Imaging Analysis of Ménière's Disease

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Abstract Advances in magnetic resonance imaging have recently allowed the demonstration of endolymphatic hydrops (EH) in human subjects. Ménière's Disease (MD) is diagnosed based on a constellation of symptoms and can be corroborated with a variety of clinical tests. Prior to the current era, however, EH in MD could only be directly visualized on postmortem human temporal bone studies. Imaging techniques using both intratympanic and intravenous contrast have progressed with the help of animal models, and imaging protocols for evaluation of EH in humans continue to evolve as image resolution and post-processing techniques improve. Although the clinical implications of these imaging modalities seem promising, the details of the specific applications of MR imaging of EH remain to be elucidated.

Keywords Endolymphatic hydrops · Ménière's Disease · Magnetic resonance imaging · Intratympanic contrast · 3D Real IR · "HYDROPS" images

Introduction

Endolymphatic hydrops (EH) is the distention of the cochlear duct (scala media) that has been associated with Ménière's disease (MD) [1]. EH has been demonstrated in patients with MD in histopathologic studies of the human temporal bone [2], and mechanisms have been proposed for how it causes symptoms of MD, such as rupture of Reissner's membrane [3]. Controversy remains in the literature regarding the clinical implications of the distention of the endolymphatic space, because EH can present with variable phenotypes and is not sufficient for the diagnosis of MD (not all patients with EH identified postmortem are symptomatic) [4]. Some have proposed that EH is an epiphenomenon linked to a variety of causal factors, including trauma [1], allergy [5], and genetic predisposition [6], among others; however, the fact that this anatomic perturbation is present in patients with MD has made it a topic of avid research.

Although much progress has been made in animal models of EH, it is difficult to research in humans in vivo because of the confines of the bony labyrinth. One way investigators have sought to define EH in humans through imaging. Attempts to visualize the distended endolymphatic space have been made on magnetic resonance imaging (MRI) with the application of both intravenous (IV) [7] and intratympanic (IT) [8] contrast (Fig. 1). Several different contrast agents have been used for IV and IT use, and various magnetic resonance (MR) sequences have been proposed to improve the visualization of the endolymphatic space [9–12]. The clinical utility of imaging of EH in humans beyond the diagnostic correlation of EH and MD has also been explored and continues to be debated in the literature [13].

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Fig. 1 3 Tesla MRI demonstrating endolymphatic hydrops 3T MR imaging of the left ear was performed using 3 inch surface coil 24 h after intra-tympanic injection of 1:7 Magnevist contrast diluted in sterile saline. **a** Heavily T2-weighted (FIESTA) sequence depicts the anatomy of the membranous labyrinth; note that the signal intensity of the endolymph and perilymph in the vestibule is equivalent. **b** On the FLAIR sequence obtained concurrently, contrast opacifies the perilymphatic space, with signal void in the vestibule corresponding to the distended endolymphatic space. Reproduced with permission from Julie Bykowski, MD, personal correspondence. Funding support from the American Society of Head and Neck Radiology William Hanafé Award

Background

Visualization of the Endolymphatic Space on MRI

The current basis for visualization of EH is by the distribution of gadolinium-based contrast agents (GBCA) into the perilymphatic space to create a negative image of the distended endolymphatic space. Zou et al. [14] demonstrated that IT gadodiamide (Omniscan, GE Health Care, NJ) is taken up into the perilymphatic space when applied to the round window in guinea pigs. These authors noted that the quick transit of contrast from the scala tympani to the scala vestibuli suggests that contrast moves by radial flow [15, 16] rather than the slow longitudinal flow of perilymph, as previous studies have demonstrated [17]. Yoshioka et al. [18] showed that round window permeability to gadolinium varies across patients with inner ear disease, which is relevant to those patients undergoing IT therapy. More recent work has revealed that gadolinium enters the perilymph through an oval window pathway in rats [19], and this pathway may be more effective than the round window pathway [20]. Moreover, intratympanically injected GBCA have shown more limited vestibular distribution in patients with EH [21].

IT contrast is typically administered with a thin-bore needle, and typically eightfold diluted contrast material is injected, usually to a volume of 0.3–0.6 mL [22]. Patients remain still after this procedure for 30 min, to ensure that the contrast remains in contact with the windows for a sufficient period of time. The timing of image acquisition after IT gadolinium administration differs from that after IV contrast, as detailed below.

Serial MR exams have demonstrated that IT contrast diffuses from the tympanic cavity into the scala tympani of

the cochlear basal turn, the vestibule, and portions of the semicircular canals near the vestibule within 2 h after IT GBCA injection [8, 14], with complete diffusion within 12 h [8]. Enhancement was noted to be fainter or absent in patients with imaging findings of endolymphatic distention [8, 18], whether symptoms were attributable to MD or other inner ear disorders. Clearance dynamics have been reported in a small set of patients, with residual GBCA persisting within the perilymph 6 days after IT injection [8].

Although IT administration is the most widely used technique for the local administration of contrast to the perilymphatic space, others have been described. Some investigators have applied contrast to the middle ear space through the Eustachian tube [23] in an effort to avoid the potential complication of tympanic perforation from IT administration [24]. Still others have shown that contrast injected directly into the endolymphatic sac in patients with MD undergoing endolymphatic sac decompression distributes to the vestibule, cochlear, and semicircular canals [25].

Contrast Agents

GBCA have been FDA approved for IV use and are applied widely in routine clinical imaging of the central nervous system. The formulation of the different agents results in slightly different properties, including T1-shortening effects, molecular weight, and thermodynamic stability, which have clinical implications regarding the conspicuity of contrast in low or diluted doses, permeability, and the risk of dissociation of free gadolinium from the chelate [26]. All GBCA are very stable compounds, with highest thermodynamic and conditional stability associated with macrocyclic agents (e.g., ProHance, Bracco, NJ), and with

ionic linear chelates (e.g., Magnevist, Bayer Health Care, NJ) having higher thermodynamic and conditional stability than non-ionic linear chelates (e.g., Omniscan, GE Healthcare, NJ) [27]. Severe, life-threatening reactions to GBCA are rare (0.001–0.01 %). GBCA should be avoided in patients with renal failure (GFR <30 mL/min/1.73 m²) [2], hepatorenal syndrome, or recent liver transplant due to the risk of nephrogenic systemic fibrosis [28, 29]. Although IV GBCA is routine, IT administration for the visualization of EH remains investigational in the United States.

It has been proposed that the movement of GBCA across the round and oval windows may be predictive of how IT steroids or gentamicin will permeate the inner ear. Lower molecular weight substrates are thought to have greater permeability across the round window membrane [30]. The components of gentamicin used intratympanically (C1, C2, and C1a) have molecular weights of 477.6, 463.6, and 449.5, compared to dexamethasone (392.5) or methylprednisolone (374.5). To date, the two GBCA used intratympanically in humans are gadodiamide (Omniscan) and gadopentetate dimeglumine (Magnevist) with molecular weights of 591.67 and 938, respectively. Other agents range from molecular weights of 558.7 (ProHance) to 1058.2 (MultiHance, Bracco, NJ).

Although 8-fold dilutions are the most widely used, IT injections of 5-fold [21] to 16-fold [11] dilutions of GBCA in sterile saline have also been reported in human subjects. A major safety concern of GBCA is the potential for the release of free gadolinium ion from the chelate and its subsequent retention within the body. Free gadolinium is known to be an inhibitor of TRPV4 (transient receptor potential channel vanilloid subfamily 4) [31], which is present in non-sensory cells of the stria vascularis that maintains the ionic composition of endolymph.

Kakigi et al. [32] performed a histopathological review after intratympanic administration of dilutions of GBCA in guinea pigs. No significant morphological difference was identified on electron microscopy in the stria vascularis between the ears injected with eightfold saline-diluted contrast agent and those in which saline alone was injected. IT GBCA have also been shown to have no adverse effects on short-term hearing in human studies [33, 34]. However, there is a need for long-term hearing evaluation after IT application of gadolinium, as well as analysis with high-frequency audiometry because of the proximity of this tonotopic region to the round window [34].

Correlation with Other Clinical Tests

Historically, EH was only observable on histopathologic specimens, and so clinical tests to infer the presence of EH were developed. Specifically, an enlarged summating potential (SP) to action potential (AP) ratio on

electrocochleography (ECOG) has been demonstrated [35], and a reduced amplitude on vestibular evoked myogenic potentials (VEMP) has also been shown in patients with MD [36]. Caloric testing may reveal a weakness in the affected ear or may be normal in these patients [37].

Although ECOG is the test most commonly used to investigate EH, an enlarged SP/AP ratio is not present in all patients who meet diagnostic criteria for MD [38], and an enlarged SP/AP ratio may not always indicate EH [39]. Some authors have found that cochlear hydrops visualized on 3D-FLAIR images after IT GBCA correlated with abnormal ECOG [40], and others have suggested that a normal SP/AP ratio in patients with EH on MRI indicates early disease or mild hydrops [41]. In contrast, Fiorino et al. [42] found that the number of inner ear sites involved by EH on 3D-FLAIR images after injection of IT contrast did not correlate with ECOG or caloric testing.

Fiorino et al. [42] did, however, find a significant correlation between abnormal VEMP and the number of inner ear sites involved. Other investigators have demonstrated a similar correlation with absence of VEMP responses and the presence of EH on MRI, as well, with a stronger correlation between vestibular hydrops and absent responses [43]. However, not all studies have supported this correlation between abnormal VEMP responses and EH on MRI [40]. As caloric responses are variable in patients with EH and MD, it is not surprising that although a trend toward correlation between EH and caloric response has been suggested [44], no definitive association has been found [45].

Fukuoka et al. [46] suggested that MRI demonstration of EH in patients with MD is more useful than the glycerol test or ECOG because a larger proportion of patients had positive findings on imaging. Results of MRI evaluation of EH must be interpreted with caution because some patients with MD may have mild EH, as indicated by postmortem histopathologic analysis [47], and this slight distention of the endolymphatic space may not be easily seen on MRI. An overestimation of EH on MRI would make comparison with other clinical measures invalid.

Development of Imaging Techniques

Animal Models

As discussed earlier, both guinea pig models and rat models have been used to demonstrate round window and oval window permeability to GBCA [14, 19]. Animal models have also permitted a comparison of the oval and round window pathways into the inner ear, with ultra-small-volume GBCA demonstrating superior uptake in the vestibule over the scala tympani, favoring the oval window as a more efficient pathway for passage of contrast [20].

MR images obtained from higher strength magnets (4.7T–7T) with animals receiving IV GBCA have provided very high resolution images of the inner ear [48–50]. This same anatomic detail is not possible in humans with magnets in clinical use (1.5T and 3T). However, animal studies have allowed for histopathologic correlation of EH demonstrated on MR images [51], thus providing the basis for extending this work to human studies.

GBCA-enhanced 4.7T MRI in the guinea pig has elucidated the diffusion mechanics and hearing safety of IT gadolinium [52]. Specifically, the optimal time for contrast diffusion was 7–24 h, with contrast clearance within 4 days in normal guinea pigs. In this study, IT GBCA was not associated with a shift in auditory brainstem response (ABR). Kakigi et al. [32] demonstrated that intercellular spaces were markedly enlarged in guinea pig's ears injected with non-diluted GBCA and endocochlear DC potential (EP) was decreased. However, when eightfold diluted GBCA was used, no changes in EP were noted and no significant morphological difference was identified on electron microscopy in the stria vascularis between the ears injected with diluted contrast agent and saline [32]. This finding indicates that the safety profile of IT contrast may be concentration-dependent.

Imaging EH in Humans

The seminal work with MR imaging of EH was performed at Nagoya University in Japan and University of Tampere Medical School, Finland, with scans in human subjects with Ménière's symptoms compared to those with other inner ear disorders. Their studies confirmed that IT injection of 8- to 16-fold volume dilution of Omniscan and Magnevist was evident in the perilymph of the cochlea, vestibule, and semicircular canals [8, 11, 18]. The diluted contrast could be detected on 1.5T systems, with improved resolution using a surface coil [53]. 3T MR systems improved in plane resolution to 0.4×0.4 mm [8], with resolution further improved using head coil arrays [54].

Subsequent studies documented efforts to improve detection through variations in pulse sequences, establishing that the contrast was more conspicuous on 3D FLAIR techniques than conventional T1-weighted imaging [8, 55]. However, because both the endolymphatic space and the surrounding bone of the modiolus have near-zero values on these sequences, the accuracy of the depicted endolymphatic space has been questioned. 3D-inversion recovery sequences with real reconstruction (3D real IR) techniques demonstrated easier segmentation of bone from endolymphatic and perilymphatic spaces (and agreed with 2D findings) [56], but were less robust than 3D FLAIR at lower contrast dilutions [11]. Modifying the 3D FLAIR sequence and decreasing the slice thickness to

0.8 mm improved the ability to reformat images and minimize partial volume effects in assessment of the perilymph signal [9]. Based on these data, the first grading scale for EH on MRI was developed [57].

Another attempt to resolve the endolymphatic space involves a subtraction image in which a positive image of the endolymph (the perilymphatic space with gadolinium is suppressed by shortening inversion time) is subtracted from a positive perilymphatic image, creating a “HYDROPS” image (HYbriD of reversed image of positive endolymph signal and native image of positive perilymph signal) [12]. Unfortunately, these separate sequences require lengthy scanning time and are subject to positive endolymphatic image failure due to a low signal-to-noise ratio [58].

Current State of the Art and Controversies

Assessment of Current Technique: Protocols, Reproducibility, Grading

Attempts at semi-quantitative characterization of the extent of endolymphatic distention have been hampered by the achievable resolution in vivo. Current state of the art imaging at 3T can achieve 0.4 mm in plane resolution and 0.8 mm through-plane resolution. As the diameter of the basal turn of the cochlea is ~ 2.2 mm [59] and the endolymphatic space represents only 20 % of that volume [60], there are inherent partial volume effects of endolymph, perilymph, and bone within any given voxel. Further distortion of the true boundaries of these spaces can occur with variation in protocol parameters, such as changes in inversion time (exploited for the HYDROPS2 protocol) [61], with chemical shift effects [62], or by the selection of window/level parameters at the workstation that affect perception.

In 2009, Nakashima et al. [57] proposed a grading scale based on the manual segmentation of the area of the signal void attributed to the endolymphatic space relative to that of the total membranous labyrinth (perilymph and endolymph) evident on 3D real IR images after IT GBCA (Table 1). True volumetric assessment was limited due to through-plane resolution of 2 mm, contributing to partial volume averaging artifact. The calculated ratio of signal void:total vestibular fluid area was used to define the extent of hydrops, and a visual assessment was used to determine the extent of cochlear hydrops. This scale attributed a vestibular area ratio of 33.3–50 % to correspond to mild hydrops, and >50 % to be significant hydrops. This grading system does not account for rupture of Reissner's membrane, when contrast may directly enter the endolymphatic space, or cases where contrast does not diffuse into the perilymphatic space.

Table 1 Grading of endolymphatic hydrops using MRI

Grade of hydrops	Vestibule (area ratio) ^a	Cochlea
None	<33.3 %	No displacement of Reissner's membrane
Mild	>33.3 %, ≤50 %	Displacement of Reissner's membrane area of cochlear duct < area of the scala vestibuli
Significant	>50 %	Area of the cochlear duct exceeds the area of the scala vestibuli

^a Ratio of the area of the endolymphatic space to that of the fluid space (sum of the endolymphatic and perilymphatic spaces) in the vestibule measured on tracings of images. Reproduced with permission from grading of endolymphatic hydrops using MRI from Nakashima et al. [57]

A separate scoring system was proposed based on an imaging series of 214 ears of 107 patients after IT GBCA injection [63••] in asymptomatic patients and patients with MD, delayed EH, and other inner ear disorders. Contrast enhancement was assessed visually and assigned points of 0 (no enhancement), 1 (partially visible), and 2 (completely visible) in each of the following anatomic locations: basal, middle, and apical cochlear turns, and each of the superior, horizontal and posterior semicircular canals. Vestibular contrast enhancement was assigned as 0 (none), 3 (partial), or 6 (complete). The derived model was significant for detecting distention of the endolymphatic space for summed labyrinth scores <14.5 of possible 18 points, and the

authors suggest that this system is accurate for radiologic diagnosis of MD.

Additional stratification attempts have been made based on smaller series with semi-quantitative scales [33] or by visual assessment [64•]. Quantitation of signal intensity remains elusive, as the signal intensity identified in a region of interest at the workstation is influenced by many factors, including the MR system, field strength, imaging sequence, acquisition parameters, coil inhomogeneity, and contrast agent. However, calculations of signal intensity ratios (e.g., cochlea to medulla) have been shown to be reproducible without having to separately correct for coil inhomogeneity [65]. Subtraction imaging has been proposed to minimize the subjectivity of observer grading [66], however, must be interpreted with knowledge of possible artifact introduced in both acquisition and processing.

IV Versus IT Contrast

The optimal route and dose of GBCA administration may be decided in part on the clinical situation and available imaging resources Table 2. IT GBCA have the benefit of improved contrast, with the concentration of gadolinium in the perilymph after eightfold IT administration estimated to be 0.1 mmol/L [11]. This improved contrast is particularly helpful in the research setting to clarify diffusion and clearance characteristics and to optimize anatomic detail as new protocols and technology improve resolution. IV GBCA provides the potential for a more acceptable clinical

Table 2 Summary of recent evidence of MRI evaluation of EH: Methods and clinical significance

Study	Study characteristics	Conclusions
IV versus IT contrast		
Yamazaki et al. [69•]	Retrospective analysis of 61 patients	IT- provides higher perilymph enhancement than the IV contrast [better separation of perilymph/endolymph; IV contrast allows bilateral evaluation]
Grading		
Barath et al. [64•]	Retrospective analysis of 53 patients	Subjective grading system for EH defined; EH detected in 73 % of possible MD, 100 % of probable MD, and 95 % of definite MD; EH identified in 22 % clinically silent side
Fang et al. [63••]	Retrospective analysis of 107 patients	EH grading based on quantitative scoring system; highly accurate for radiologic diagnosis of MD; no significant difference between delayed EH and MD
Clinical significance of imaging EH		
Pyykko et al. [79••]	Evaluation of 340 patients from a tertiary referral hospital; Cross-sectional study of patients from Finnish Meniere Federation; MRI of 224 patients with MD in Japan	20 % of patients with MD have a delay in diagnosis of more than 5 years; EH is often bilateral in patients with unilateral MD; asymptomatic EH may be a harbinger of early disease
Fiorino et al. [83•]	Cohort of 32 patients	3D-FLAIR MRI with IT contrast demonstrates increased enhancement abnormalities and increased EH severity with MD duration

protocol, as the agents are already FDA approved, IT injection is not required, and simultaneous evaluation of both the ears can be performed. Both the 4 h imaging delay after IV and 24 h imaging delay after IT GBCA have their own advantages and disadvantages for patient scheduling, however, in both settings, pre-injection imaging should be performed to exclude signal alterations suggestive of hemorrhage, which may be obscured on post-contrast images.

Ultimately, these two routes appear to provide distinct and complimentary information regarding physiologic changes in MD and other inner ear disorders, with the IV route reflective of blood-labyrinthine barrier breakdown [64•, 67, 68] and the IT route reflective of round and oval window permeability [14, 18, 21, 69•]. It is important to remember that all GBCA are not equal, and efficacy and toxicity profiles have not been developed for IT injection, which remains off-label use [70].

What are the Therapeutic Implications of EH Imaging?

Because EH can be clinically silent and the severity of EH does not necessarily correlate with the severity of symptoms in MD, the clinical utility of detection of EH on MRI has been brought into question. In fact, in some studies, the degree of EH demonstrated on MRI has not been shown to correlate with hearing level in patients with MD [46], and MRI has identified many subjects with EH who are asymptomatic [71]. Despite this, the MRI evaluation of EH remains a topic of interest not only in classical MD, but also in the evaluation of patients with atypical MD [72, 73], post-traumatic or delayed EH [74, 75], EH associated with sudden sensorineural hearing loss [76], and EH in patients with vestibular migraine [77]. In MD, investigators have explored whether the demonstration of EH on MRI is useful for the early detection of EH, in predicting response to therapy, and in the progression of the disease.

The correlation between the severity of EH demonstrated on MRI and symptoms of MD is debated in the literature. Fukuoka et al., found that the degree of EH demonstrated on MRI did not correlate with hearing level in patients with MD [46]. However, Gürkov et al. [78] found that in patients with MD, hearing loss correlated significantly with cochlear hydrops and that saccular dysfunction (as measured by VEMP) correlated significantly with vestibular hydrops. The strict inclusion criteria in the latter study, adding ECOG results to the AAO-HNS criteria for MD, may account for the different results of these two studies.

The second clinical application of MR evaluation of EH is that it may allow early detection of MD [22]. In fact, a recent cross-sectional study showed a significant time delay to diagnosis (and initiation of treatment) of MD, with 20 % of patients having a delay of more than 5 years

[79•]. Some have proposed that asymptomatic EH may actually be early detection of the disease [71], which is particularly salient when the unaffected ear of a patient with MD shows EH on MRI.

Beyond timely diagnosis, MRI evaluation of EH may provide valuable information about IT treatment modalities. For instance, studies by Zou et al. [19, 20] demonstrating an oval window pathway of GBCA diffusion is clinically relevant because IT gentamicin treatment may selectively affect the vestibule (its target) rather than the cochlea (which can cause hearing loss) through the oval window. Moreover, these authors and others suggest that imaging with IT GBCA can be used to evaluate the permeability of the windows to medications such as steroids and gentamicin prior to treatment [11]. However, as of yet, IT GBCA have not been shown to be useful in predicting the efficacy of gentamicin partial chemolabyrinthectomy [80, 81].

Finally, MRI has been used to document progressive changes of MD [82]. Fiorino et al. [83•] demonstrated that ears of patients with MD show various degrees of impaired perilymphatic enhancement in addition to cochlear duct distention. Moreover, the prevalence of abnormal intralabyrinthine enhancement and the severity of EH were found to be proportional to MD duration. These authors suggest that MRI, thus, chronicles the progressive degeneration of intralabyrinthine structures in MD. Although the evolution of the disease may be seen on imaging, MRI has not been able to document a change in EH after treatment with IT gentamicin in patients with MD [84].

Clinical Underestimation or MR Overestimation of EH

Both the ears can be evaluated simultaneously after IV GBCA, and a few studies have performed bilateral IT GBCA in patients with MD. These internal comparisons have generated discussion mirroring the ongoing clinical question of who develops bilateral MD symptoms, when the second ear becomes affected, and the potential benefits of early detection. MR findings categorized as hydrops have been reported in 22 % of asymptomatic ears in patients with MD [64•], similar to rates identified in autopsy series [85], glycerol and ECOG tests [86], and longitudinal clinical series of progression [87]. In a recent series, hydrops was described in 29 of 45 (65 %) asymptomatic ears [79•].

At this point, it is unclear if mild endolymphatic distention evident on MR in asymptomatic ears is a deviation from their baseline or if it will progress. Therefore, MR evaluation with IV GBCA may help to identify or stratify an “at risk” population for future natural history or interventional studies. It is important to remember that 5–10 % of patients with MD have no evidence of endolymphatic

distention on IV or IT GBCA MRI [46, 64•, 79•], and that none of the present imaging studies have been confirmed with the gold standard of postmortem histopathologic analysis. This dilemma of clinical underdiagnosis or imaging overdiagnosis deserves ongoing debate.

Conclusion

These studies have highlighted the challenges implicit in the development of a technique for MR demonstration of EH, while simultaneously assessing its clinical significance. Resolution and signal-to-noise ratio have improved with MR technologic advances and post-processing techniques; however, there remains a need for improved spatial resolution and contrast of the membranous labyrinth before this technique can be rigorously applied. In addition, the correlation of progressive imaging findings in MD with the natural history of the disease and, eventually, with final histopathology, would provide greater confidence in interpreting the findings of these initial clinical studies.

The ideal MRI protocol for demonstration of EH would not only clearly define the endolymphatic space, but also allow evaluation of the internal auditory canals and other extra-labyrinthine structures. Ultimately, any protocol proposed for clinical assessment and grading of EH needs to be reproducible in the clinical setting and achieves a high inter-rater reliability in interpretation of images.

Key points are:

1. While MR imaging of the inner ear with IT or IV GBCA continues to improve in resolution and reproducibility, it remains an indirect assessment of the endolymphatic volume and does not reflect endolymph composition or dynamics.
2. IV versus IT GBCA each have advantages and disadvantages for visualization of the perilymphatic space, and may serve complimentary roles in clinical and research settings to understand the pathophysiology and natural history of EH and MD.
3. The current best resolution has been demonstrated with heavily T2-weighted 3D FLAIR sequences on 3T MR systems using a 32 channel head coil, achieving $0.4 \times 0.4 \times 0.8$ mm resolution. Variations in scanner model, software, protocols, and coils may all contribute to reproducibility of findings.
4. Commercially available IV contrast agents are not approved for IT use, and further data regarding individual profiles of permeability across the round window membrane, potential toxicity, and clearance have yet to be performed.
5. Caution should be taken in diagnosing a patient with EH based on imaging alone, given the known

limitations of the emerging technique and lack of consensus or data regarding grading.

6. The MR demonstration of EH may allow more timely diagnosis of MD and may elucidate changes that occur with disease progression, but definitive clinical applications remain to be elucidated.

Compliance with Ethics Guidelines

Conflict of Interest Mia E. Miller and Julie Bykowski declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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