

Progression of Endolymphatic Hydrops in Ménière's Disease as Evaluated by Magnetic Resonance Imaging

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Objective: To evaluate the presence and the degree of endolymphatic hydrops (EHs) in patients with unilateral Ménière's disease (MD), as a function of duration of the disease, estimated using a 3-dimensional fluid-attenuated inversion recovery sequence in a 3-Tesla magnetic resonance imaging unit, after intratympanic gadolinium administration.

Patients: A total of 32 patients (21 male and 11 female subjects, aged 25–78 yr; median, 56 yr) participated in the investigation. The duration of the disease ranged from 2 months to 10 years (median, 3 yr), with a prevalence of vertigo spells in the last 6 months ranging from 0.5 to 8 per month (median, 2.5).

Intervention: A 0.6-ml solution of gadobutrol (1 mmol/ml) diluted 1:7 in saline was injected in the affected ear through the inferior-posterior quadrant of the tympanic membrane, using a 22-gauge spinal needle. The patient was kept with the head rotated 45 degrees contralaterally for 30 minutes after each injection. Twenty-four hours later, a 3-dimensional fluid-attenuated inversion recovery magnetic resonance imaging was performed.

Main Outcome Measure: Perilymphatic enhancement was evaluated in different portions of the labyrinth as a function of MD duration.

Results: Reduced or absence of enhancement of the vestibule occurred precociously and occurred in all subjects at long term. The prevalence of enhancement abnormalities in the cochlea and the semicircular canals was directly proportional to MD duration. At long term, the vestibule and the cochlea showed a more severe hydropic involvement compared with semicircular canals. A statistical significant correlation between enhancement abnormalities and MD duration was observed for most inner ear sites.

Conclusion: The increased prevalence and severity of EH with the duration of MD indicates that hydrops is a progressive degenerative phenomenon. The frequent abnormality in the vestibule and, secondarily, in the cochlea is in line with some histopathologic investigations. It remains to be clarified whether hydropic changes are related to specific signs and symptoms of MD.

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Endolymphatic hydrops (EH) is a typical marker of Ménière's disease (MD) as demonstrated in autptic specimens (1–5) and reproduced in animal models after surgical obliteration of the endolymphatic sac or systemic administration of drugs, for example, aldosterone or vasopressin (6–8). However, these methods of investigating EH have a number of drawbacks. Postmortem pathologic investigation is limited by the scarce availability of temporal bones of patients with MD, the possibility of artifacts, the difficulty of adequate correlation with the natural history of the disease, and the outcomes of diagnostic tests. On the other hand, interspecies differences are unable to reproduce

the symptoms typical of MD after the induction of EH in animal models. As a consequence, the role of EH as a cause of the specific symptoms, such as vertigo spells or hearing loss, or other neurotologic correlates is not completely clear, and some authors consider it only an epiphenomenon of the disease (9,10).

Recent studies have highlighted the possibility of visualizing EH during life in patients with MD, using a 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence in 3-Tesla (3T) magnetic resonance imaging (MRI) unit, after intratympanic gadolinium (ITGad) administration (11–13). Imaging of EH relies on the enlargement of the space occupied by nonenhancing endolymph-filled membranous structures, which reduces visualization of enhancing perilymphatic compartments (11).

The present imaging study was conducted to investigate a particular aspect of the EH in patients with unilateral MD, that is, its progression as estimated on the

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basis of the presence and the degree of enhancement abnormalities in the inner ear, as a function of duration of the disease.

MATERIALS AND METHODS

From January 2008 to November 2010, 32 patients (21 male and 11 female subjects, aged 25–78 yr; median, 56 yr) with definite MD (14) were examined with 3D-FLAIR MRI using ITGad as a contrast medium. They were included in the study on the basis of the following criteria: unilateral disease, recurrent vertigo attacks, absence of disorders eventually responsible for secondary hydrops, and no history of middle-ear and neurologic disorders. The duration of the disease ranged from 1 month to 10 years (median, 3 yr), with a prevalence of vertigo spells of 0.5 to 8 per month (median, 2.5), as calculated in the last 6 months or in the available time range in shorter-duration MD. The pure-tone average at 500 to 3,000 Hz (14), ranged from 17 dB hearing level (HL) to 91 dB HL (median, 53 dB HL) in the affected ear. The contralateral ear showed a pure-tone average equal to or better than 15 dB HL. Most patients had been treated with different medical therapy regimens, mainly based on low-salt diet and diuretics, which were withdrawn at least 1 month before the time of MRI examination. However, symptomatic drugs, such as benzodiazepine and antiemetics, were occasionally administered after an acute vertigo spell during this period.

All the patients were submitted to ITGad solution administration in the affected ear 24 hours before MRI investigation. The Hospital Medical Management was informed on the off-label intratympanic use of gadolinium, and all patients gave a

MD duration (months/years)	CAT	CMT	CBT	Vest	SSC	PSC	LSC
1 m							
5 m							
6 m							
7 m							
7 m							
8 m							
10 m							
1							
1							
1							
1							
1							
1.5							
1.5							
2							
2							
2							
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4							
4.5							
5							
5							
5							
6							
8							
8							
9							
10							
10							

FIG. 1. Individual outcomes of 3D-FLAIR MRI performed 24 hours after ITGad administration in the patients with MD. Each single inner ear site is represented. *White boxes:* normal enhancement; *gray boxes:* reduced enhancement; *black boxes:* absent enhancement.

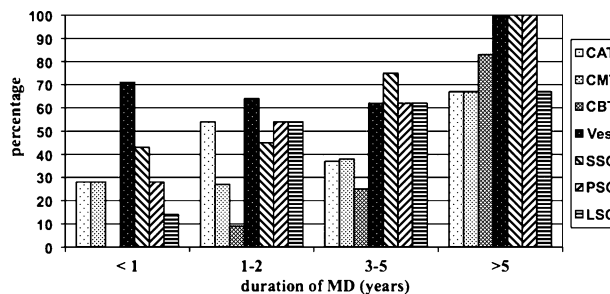


FIG. 2. Prevalence of enhancement abnormalities (reduced or absent) observed at the different inner ear sites as a function of duration of the MD.

written informed consent. The methods of ITGad administration had been reported in previous articles (15,16). Briefly, 0.6 ml of 1:7 gadobutrol (1 mmol/ml) was injected through the tympanic membrane, using a 22-gauge spinal needle. The patient was kept with the head rotated 45 degrees contralaterally for 30 minutes after the injection. The MRI was performed with a 3T unit (Allegra, Siemens, Erlangen, Germany) using a receive four-channel phased-array coil. The 3D-FLAIR was acquired using the generalized autocalibrating partially parallel acquisition imaging technique with an acceleration factor of 4, and the sequence parameters were as follows: voxel size = 0.4 × 0.4 × 2 mm, signal-to-noise ratio = 1, scan time = 20 minutes, 12 slices, TR = 9000 ms, TE = 128 ms, inversion time = 2500 ms, flip angle = 180 degrees, slice thickness = 2 mm, echo train length = 23, field of view = 16 cm, and matrix size = 384 × 384.

Images were evaluated by 2 neuroradiologists (A. B. and F. B. P) with long-standing experience, blinded to the patient's identity and clinical data. Each portion of the labyrinth, that is, basal (CBT), middle (CMT), and apical (CAT) turns of the cochlea and vestibule (Vest), superior (SSC), posterior (PSC), and lateral (LSC) semicircular canal was separately evaluated and judged to have a normal, reduced, or absence of enhancement. When the endolymphatic content of the considered structure was clearly visible, the ratio of its area to the total area of fluid space (endolymphatic and perilymphatic) was calculated, and a value exceeding one-third was attributed to the EHs and classified as reduced enhancement (13). Enhancement was considered absent when the examined structure was not visible. If there was no visual evidence of separation between the endolymphatic and the perilymphatic compartments, the contrast-to-noise ratio of the considered structure was calculated (13). The signal of the different portions of the inner ear in both the groups of patients was considered reduced when inferior to the tolerance limit of 54.1 contrast-to-noise ratio, calculated at the basal turn of the cochlea in a group of patients without MD (16).

RESULTS

No adverse effects or complications occurred after intratympanic application of gadolinium.

Figure 1 graphically shows the individual outcomes observed with the 3D-FLAIR MRI, 24 hours after ITGad administration, arranged with increasing time duration of the disease. The prevalence of abnormal (reduced or absent) enhancement, grouped at different levels of MD onset, is summarized in Figure 2. Figure 3 shows the prevalence of absent enhancement only. As a whole, prevalence of abnormalities increased as a function of time. The number

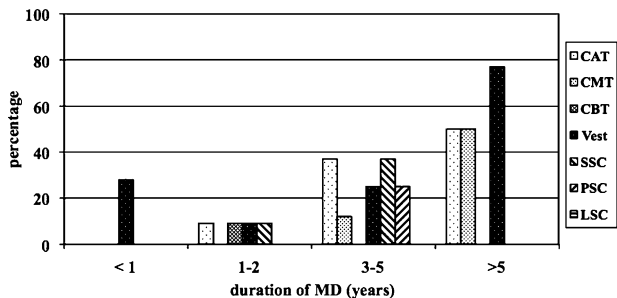


FIG. 3. Prevalence of absence of enhancement observed at the different inner ear sites as a function of duration of the MD.

of involved sites for each single patient significantly correlated with the duration of the disease in Spearman's tests ($r = 0.475$; $p = 0.007$).

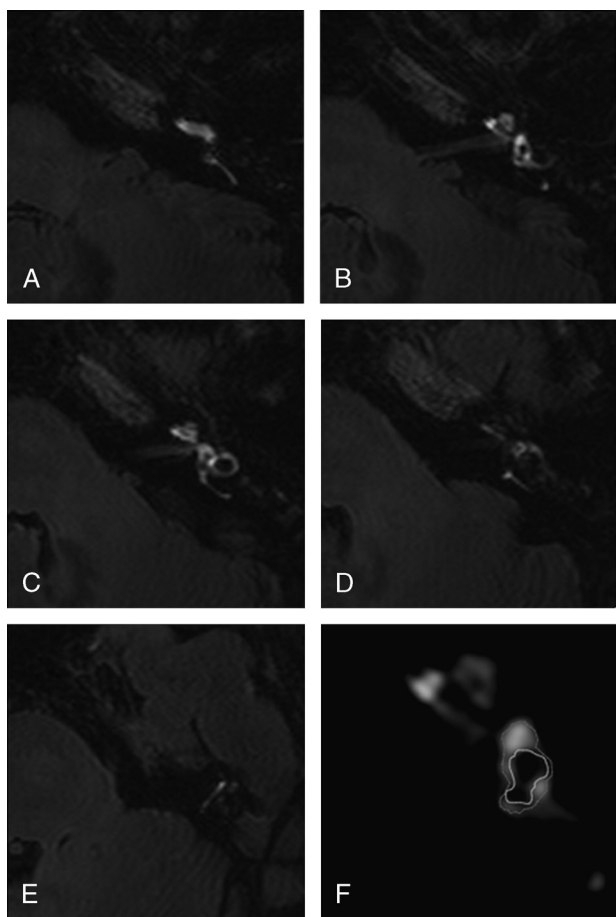


FIG. 4. A–F, 3D-FLAIR MRI taken 24 hours after the intratympanic injection of gadolinium in a 28-year-old patient with left MD. A–E, Axial-view images are shown in a caudal-to-cranial progression from the round window to the middle fossa floor level. All cochlear turns and semicircular canals show a normal enhancement. The membranous Vest shows a clear EH. F, Magnification of the image obtained at the level of the Vest enables the calculation of an abnormal ratio of 0.48 between the endolymphatic space and the area of the entire Vest. Inner and outer lines contour the endolymphatic and perilymphatic spaces, respectively.

Reduced or absent enhancement of the Vest occurred precociously and was of interest to all the subjects at long term, that is, MD onset of more than 5 years. A typical case of early vestibular involvement is represented in Figure 4, A–F. The patient presented 2 vertigo spells spaced out by 3 weeks and characterized by the classical triad of symptoms with documented low-frequency sensorineural hearing loss in the left ear. One week after the last vertigo spell, a 3D-FLAIR MRI was performed with ITGad, which showed an isolated enlargement (48%) of the membranous endolymphatic content of the vestibule.

The prevalence of reduced or absent enhancement of the semicircular canals was directly proportional to MD duration. At long term, enhancement abnormalities were always present in the SSC and PSC and observed in 67% of subjects in the LSC. Cochlear sites showed a lower prevalence of hydropic involvement compared with vestibular sites. Enhancement alterations were progressive, reaching a prevalence of 67% for the CMT and the CAT after the fifth year. On the other hand, EH interested only occasionally the CBT in the first 2 years of the disease, whereas it reached a prevalence of 83% at long term.

Absence of enhancement, indicative of severe EH, was more delayed compared with reduced enhancement and was observed only in the Vest during the first year. It was more frequent after the second year of the disease and reached a prevalence of 77% in the Vest and 50% in the CAT and the CMT of the cochlea after the fifth year.

Images obtained in a patient with a 10-year history of MD are presented in Figure 5, A–D. All 7 sites showed a reduced or absent enhancement. In particular, the CAT, the CMT, and the Vest did not enhance, whereas the remaining structures all showed a decreased enhancement.

Spearman's test was used to correlate the MRI outcome (normal, reduced, or absent enhancement) to the duration

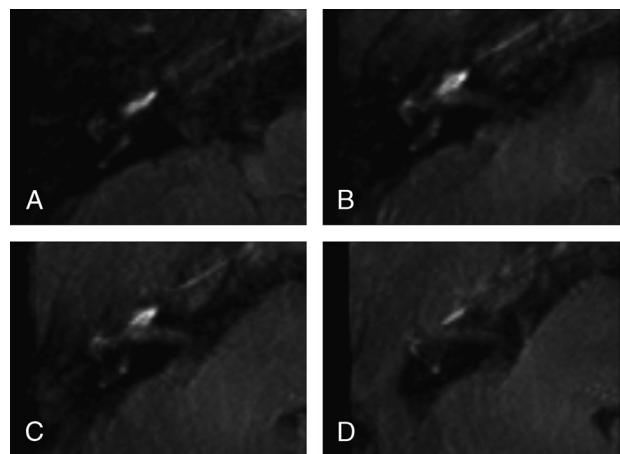


FIG. 5. A–D, 3D-FLAIR MRI taken 24 hours after right intratympanic injection of gadolinium in a 49-year-old patient with right MD since 10 years. Axial-view images are shown in a caudal-to-cranial progression from the round window to the middle fossa floor level. Perilymphatic enhancement is lacking at the level of the Vest, and CAT and CMT. The CBT and all semicircular canals show reduced enhancement.

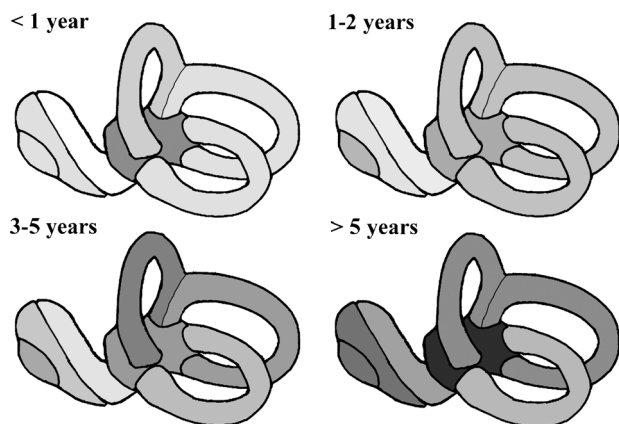


FIG. 6. Visual representation of the degree of the enhancement alterations in the different portions of the inner ear at different time intervals of MD duration. The gray intensity gives an appreciation of the degree of enhancement defect. A darker filling indicates a higher prevalence and severity of the EH. To obtain this graphic representation, a value of 0 was attributed to normal enhancement, 1 to reduced enhancement, and 2 to absent enhancement; these values were averaged for each single site and groups of MD duration. A percentage of gray intensity was used, with a value of 0 (white) corresponding to full enhancement and 100% (black) to complete lack of enhancement. A commercial software (Photoshop Elements, 8.0; Adobe System Inc, San Jose, CA, USA) was used to reproduce graphically the gray scale. The different inner ear portions have been arbitrarily separated in the drawing. In particular, the common crus has been split in two portions, which have been attributed to the SSC and the PSC.

of the disease, for each single inner ear site. Enhancement alterations observed at the CAT, the Vest, and the LSC did not show significant correlation with the duration of the disease ($r = 0.325$, $p = 0.75$; $r = 0.277$, $p = 0.130$; and $r = 0.325$, $p = 0.75$, respectively). On the other hand, a significant correlation was observed for the CMT ($r = 0.4$, $p = 0.026$), CBT ($r = 0.618$, $p = 0.001$), SSC ($r = 0.404$, $p = 0.025$), and PSC ($r = 0.428$, $p = 0.017$).

Figure 6 yields a graphic qualitative representation of the degree of the EH obtained by averaging, for each inner ear portion, the prevalence and severity of enhancement abnormalities at different time intervals of MD duration. The darker the filling is, the higher is the degree of enhancement abnormalities. The early onset of hydrops in the Vest and the progression in the prevalence of enhancement defect in all cochlear and vestibular sites are evident. At long term, the Vest and the cochlea showed a more severe hydropic involvement compared with the semi-circular canals.

DISCUSSION

A close correspondence between EH and symptoms and signs of MD constitutes the so-called central dogma, which implies that EH causes clinical manifestations as episodic vertigo and hearing loss. However, a series of clinical and experimental data have undermined this dogma. First, temporal bone studies have evidenced that EH also may occur in the absence of symptoms typical of MD (10,17).

Second, experimental investigations have shown that the dysregulation of inner ear fluids caused by cytochemical and ultrastructural disruption of the fibrocytes of the spiral ligament and hair cells precede EH, which may therefore be only a secondary phenomenon (18,19). Finally, from the clinical point of view, it is not always possible to correlate many characteristics of MD to EH, owing to the lack of reliable indicators of hydrops in life. To this end, oto-neurologic tests such as electrocochleography, with the calculation of the ratio between summating and action potentials, have not demonstrated a high diagnostic accuracy (20).

Histopathologic investigation is unable to overcome these drawbacks. In fact, it yields a static picture on the localization and severity of hydrops in temporal bones, with difficulties evident in demonstrating clear relationships with the clinical characteristics of the disease. Ideally, EH should be evidenced, localized, and quantified in life and directly correlated with symptoms and signs. Advances in imaging have recently made possible visualization of the endolymphatic and the perilymphatic spaces of the inner ear in humans, using the 3T-MRI with 3D-FLAIR sequences after ITGad injection (11–13,15,16). Imaging of EH relies on the enlargement of the space occupied by nonenhancing endolymph-filled membranous structures, which reduces visualization of enhancing perilymphatic compartments (11). The reasons of selective enhancement of perilymph are not completely understood because it is well known that other drugs, such as gentamicin, are able to penetrate the endolymphatic space and reach the cochlear and vestibular sensory cells (21,22). This phenomenon may be due to the impermeability of the perilymph/endolymph barrier to gadolinium, which has a molecular weight one-third greater than gentamicin or to a low concentration in the endolymph unable to produce an enhanced signal.

The technique of perilymphatic enhancement after ITGad administration has revealed to be highly reliable in identifying the EH in subjects with MD, yielding very high values of sensitivity and specificity (16), and has opened very interesting perspectives in the diagnosis of MD and comprehension of the role of EH. This possibility has paved the way toward a true understanding of hydropic phenomena of the inner ear and their correlation with the clinical picture. Examples of this new trend in clinical research have been furnished by the significant correlation between the severity of hydrops and the alteration of the vestibular evoked myogenic potentials and duration and stage of the disease (15,23). On the other hand, no correlation has merged with tinnitus, fullness, frequency of vertigo attacks, time interval from the last attack, functional scale level, electrocochleography, and caloric testing (15). The first conclusion that may be drawn from these studies is that EH is probably the consequence of progressive degenerative phenomena related to the stage and the duration of the disease, without a clear relation with specific cochlear or vestibular symptoms and signs.

The present investigation correlated the localization and the degree of EH, as visualized using 3D FLAIR

MRI, with time duration of the MD, in an attempt to achieve an estimation of the progression of hydrops. To the best of the authors' knowledge, this issue has never been addressed radiologically and only partially in histopathologic studies (2). The enhancement defect of the Vest was precocious and, therefore, not significantly correlated with the duration of the disease. However, subjects with MD lasting more than 5 years always showed vestibular hydropic enlargement, with a total absence of enhancement, indicating a severe EH, in 50% of cases. Imaging abnormalities in the CAT and LSC also did not show any clear correlation with MD duration. Pathologic outcomes in other inner ear sites significantly correlated with duration of the disease, with a highly significant value for what concerns the CBT, which showed a delayed reduction of enhancement.

At long term, cochlear sites and Vest showed more severe abnormalities compared with the semicircular canals. This was particularly evident when considering the prevalence of absence of enhancement. These findings agree with some histopathologic investigations that have shown a prevalent involvement of the pars inferior of the labyrinth (1–5), albeit a direct comparison is not possible as 3D FLAIR MRI does not distinguish between the sacculle and the utricle. The sacculle has demonstrated to be particularly involved in the most severe forms of MD (4,5). The central role of saccular pathology in MD also is testified by the outcome of VEMPs that may be considered a reliable indicator of severity of EH (15,23).

The relationship between the duration of the disease and the increased volume of the cochlear duct and the sacculle was evidenced by Frayssse et al. (2) in a temporal bone study. The group of 17 patients was, however, heterogeneous, comprising subjects with definite, and probable MD, congenital syphilis and sensorineural hearing loss and with a duration of the disease ranging from 2 to 53 years (mean duration, 19 yr), thus hampering comprehension of the behavior of EH in the first stages of the disease.

Progression of the EH from the apex to the base of the cochlea, as observed in the present investigation, is in agreement with the well-known phenomenon of fluctuating low-tone hearing loss in initial MD, followed in the subsequent years by pantonal involvement during the progression of the disease (24,25).

The pars superior of the labyrinth generally shows less frequent and severe changes compared with the pars inferior (1–5). Hydropic involvement of the semicircular canals in the present investigation was progressive but rarely severe. This also is compatible with the findings of caloric excitability, which deteriorates in MD patients of approximately 35% to 50% (26,27). Only a few patients have a severe decrement or even absence of caloric responses (26,27).

In conclusion, the increased prevalence and severity of EH with the duration of MD indicates that hydrops is a progressive degenerative phenomenon. Some aspects of EH imaging agree with the clinical picture of MD, such as the behavior of auditory threshold, but it is not clear

whether there is a direct cause-effect relationship or both are a consequence of more subtle biochemical and ultrastructural modifications. Further studies are certainly necessary. Prospective investigations on larger series, including imaging, symptom, and instrumental data, are desirable to yield a better understanding of the role of hydropic changes in the generation of clinical manifestation of MD. Ideally, repeated MRI could better elucidate the modification of EH related to symptomatology and objective outcomes. Obviously, this kind of study is difficult to realize owing to ethical and economic reasons.

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