patients with unilateral definite MD. In addition to this limitation, the time between the vestibular or auditory test and the MRI was not considered as a contributing factor, even though there was quite some variability. It might be interesting to investigate the influence of this variable on the occurrence and consistency of endolymphatic hydrops and/or perilymphatic enhancement. In addition, to understand how EH and PE evolve and how they are possibly related to the damage of the inner ear tissues, the total number of attacks should be considered in future studies.

Another limitation of this study is that the visualization of the semicircular canals (SCCs) with the used 3D FLAIR sequence was not consistent, which limited the analyses to the vestibule and the cochlea. Data on the extent of EH of the horizontal SCC may provide an explanation for the observed increased caloric responsiveness of the cases with vestibular EH grade I.

Furthermore, the perilymphatic enhancement was subjectively evaluated and not quantified by comparison with a reference structure. van Steekelenburg et al. [13] used the left middle cerebellar peduncle as a reference and concluded that the absence of this objective evaluation increased the sensitivity. The observed increment was, however, limited to 4% (from 82 to 86%).

Concluding, cochlear EH grade II and vestibular EH grade III are associated with decreased low to middle-frequency PTA. Furthermore, cochlear EH grade II is associated with a decreased caloric sum in the MD ear and an increased side-specific unilateral weakness. The latter is also significantly increased when the vestibular PE in the symptomatic ear is higher than contralaterally. The ears with vestibular EH grade I (n = 6), however, appear to have an increased ipsilateral caloric sum when being compared to vestibular EH grades 0, II, and III.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sloydts Morgana, Bernaerts Anja, Casselman Jan, De Foer Bert, Blaivie Catérine, Zarowski Andrzei, van Dinther Joost, Offeciers Erwin, Wuys Floris L, Vanspauwen Robby. The first draft of the manuscript was written by Morgana Sloydts and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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