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Delayed Contrast MRI for the Evaluation of Ménière's Disease – An Australian Perspective

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ABSTRACT

Introduction. Ménière's Disease is a chronic inner-ear disease attributed to endolymphatic hydrops. Magnetic resonance imaging with gadolinium allows visualisation of endolymphatic hydrops in vivo and may be an adjunct to diagnosis.

Methods. Thirty-eight patients suspected of having Ménière's Disease underwent T2 weighted 3D FLAIR and True Inversion Recovery sequence MRI 4-hours post double-dose intravenous gadolinium. Presence of endolymphatic hydrops was graded by two radiologists at 0 and 4-months. Correlation to clinical diagnosis was assessed using Fisher's exact test.

Results. Hydrops was identified in 88%, 17% and 27% of patients with Definite Ménière's, Probable Ménière's and Undifferentiated disease respectively. A significant correlation existed between diagnosis and presence of hydrops. Sensitivity and specificity was 88% and 67% respectively. Intra- and inter-observer agreement for presence and grading of hydrops was near-perfect, and substantial to near-perfect respectively.

Conclusion. MRI demonstrates radiographic hydrops with significant correlation to clinical diagnosis, and good intra- and inter-observer agreement.

Keywords: Vertigo, Tinnitus, Magnetic resonance imagery, Inner ear, Sensorineural hearing

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INTRODUCTION

Ménière's Disease (MD) is a chronic condition, presenting with episodic vertigo, hearing loss, tinnitus, and aural fullness.[1] Delays in diagnosis frequently occur due to the fluctuating nature of symptoms, and reliance on patients meeting clinical criteria, which can take up to 5 years in 20% of patients.[2] Currently, diagnosis remains based on the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) criteria for stratification of patients into definite or probable MD, which was proposed in 2015.[1] However, patients frequently present with symptoms which fall outside of these criteria, and may take many years to fully present.[3] Further complicating the presentation, symptoms may be permanent in the late stages of the disease.[4]

In order to aid in the diagnosis, many clinicians refer patients for audio-vestibular assessment. However, there is no definitive gold standard objective diagnostic test.[3] In part, this is likely due to the fluctuating nature of the disease and a poor understanding of the pathophysiology of MD.[5] MD is attributed to the presence of endolymphatic hydrops (EH),[5] but the presence of EH does not appear to fully explain the symptoms of MD and is not exclusive to the condition, having been reported to be present in other vestibular diseases.[6]

Imaging has long played a role in excluding pathology involving the retro-cochlear pathways, most commonly vestibular schwannoma. However, advancements in MRI hardware and pulse sequences have led to the adoption of magnetic resonance imaging (MRI) to identify EH in vivo, initially using delayed MRI about 24 hours after intratympanic administration of dilute gadolinium based contrast agents (GBCA), but now most commonly using 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) and 3-dimensional real

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(ie phase-sensitive) inversion recovery (real IR) sequences four hours after intravenous (IV) GBCA administration.[7] Both the intratympanic and intravenous methods rely on the uptake of contrast into the perilymph on delayed MRI, allowing identification of the non-enhancing endolymphatic spaces, specifically the cochlear duct, utricle and saccule.

There is currently very little Australian data regarding MRI for MD, apart from one recent study in South Australia.[8] We aimed to evaluate the sensitivity and specificity of delayed contrast MRI for patients with suspected MD, and assess the correlation between clinical diagnosis and presence of hydrops on MRI in a Western Australian context.

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METHODS

Approval for this retrospective study was sought from the North Metropolitan Health Service Quality Improvement Department (49176).

Patients. Between December 2022 and July 2023, 38 patients presenting with audio-vestibular symptoms to a single otologist were referred for MRI with hydrops protocol at Perth Radiological Clinic.

Clinical Assessment. Patients were reviewed by a single otologist following referral for audio-vestibular symptoms. Age, comorbidities, presence of previous ear disease, laterality, and nature of symptoms was collected from patient notes. Results of tuning fork tests, audiometry and vestibular function (caloric testing, electrocochleography, cervical vestibular evoked-myogenic potentials, virtual head impulse test) were also recorded. Patients were grouped as Definite MD or Probable MD according to the AAO-NHS Criteria.[1] A third group was included of Undifferentiated patients not meeting the above criteria.

Imaging. All MRI was performed on a 3T MRI scanner using a 32-channel phased array coil (Philips Ingenia Elition). Initial standard MRI of the brain was performed, including a volumetric high resolution heavily T2-weighted sequence and volumetric T1-weighted sequences immediately following intravenous gadobutrol (Gadovist 1.0; Bayer) using double the standard dose of contrast (ie 0.2 mmol/kg). Following a four hour delay after contrast administration, two dedicated sequences targeted to the temporal bones were performed for assessment of endolymphatic hydrops and abnormal perilymph enhancement: (1) a Fluid Attenuated Inversion Recovery sequence (parameters: TR 6000ms; TE 178ms; TI 2250ms, echo train length 40; flip angle 90 degrees; slice thickness

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1.6mm with 0.8mm separation) and (2) a 3D True Inversion Recovery sequence (parameters TR 7000ms; TE 300ms; TI 1650ms, echo train length 123; flip angle 90 degrees; slice thickness 1.3mm with 0.65mm separation).

Image Interpretation. Images were interpreted by two head & neck radiologists each with 19 years' experience in head & neck imaging, blinded to the clinical information. Images were assessed for the presence of abnormal perilymphatic enhancement, and for the presence and severity of cochlear and vestibular endolymphatic hydrops. If present, cochlear and vestibular hydrops were graded on a 3- or 4-point grading system respectively, according to the system described by Bernaerts et al (Figures I and II). Interpretation was repeated at 4 months post initial readings to allow for intra-observer analysis.[4] Interobserver discrepancies were reviewed, and consensus reached.

Statistical Analysis. Interobserver and intraobserver reliability was assessed using a Cohen's Kappa test. Correlation between clinical diagnosis of MD with both vestibular function results (caloric weakness, elevated SP/AP ratio, reduced or absent cVEMP and abnormal vHIT) and presence of hydrops on MRI was assessed using Fishers Exact Test. Specificity and sensitivity was calculated across three groupings of clinical diagnosis: (1) Definite/Probable vs Undifferentiated, (2) Definite vs Undifferentiated and (3) Definite vs Probable/Undifferentiated.

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RESULTS

Thirty-eight patients, 18 males and 20 females were assessed over the period 8 months. The mean age was 58.5 years (range 25-89), of whom 4 had reported previous ear disease. Of these, 17 were diagnosed as Definite MD, 6 as Probable MD and 15 as Undifferentiated. Hydrops was found in 20 patients (53%), of which 3 had bilateral disease (Table I). Using a Fishers Exact Test, there was no significant correlation between clinical diagnosis and vestibular function results supporting a diagnosis of MD (caloric weakness ($p=0.11$), ECOG with elevated SP/AP ratio ($p=0.61$), absent or reduced cVEMP ($p=0.43$), abnormal vHIT ($p=1$)).

Interobserver agreement was calculated using a Cohens Kappa test (Table II). Agreement for presence of cochlear and vestibular hydrops was 0.89 and 0.79 respectively. Agreement for presence of perilymph enhancement was 0.62. Agreement for presence of cochlear and vestibular hydrops irrespective of grade was 0.67 and 0.65 respectively.

Similarly, intraobserver agreement was calculated using a Cohens Kappa test (Table II). Agreement for presence of cochlear hydrops was 0.89 and 0.89 for Observer 1 and 2 respectively, and 0.89 and 0.80 for presence of vestibular hydrops. Agreement for presence of perilymph enhancement was 0.64 and 0.62 for Observer 1 and 2 respectively. Agreement for cochlear hydrops grading was 0.80 and 0.80, and 0.73 and 0.67 for grading vestibular hydrops for Observer 1 and 2 respectively.

Fifteen of 17 (88%) patients with Definite MD, 1 of 6 (17%) with Probable MD and 4 of 15 (27%) of undifferentiated patients had hydrops on MRI (Table I). Fishers exact test for correlation between clinical diagnosis and presence of hydrops was 0.00035 ($p<0.05$).

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Sensitivity and specificity was calculated at 88% and 67% respectively, when comparing only Definite MD and Undifferentiated patients. This decreased to 70% and 67% respectively when grouped as Definite MD/Probable MD and Undifferentiated patients, or increased to 88% and 71% respectively when comparing Definite MD and Probable MD/Undifferentiated patients (Table III).

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DISCUSSION

MD commonly presents with episodic vertigo, hearing loss, tinnitus, and aural fullness.[1] Patients regularly undergo a range of vestibular testing, although these have failed to demonstrate adequate sensitivity.[9] Therefore, patients presenting with variable or atypical symptoms frequently experience a delay in diagnosis due to reliance on meeting clinical criteria and lack of definitive diagnostic test. Differentiating between MD and alternative vestibular diagnoses becomes important when initiating and continuing management.

The pathophysiology of MD remains poorly understood. The presence of endolymphatic hydrops has been recognised as the pathologic correlate, but can also be present in asymptomatic patients and other ear diseases.[4, 10, 11] Previously, identification of hydrops was only possible at post-mortem.[2, 12] Outside of Australia, MRI with administration of contrast has been used to visualise hydrops in situ.[4, 6, 10, 11, 13, 14] This technique relies on the increased permeability of the blood-labyrinth barrier associated with MD and hydrops, allowing increased contrast ingress into the membranous labyrinth which can then be assessed at MRI.[15] Commonly, MRI is performed using a 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence or real 3-dimensional inversion recovery sequence,[4] with either intra-tympanic or intravenous gadolinium.[4, 15-17] Intravenous dosing has the benefit of reduced time between gadolinium administration compared to intra-tympanic administration, as well as being less invasive and allowing simultaneous imaging of both ears.[4, 11] The protocol evaluated employed a heavily T2 weighted, 3D FLAIR and 3D-True Inversion Recovery sequences, following IV gadolinium administration.[4]

Intraobserver and Interobserver Agreement. There have been multiple proposed criteria for interpreting imaging findings;[18] this study used the system developed by Bernaerts et al.[4]

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Bernaerts et al outline a 4-point system for vestibular hydrops (Figure I), a 3-point system for cochlear hydrops (Figure II), and assesses presence of perilymphatic enhancement.[4] As seen in the current study, intra- and interobserver was substantial to near perfect across groups when using this system, and comparable to previously published data.[6] Previous systems have been proposed, including evaluating the ratio of the endolymph space[19] and use of 3-point grading of vestibular and cochlear hydrops,[11] however, the addition of a low-grade vestibular hydrops and evaluating perilymph enhancement improved sensitivity without compromising specificity.[4] It is also worth noting that Bernaerts et al assessed interobserver reliability in clinical evaluation and radiological diagnosis, and found a greater interobserver reliability in radiological diagnosis, as compared to clinical diagnosis using the AAO-HNS 2015 criteria.[4]

Hydrops on MRI. Presence of EH in clinically definite MD was 88% (15/17), which is comparable to other published data.[6, 11] A significant correlation was also noted between clinical diagnosis as Definite, Probable or Undifferentiated and presence of EH on MRI. Higher rates of hydrops was reported in the Undifferentiated group (27% or 4/15) compared to other studies.[11] Notably many of these studies compared contralateral asymptomatic ears, patients with alternative vestibular diagnoses or healthy patients with patients with clinically diagnosed Definite MD, thus accounting for a wide variation in reported rates of hydrops in patients not diagnosed with MD.[3, 6, 11] The current study's patient population consisted entirely of patients who were offered the MRI as part of evaluation for MD. It is also reported that endolymphatic hydrops may be a common endpoint for multiple pathological processes.[11] The presence of EH therefore does not provide definitive conclusions regarding pathophysiological sequence, disease development or disease progression, nor has EH been established as the cause of symptoms in MD. This makes

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interpretation of the significance of hydrops being present in patients with clinically alternative diagnoses challenging.[4, 10, 11]

Sensitivity and Specificity. The current study reported sensitivity and specificity of 88% and 67% for clinically definite MD compared to the undifferentiated group. The reported sensitivity is comparable to other published data,[4, 6, 20] however the current study's specificity is lower. Possible explanations for this include the current study's patient population including only those patients being evaluated for MD. Van Steekelenburg et al also compared clinical diagnosis and MRI findings in patients presenting with suspected MD.[6] Following assessment by three otolaryngologists, patients were diagnosed as Probable MD, Definite MD, other Vertigo-associated inner ear pathology, or asymptomatic. All patients subsequently underwent MRI assessing for EH, and sensitivity and specificity was reported at 92% and 93% respectively. These figures were calculated from the Definite MD and other Vertigo-associated inner ear pathology groups only as opposed to the current study comparing patients who have all been suspected of MD during their clinical course. This same difference in patient population is present in other studies reporting on sensitivity and specificity[4, 6, 20] and may account for this current study's lower specificity. Due to the good sensitivity but moderate specificity, the current study supports use of MRI as an aid to diagnosis, particularly in patients suspected of having MD but who may not give clear histories.

Strengths of this study include the evaluation of both intra- and interobserver agreement across all elements of image interpretation, as well as cohort size. A key limitation however is the inability to include asymptomatic patients as a control group for imaging.

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CONCLUSION

The use of MRI following the current protocol of a heavily T2 weighted sequence, 3D FLAIR and 3D True Inversion Recovery sequences four-hours post double-dose IV gadolinium is useful in detecting hydrops in vivo, with good sensitivity. Images can be interpreted with substantial intra- and interobserver agreement, and presence of hydrops is significantly correlated to a clinical diagnosis of Definite MD. Limitations exist due to reduced specificity in the population studied. We suggest the utility of the hydrops protocol studied lies in the use of MRI to aid diagnosis of patients with suspected MD, but with unclear history or not meeting the AAO-HNS 2015 criteria.

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TABLES

Table I

Presence of hydrops on MRI vs clinical diagnosis of Ménière's Disease.

Clinical Diagnosis	Hydrops Present	Hydrops Absent	Total (n)
Undifferentiated	4 (27%)	11 (73%)	15
Probable MD	1 (17%)	5 (83%)	6
Definite MD	15 (88%)	2 (12%)	17
Total	20 (53%)	18 (47%)	38

Table II

Cohen's kappa coefficient for interobserver and intraobserver agreement for presence of cochlear hydrops, vestibular hydrops and perilymph enhancement.

		Interobserver	Intraobserver	
			Observer 1	Observer 2
Presence of hydrops	Cochlear hydrops	0.89	0.89	0.89
	Vestibular hydrops	0.79	0.89	0.80
	Perilymph enhancement	0.62	0.64	0.62
Grading of hydrops	Cochlear hydrops	0.67	0.80	0.80
	Vestibular hydrops	0.65	0.73	0.67

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Table III

Sensitivity and specificity for MRI detection of hydrops by clinical diagnosis of Ménière's disease, for patient cohort groups of (1) Definite MD vs Undifferentiated, (2) Definite MD/Probable MD vs Undifferentiated and (3) Definite MD vs Probable MD/Undifferentiated.

	Sensitivity	**Specificity**
Definite MD vs Undifferentiated	88%	67%
Definite MD/Probable MD vs Undifferentiated	70%	67%
Definite MD vs Probable MD/Undifferentiated	88%	71%

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FIGURES

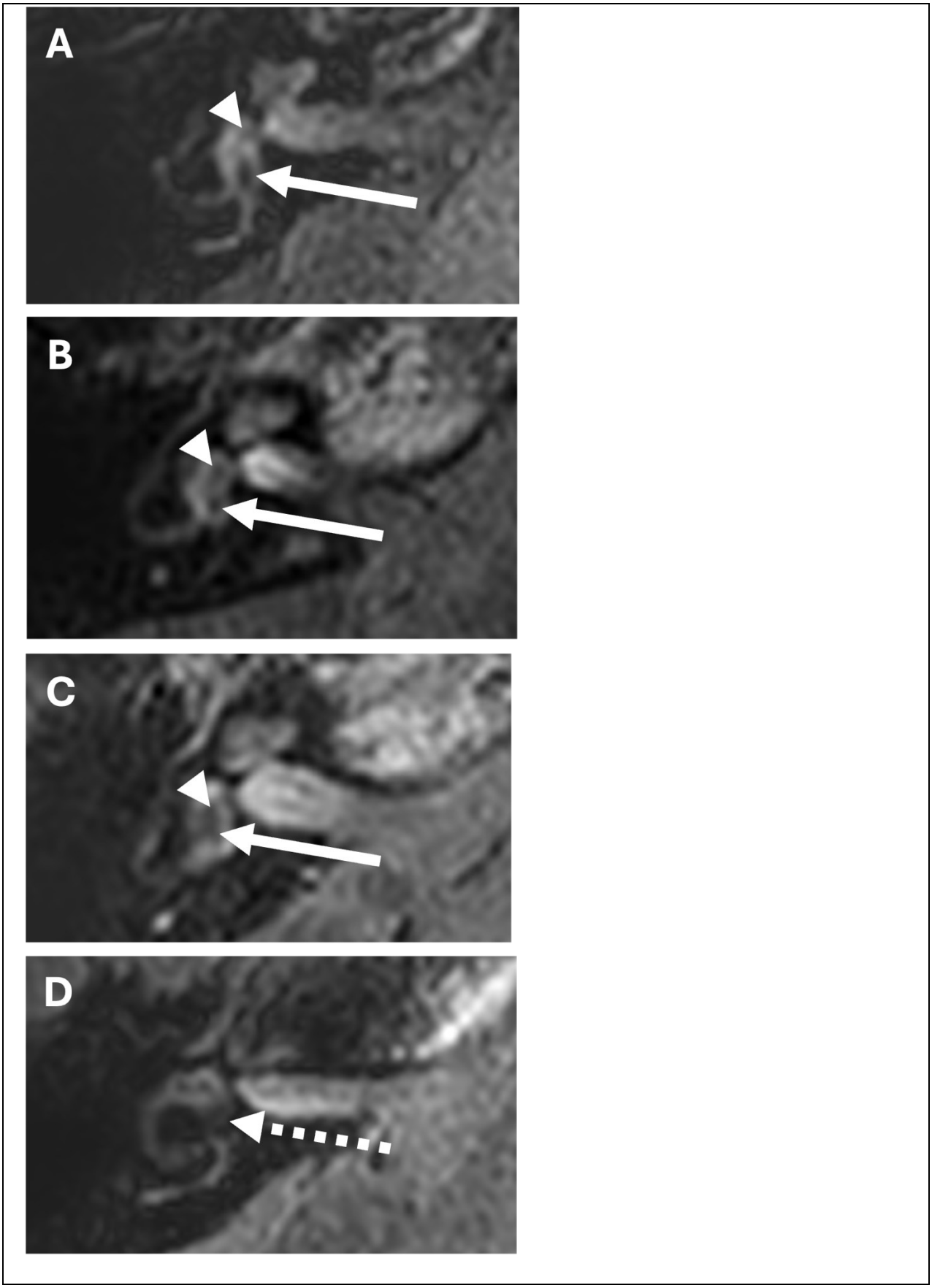

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Figure I. 3D FLAIR-weighted MR Images of the right inner ear acquired 4 hours after intravenous administration of gadolinium-based contrast, illustrating Bernaerts et al grading of vestibular hydrops.[4] (A) Normal smaller saccule (arrowhead) anterior and slightly medial to the larger utricle (arrow), on an axial image through the inferior part of the vestibule. The saccule and utricle appear as non-enhancing endolymphatic "filling defects" surrounded by enhancing perilymph. (B) Grade 1 vestibular hydrops with mild enlargement of the saccule (arrowhead), of similar size to the utricle (arrow) but remaining separated by enhancing perilymph. (C) Grade 2 vestibular hydrops with confluence of the saccule (arrowhead) and utricle (arrow), with surrounding perilymph still visible. (D) Grade 3 vestibular hydrops with confluence of the saccule and utricle (dotted arrow), and with effacement of the surrounding enhancing perilymph in the vestibule.

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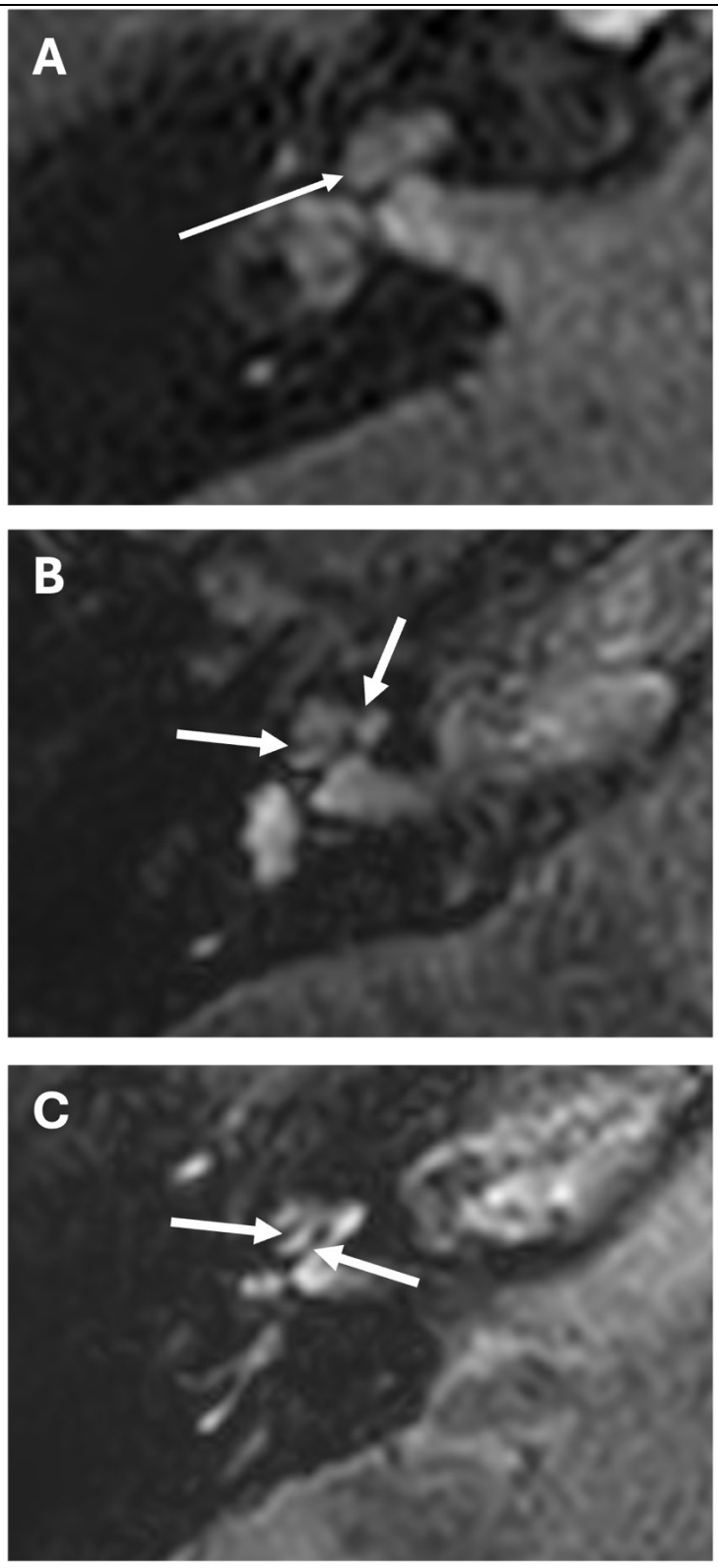

Figure II. 3D FLAIR-weighted MR Images of the right inner ear acquired 4 hours after intravenous administration of gadolinium-based contrast, illustrating Bernaerts et al grading of cochlear hydrops.[4] (A) Normal cochlear duct (arrow) barely

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visible as a thin non-enhancing line between the enhancing perilymph within scala vestibuli and the scala tympani. (B) Grade 1 cochlear hydrops with dilatation of the cochlear duct appearing as indenting non-enhancing hypointense nodules peripherally (arrows). (C) Grade 2 cochlear hydrops with band-like hypo-intensities (arrows) of the markedly dilated cochlear duct.

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SUMMARY STATEMENT

- Meniere's Disease is attributed to the presence of endolymphatic hydrops but diagnosis remains clinical through use of the AAO-NHS Criteria
- Endolymphatic hydrops was previously diagnosed at post-mortem examination but improvements in technology have seen increasing use of MRI enhanced by intravenous gadolinium to visualise hydrops in vivo
- Use of MRI in assessing Meniere's Disease has not yet been studied in Western Australia with the Perth Radiological Clinic protocol
- The current study found presence of radiographic hydrops correlates significantly to clinical diagnosis, with good intra- and inter-observer agreement for presence and grading of radiographic hydrops and sensitivity and specificity was 88% and 67%
- The use of MRI may be of greatest value to aid diagnosing Meniere's Disease in patients with unclear presentation

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