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The vestibular aqueduct sign: Magnetic Resonance Imaging can detect abnormalities in both ears of patients with unilateral Meniere's Disease.

Arnaud Attyé, MD, MSc^{1,2,3} – Marion Barma, MD¹ – Sébastien Schmerber, MD, PhD^{2,4} – Georges Dumas, MD, PhD^{2,4} – Michael Eliezer, MD⁵ – Alexandre Krainik, MD, PhD^{1,2,3}

1. Department of Neuroradiology and MRI, Grenoble University Hospital, 38000 Grenoble – France
2. Univ. Grenoble Alpes, 38000 Grenoble – France
3. IRMaGe, Inserm US 17, CNRS UMS 3552, 38000 Grenoble – France
4. Department of Otolaryngology, Grenoble University Hospital, 38000 Grenoble – France
5. Department of Radiology, Lariboisiere University Hospital, 75000 Paris – France

Corresponding author

Arnaud ATTYE, MD
Neuroradiology and MRI Department
CS 10217- Grenoble University Hospital
F-38043 Grenoble cedex 9, France
Tel: +33 4 76 76 76 60
Fax: +33 4 76 76 52 86
E-Mail: arnaudattye@gmail.com

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The vestibular aqueduct sign: Magnetic Resonance Imaging can detect abnormalities in both ears of patients with unilateral Meniere's Disease.

Highlights:

- Vestibular aqueduct obstruction with MRI is frequent in Meniere's Disease
- It can be seen in both ears of patients with unilateral Meniere's Disease
- Vestibular aqueduct morphology can be analyzed without contrast media injection

Keywords:

Inner ear ; Meniere's disease ; Magnetic Resonance Imaging ; Endolymphatic Hydrops ; Vestibular Aqueduct

Abbreviations:

MD: Meniere's disease

SURI: Sacculle to utricle ratio inversion

AAO-HNS: American Academy of Otolaryngology-Head and Neck Surgery

FLAIR: Fluid Attenuated Inversion Recovery

VA: Vestibular aqueduct

ED: Endolymphatic duct

ABSTRACT

BACKGROUND AND PURPOSE:

In patients with Meniere's disease (MD), saccular hydrops can only be studied by MRI at a late stage when the disease is already responsible for moderate to severe hearing loss. However, these patients may also present vestibular aqueduct (VA) abnormalities.

MATERIALS AND METHODS:

In this prospective study (38RC14.428 for healthy subjects / 38RC15.173 for patients), imaging was carried out on a 3T MRI scanner. Twenty healthy subjects (13 women, median age 53.5 [52.2-66.7]) and twenty MD patients (9 women, median age 54.5 [52-66.7]) had MRI scans with 3D-FLAIR sequences without injection, then 4 hours after a single intravenous dose of contrast agent. Two radiologists independently ranked the morphology of the VA in the healthy subjects and in MD patients, using a three-level score (completely visible, discontinuous and not visible). Each subject was then graded, based on both the VA's appearance and on saccular hydrops presence. Inter-reader agreement tests were performed.

RESULTS:

In controls and patients, VA modifications were symmetrical without significant difference between the symptomatic and asymptomatic ears. The presence of at least one ear with discontinuous VA showed a correlation with clinical MD ($p < 0.001$) with a sensitivity of 90%. Ten patients had saccular hydrops, but only in the symptomatic ears.

The evaluation of VA did not differ between MRI, both within MRI series or between the two radiologists (kappa without and with contrast agent=0.9 and 0.92 respectively).

CONCLUSION:

Analysis of the vestibular aqueduct by MRI detects abnormalities in both ears of patients with unilateral MD.

Introduction:

Endolymphatic hydrops was first described by Hallpike and Cairns [1] as the foremost pathological change observed in patients with Meniere's disease (MD) in post-mortem studies, and by Naganawa and Nakashima [2] using single-dose intravenous injections of gadolinium and delayed Magnetic Resonance Imaging (MRI) acquisitions. Selective enhancement of the perilymphatic fluid, 4 hours after injection of gadolinium, allows the qualitative estimation of the endolymph area on labyrinthine slices. More recently, the presence of saccular endolymphatic hydrops has proved to be a valuable means of differentiating patients from healthy subjects [3], but only in patients with moderate or severe low-tone sensorineural hearing loss [4,5].

However, altered distribution of the endolymph is not the only morphological modification of the temporal bone area in patients with MD. Previous histological studies have demonstrated atrophy of the endolymphatic sac, hypoplasia of the vestibular aqueduct (VA) and narrowing of the lumen of the endolymphatic duct in these patients [6,7]. Similar findings have been highlighted with 2D computed tomography, 3D-Cone beam CT and with MRI [8–10] describing a correlation between the lack of a visible endolymphatic duct and the clinical course of MD. One hypothesis to explain VA modification relies on calcium ion (Ca^{2+}) augmentation in hydropic ears, as demonstrated in biological samples [11,12] and more recently with mineralized cells around the VA on pathological analysis [7]. In addition, controversies persist as to whether the abnormal [Ca^{2+}] increase in endolymph is a secondary consequence of endolymphatic hydrops or its primary cause [12]. It is likely that changes in endolymph [Ca^{2+}] contribute to functional losses found in the

hydropic cochlea of animals, and possibly in the ears of humans with Meniere's disease.

The correlation between VA changes and saccular hydrops assessed by MRI has not been previously studied. Here, we performed a case-controlled study to obtain an overview of the normal vestibular aqueduct appearance on 3D-FLAIR sequences in healthy subjects and also to compare saccular hydrops imaging with variations in VA morphology.

We raise the hypothesis that VA abnormalities can be detected in the inner ear of patients with Meniere's disease in the absence of saccular hydrops.

Methods:

Healthy subjects and Patients

This single center parallel-group imaging study was registered with ClinicalTrials.gov (38RC14.428 for healthy subjects / 38RC15.173 for patients) and was approved by our local ethics committee. Signed informed consent was obtained from all healthy volunteers and patients. MRI Data extracted from healthy volunteers have been previously reported [3,5] and can be downloaded on an open source medical platform [13].

Twenty consecutive patients with a definite clinical diagnosis of unilateral MD based on the latest AAO-HNS guidelines [14] and twenty healthy volunteers with no history of inner ear disorders were recruited between August 2015 and April 2018.

Exclusion criteria for all study participants were contraindication to MRI or contrast injection.

The patients (9 women) had a median age of 54 (52-67) years and the healthy volunteers (13 women) had a median age of 53.4 (52-67) years. There was no significant difference in the mean ages or sex of the two groups. Patients referred with unilateral MD, 8 on the right and 12 on the left were confirmed with AAO-HNS criteria, with a median hearing loss of 52.50 (30-67.50) dB.

Imaging acquisition

Imaging examinations were carried out on a 3T Philips Achieva[®] (Best, The Netherlands) MRI scanner with a 32-channel SENSE head coil. A 3D-FLAIR sequence was acquired in the plane of the lateral semi-circular canal without contrast media administration and again 4 hours after a single intravenous dose of gadoteric meglumine (Dotarem[®], 0.1 mmol/kg). The Brainview[®] technique was used with the following parameters: SENSE parallel imaging technique with an acceleration factor of 2.5, scan time of 9 minutes, TR: 8000 ms, TE: 345 ms, TI: 2300 ms [15], and isotropic voxel size of 0.8 mm for acquisition and 0.4 mm for reconstructions as previously described [16]. The 3D-FLAIR sequences were added to our standard protocol including 3D heavily T2-weighted images (Balanced Fast Field Echo sequence, TR: 5.4 ms, TE: 2.2 ms; acquisition voxel size: 0.45 mm isotropic) and 3D-FLAIR sequence with whole-brain coverage.

Inner ear analysis

The imaging data were analyzed with Osirix MD[®]. Images were evaluated independently by two senior radiologists (with added certification in head and neck imaging), who were blinded to the clinical data. The presence the vestibular aqueduct; a linear duct starting from the posterior edge of the temporal bone to the

vestibule, was visually evaluated with a three-level ranking system (Figure 1) as follows:

Score 0: Continuous VA. The absence of a visible VA just before the vestibule structure was not taken into account for the visual analysis of the VA, due to the perichondrial tissue lying between the otic capsule and the vestibule [17], which appears as a hyposignal with 3D-FLAIR sequences.

Score 1 : Discontinuous VA.

Score 2 : No visible VA.

Besides evaluating the VA, we determined the presence of saccular hydrops, defined as a ratio ≥ 1 between the area of the saccule and the area of the utricle (SURI), evaluated on a axial and sagittal slice of one reference image [3]. The sagittal reference slice was obtained using multiplanar reconstructions with a coronal slice and axial slice in the vestibule plane. This is a qualitative method for imaging diagnosis of saccular hydrops and readily reproducible in MD patients [3]. A diagnosis of saccular hydrops was retained when the saccule appeared equal or larger than the utricle in both radiologists' qualitative evaluations (Figure 2).

Statistical analysis:

Data were analyzed using Statistica 5.0. Between-group comparisons were analyzed with the Student's t-test to assess differences between healthy subjects and MD patients regarding the number of subjects with saccular hydrops and the number with VA.

Age and sex differences between healthy participants and patients was tested using the Student's t-test. Categorical data are reported as frequency and percentages.

The Pearson chi-squared test was used to test the independence of the side of the VA pattern and the clinical side of deafness in the patient group. Sensitivity, specificity, and the positive/negative predictive values of the MRI examination were calculated, taking the clinical examination as the gold standard. We set the significance threshold (p-values) at 0.05.

Inter-reader agreement was estimated using Cohen's kappa coefficient. We considered a k value greater than 0.80 as very good agreement [18].

Results:

Vestibular aqueduct analysis

The VA was normal (grade 0) in 27 (67.5%) ears of the healthy subjects (Video 1 in Supplemental Material). In 8 healthy ears (20%) we found a discontinuous VA (grade 1) and in 5 healthy ears (12.5%) the VA was undetectable (grade 2) (table 1).

In MD patients, the VA was normal (grade 0) in 5 ears (12.5%) while 16 ears (40%) and 19 ears (47.5%) had respectively discontinuous VA (grade 1) or non-visible VA (grade 2) ($p < 0.001$) (Video 2 in Supplemental Material).

In the symptomatic ears of MD patients, we found 3 ears with VA grade 0, 8 ears with grade 1 and 9 ears with grade 3. In contralateral, asymptomatic ears, we found 2 ears with grade 0; 8 ears with grade 1 and 10 ears with grade 2.

No significant difference was seen between the number of inner ears with vestibular aqueduct abnormalities (grade 1 and grade 2) between right and left sides, both in the control group and in the patient group, reflecting symmetric changes.

In comparison to healthy controls, the presence of at least one ear with VA grade ≥ 1 showed a correlation with clinical MD ($p < 0.001$) with a sensitivity of 90% and specificity of 60%. VA grade 2 (no visible VA) was more specific (85% vs 60%) but less sensitive (45% vs 90%).

In VA image analysis of both MD patients and healthy subjects, there was no significant difference in the 3D-FLAIR acquisitions before and after contrast injection, and the inter-observer agreement was estimated at 89.9% and 92% respectively before and after contrast injection.

Correlation with saccular hydrops

Saccular endolymphatic hydrops was confirmed only in 10 symptomatic inner ears among MD patients ($p < 0.001$), and not in the asymptomatic ear or in healthy controls, with a specificity of 100% and a sensitivity of 50%.

Absence of visible VA (at least grade 1) was significantly correlated with diagnosis of saccular hydrops ($p < 0,05$) with a sensitivity of 85% and a specificity of 50%. A VA of normal appearance would eliminate the presence of saccular hydrops with a negative predictive value of 77%, while a VA grade 1 or 2 would predict the presence of saccular hydrops with a positive predictive value estimated as 63%.

Discussion

Here we demonstrated that VA abnormalities were more frequent than saccular hydrops in MD patients, and were also found in asymptomatic ears ($p < 0.001$). We also showed that there was no added value of enhanced MRI sequences in the VA analysis.

What do we see with FLAIR imaging on vestibular aqueduct analysis?

In our study, the vestibular aqueduct frequently appeared in healthy subjects as a tubular structure (grade 0) linking the medial wall of the vestibule to the intraosseous part of the endolymphatic sac on the posterior side of the temporal bone. This structure contains the endolymphatic duct (ED), which connects endolymph in the saccule to the lumen of the endolymphatic sac [7].

The endolymph, which normally appears as hypointense with FLAIR imaging and delayed acquisition after contrast media injection, was not visible on our sequences probably due to the relatively low spatial resolution as well as to liquid disturbance due to augmented Ca^{2+} levels. Thus, grade 0 probably corresponds to the VA dimensions obtained through the analysis of the VA wall signal both on non-enhanced and enhanced 3D-FLAIR sequences. 3D-FLAIR acquisition with contrast injection showed enhancement of the VA wall suggesting a vessel-rich layer of the otic capsule, but whose dimensions, length and width appear similar to those in non-enhanced sequences. We hypothesize that the normal cellular appearance of the VA on non-enhanced 3D-FLAIR sequences could reflect a skeletal cell population, as described by Michaels et al. [7,17]. In their pathological analysis, the loss of these skeletal cells and necrosis of the osteoblasts in the walls of Volkmann's canal are presumed to precede the development of endolymphatic hydrops.

The delayed contrast MRI acquisition did not have any advantage for VA characterization over the initial acquisition. We could hypothesize that a 3D-FLAIR acquisition just after contrast administration would be also helpful. This could be relevant because this MR sequence is now recognized as being more sensitive than T1-weighted imaging to detect subtle inner ear abnormalities, for example in the labyrinthitis or perilymphatic fistulae , which are differential diagnoses of MD [16,19].

Physiopathological aspects

Like Michaels et al. [7,17], we also assumed that the high prevalence of indiscernable VA in Meniere's disease patients could be explained by the narrowing of the VA in these patients, as already reported in CT and CBCT studies [8,9]. In our study, narrowing of the VA was mainly observed symmetrically, in both ears, of unilateral MD patients. These modifications support the suggestion that MD is a bilateral disease starting with modifications in the composition of the inner ear liquid before hydrops develop. Strial abnormalities and loss of spiral ganglion neurons associated with the evolution of MD, in both the ipsilateral and contralateral ears in patients with clinically unilateral MD support this assumption [20].

The endolymph is mainly produced from the cerebrospinal fluid [21]. Recently a new system, the "glymphatic system" was described which cleans up macroscopic waste produced by central nervous system activity [22]. The disruption of this system might be a marker of endolymphatic hydrops [23] with endolymph fluid homeostasis and volume depending on the quality of CSF cleaning. Waste accumulation could lead to ion transport disorders and favor $[Ca^{2+}]$ augmentation in the endolymph, leading to calcification and eventually ossification of the VA.

Thus, we suggest that hydrops consists of an epiphenomenon of MD reflecting a more general change in the composition of brain fluids and explaining the bilateral modifications of the VA and otic capsule.

Endolymphatic hydrops grading

Currently, imaging diagnosis of endolymphatic hydrops can be made using the semi-quantitative ranking proposed by Nakashima et al [24] or with a saccular morphology-based index (SURI) as a marker of the disease [3]. The advantage of the semi-quantitative ranking score over the SURI is that it encompasses the cochlear endolymphatic compartments in the classification. Although controversies persist as to whether this location is directly responsible for patient symptoms due to the relatively high number of cases of cochlear hydrops in healthy controls [3,25].

The semi-quantitative evaluation technique of Nakashima et al. appeared highly dependent on sequence parameter variations such as the Inversion Time when using a 3D-FLAIR sequence [15]. In contrast, the SURI technique is a criterion that is highly specific to MD but mostly correlated with hearing loss, having a low sensitivity in typical MD [5].

We anticipate that the detection of VA abnormalities would allow early diagnosis of MD, particularly as this analysis is feasible without contrast media injection and without post-processing techniques, unlike the hydrops protocol [28,29].

With the VA grade, we propose provides a sensitive criterion, which can also be studied along with the saccular ranking on delayed acquisition. This could be relevant in the context of bilateral hearing loss.

Perspectives for MD preoperative imaging

The treatment strategy for MD patients with intractable vertigo includes endolymphatic sac surgery (ESS), intratympanic aminoglycoside therapy and vestibular neurectomy [30]. ESS consists of a broad decompression of the endolymphatic sac and peri-saccular area, and its results on hearing loss improvement are controversial [31]. Here we suggest that in MD patients, ESS should be discussed in the light of results of a MRI 3D-FLAIR sequence, and particularly the degree of VA ossification. In cases with no visible VA, vestibular neurectomy in patients with a preserved hearing level or gentamycin intratympanic administration in those with severe hearing loss could be alternative treatments.

Limitations of the study

We hypothesize that VA modifications occur earlier than saccular hydrops and more generally before the development of endolymphatic hydrops, yet because of the design of this study we cannot confirm this assumption. It should therefore be considered as a preliminary study, which should be followed by longitudinal studies.

The absence of utricular and cochlear location description for hydrops is also a limitation of this study, particularly with regards to the previous theory of Pender [32] which has described a cochlear distribution of the hydrops disease, successively encompassing the cochlea, the saccule, the utricle and the semicircular canal ampullae.

We should mention that the distinction between utricle and saccule structures has only been described using a Philips 3T scanner and that controversies remain about the possibility to distinguish the two structures in more advanced cases of MD [26]. In previous pathological and imaging studies, the abnormal utricle expansion was

described into the lateral semicircular canal rather than to the inferior part of the vestibule [27], thus one can consider that a close contact between utricle and saccule in the vestibule is mainly due to saccular superior displacement. Yet, the absence of clear distinction between the utricle and the saccule in most advanced MD cases remains a limitation of the SURI classification.

Due to the difference in negative predictive value between ossification of the VA and the presence of saccular hydrops, 23% of MD patients could have saccular hydrops with a VA of normal appearance. This could be explained either by a different physiopathological mechanism, or by calcification that is too subtle to be detected by the MRI procedure. Recent developments in CBCT and CT with iterative reconstructions are promising and less onerous techniques to display subtle variations in VA osseous morphology. An evaluation of the state of the VA could become a complimentary factor to support the diagnosis of MD because of its high sensitivity.

In contrast to saccular hydrops which is always observed on the same side as the clinical hearing loss, analysis of the VA by MRI detects abnormalities in both ears in comparison to controls. MD is a heterogeneous condition which can be associated with VA obstructions, as evaluated with 3D-FLAIR sequences.

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TABLE 1. Vestibular aqueduct visualization and saccular hydrops presence in healthy volunteers and MD patients.

			Chi ² (p-value)	Se(%) / Sp(%)	PPV(%) / NPV(%)
At least one ear	Meniere's Disease	Healthy Controls			
VA = 0 (%)	3 (15)	16 (80)	16.94 (p<0.001***)	15 / 20	16 / 19
VA ≥ 1 (%)	18 (90)	8 (40)	10.99 (p<0.001***)	90 / 60	69 / 86
VA = 2 (%)	9 (45)	3 (15)	4.29 (p<0.05)	45 / 85	75 / 61
At least one ear	Meniere's Disease	Healthy Controls			
Saccular Hydrops absent	10 (50)	20 (100)	13,33 (p<0.001***)	50 / 0	33 / 0
Saccular Hydrops present	10 (50)	0 (0)	13.33 (<0.001***)	50 / 100	100 / 67
Only in MD patients	Symptomatic ear	Saccular hydrops			
VA = 1 (%)	8 (40)	10 (50)	0.4 (ns)	40 / 50	44 / 45
VA = 2 (%)	9 (45)	10 (50)	0.1 (ns)	45 / 50	47 / 48
VA = 1 + 2 (%)	17 (95)	10 (50)	5.58 (p<0.02*)	85 / 50	63 / 77

Figure 1: VA grading on axial slices enhanced 3D FLAIR sequences.

A-D: Grade 0 in a healthy volunteer with a normal VA (yellow arrow). The presence of the vestibular aqueduct was confirmed with a linear duct starting from the posterior edge of the temporal bone to the vestibule. The absence of a visible VA just before the vestibule structure was not taken into account due to the perichondrial tissue.

B-E: Grade 1 in a MD patient with a discontinuous VA (yellow arrow). It is interesting to mention that the presumed partial ossification was located at the posterior part of the VA, directly connected to the endolymphatic sac.

C-F: Grade 2 in a MD patient with complete absence of visible VA.

Figure 2: Effect of gadolinium injection on score evaluation in a healthy volunteer.

The slice without contrast media (A) has less signal in the vestibule. VA normal appearance after gadolinium contrast (B) shows a strengthened signal, but the boundaries of the VA have the same extension both in length and width (yellow arrow) when compared to non-enhanced sequence.

Figure 3: Relationship between saccular hydrops presence and VA appearance on axial slices enhanced 3D FLAIR sequences.

SURI score illustrations in the axial slice of reference (3D-FLAIR sequence) through the inferior part of the vestibule in healthy subject (A and B) and MD patient with Saccular Hydrops (C and D).

A: The saccule (white arrow) appears smaller than the utricle (dotted arrow). No saccular hydrops is detected. The VA was classified as grade 0.

C: The saccule (white arrow) appears large, utricle is not visible on this slice. Saccular hydrops is detected. The VA was classified as grade 1.

B and D: Illustrations of the MRI slices. The normal anatomy of the brain and skull has been drawn for spatial orientation. In the vestibule (yellow dotted arrow), the saccule has been drawn with green color and the utricle with orange color. The cochlea (yellow arrow) contained small amount of endolymph liquid (hypointense on 3D-FLAIR sequences, i.e non-enhanced after contrast media injection and delayed acquisition).

Video 1: Example of healthy volunteer with absence of saccular hydrops and VA grade 0.

The lower slices showed a normal saccul, which is located near the spherical recess of the medial and anterior wall of the vestibule. It is normally smaller than the utricle, which occupies the superior part of the vestibule. The presence the vestibular aqueduct was confirmed with a linear duct starting from the posterior edge of the temporal bone to the vestibule

Video 2: Example of MD patient with saccular hydrops and VA grade 2.

There is an inversion of the saccul to utricle ratio associated with absence of visible VA below the posterior semicircular canal.





