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Review Article

Recent Trends in The Management of Meniere's Disease

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Abstract

Background: Meniere's disease is a chronic illness affecting the quality of life and productivity of patients with minimal diagnostic tools available, limited options of treatment and a lot of follow up difficulties. we discuss old and recent tools helping in the diagnosis and the treatment of Meniere's disease. **Aim of the study:** Discussing recent modalities in the management of Meniere's disease including diagnosis, treatment and follow up. **Methods:** A literature review of recent tools in the management of Meniere's disease. **Conclusion:** Post contrast magnetic resonance imaging of endolymphatic hydrops is a very important diagnostic tool in the definite diagnosis of Meniere's disease and we should consider intratympanic injection of gadolinium as another tool of contrast delivery in cases with no contraindications to this method. Follow up for Meniere's disease cases is so substantial in the management of these cases so recent mobile applications helping in that should be put into consideration. Another field that light should be directed to is the regeneration of vestibular hair cells, also this field is still under research but it has a very essential role in the treatment of Meniere's disease and more researches should be directed to this scope.

Key words: Magnetic resonance imaging, endolymphatic hydrops, intratympanic injection, follow up, vestibular hair cells regeneration.

Introduction

Ménière's disease (MD) is a condition affecting the inner ear that disrupts both hearing and balance. It is distinguished by symptoms such as dizziness, ringing in the ears, hearing loss caused by damage to the sensory nerves, feelings of nausea and vomiting, and a sensation of fullness in the ears .[1]

The prevalence of the condition can't be determined accurately due to the rarity of the condition and methodological limitations and it ranges from 3.5 to 513 per 100,000.[2]

Although the disease was discovered by prosper Meniere 150 years ago [3] still certain diagnoses are unavailable and definite or probable diagnosis as classified and revised by the Classification Committee of the Barany Society [4] [5] depends mainly on history and frequent audiometric evaluation which may be sometimes confusing specially with other vestibular disorders and make diagnosis not made at one point in time; rather, it may take

months or even years to fully evaluate the clinical symptoms and signs leading to definitive diagnosis.[6]

The exact etiology of MD is still not completely clear. However, one of the most accepted pathophysiologies of MD is the presence of endolymphatic hydrops (EH) [7][8], and the presence of EH in patients with MD is an important tool in the diagnosis of the disease which will be discussed later.

MD is associated with severe disability, especially during acute attacks which may hinder work, domestic or even leisure activities due to sensory hearing loss or sudden episodic attacks of vertigo [9] [10], so searching for recent methods of treatment is very important.

Different classifications of Meniere's disease

1-Definite, probable and possible Meniere's disease:

TABLE 1
Ménière's Disease: Diagnostic Criteria from AAO-HNS

Symptom Criteria	Certain Ménière's Disease	Probable Ménière's Disease	Possible Ménière's Disease
Spontaneous vertigo	> 2 vertigo episodes > 20 minutes' duration	1 vertigo episode > 20 minutes' duration	Episodic vertigo without documented hearing loss
Hearing loss	Audiometrically documented on at least 1 occasion	Audiometrically documented on at least 1 occasion	Fluctuating or fixed sensorineural hearing loss with disequilibrium, but without definitive episodes
Tinnitus or aural fullness	Present	Present	Not present
Other causes	Excluded	Excluded	Excluded

Abbreviation: AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery
Source: Otolaryngol Head Neck Surg. 1995.[1]

These criteria were established by the American Academy of Otolaryngology - head and neck surgery (AAO - NHS) in 1995 [11].

2-Definite and probable Meniere's disease:
The previous criteria were revised by the classification committee of the Barany Society and four other national and international organizations in 2015 [6] [7].

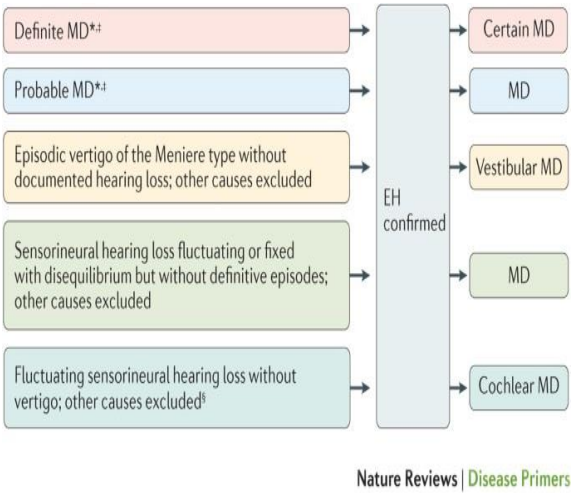
Table 2
Revised diagnostic criteria of Meniere's disease

Classifications	Criteria
Definite	• 2 or more episodes of vertigo, 20 min–12 h
	• Fluctuating aural symptoms
	• Not better accounted for by another vestibular diagnosis
	• Audiometrically documented hearing loss
Probable	• 2 or more episodes of dizziness or vertigo, 20 min–24 h
	• Fluctuating aural symptoms
	• Not better accounted for by another vestibular diagnosis

Adapted from the Classification Committee of the Bárány Society, The Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), and the Korean Balance Society.

3-Classification according to the presence of endolymphatic hydrops:

A new classification for Meniere's disease was proposed in 2016, which incorporates the use of endolymphatic hydrops imaging [1]. However, the terms "cochlear MD" and "vestibular MD" that were introduced by the Committee on Equilibrium of the American Academy of Ophthalmology and Otolaryngology in 1972 [12] were removed in the 1995 criteria set by the AAOHNS [11]. This removal was due to doubts regarding the presence of endolymphatic hydrops in atypical types of Meniere's disease. Recent MRI investigations have demonstrated that both cochlear MD and vestibular MD should be incorporated into the diagnosis of MD due to the presence of EH in numerous atypical patients [1].



Imaging of endolymphatic hydrops (EH) is highly beneficial for diagnosing Meniere's disease (MD). It particularly assists in distinguishing Meniere's disease from vestibular migraine, especially in patients who have auditory symptoms and are clinically suspected of having vestibular migraine [13][14]. Furthermore, studies have demonstrated a gradual development of endolymphatic hydrops (EH) in patients with Meniere's disease (MD) through the use of sequential magnetic resonance imaging (MRI) scans [15]. Additionally, a relationship has been detected between the evolution of EH and the deterioration of cochlear, saccular, and horizontal semi-circular canal functions [16][17][18]. Eccentric hypertrophy (EH) is observed in all individuals diagnosed with confirmed muscular dystrophy (MD). The information is referenced by footnotes 19 and 20.

Quantification and grading of endolymphatic hydrops

- Quantification of endolymphatic hydrops by post-contrast MRI is very helpful in certain diagnoses of MD, various semi-quantitative grading criteria have been proposed, one of these gradings is as follows : [21]

 Normal cochlear duct: The cochlear duct is hardly visible and does not show enhancement. It is located inside the augmenting scala vestibuli and scala tympani (Figure 1a).

 Grade I cochlear hydrops refers to a condition where there is a slight enlargement of the cochlear duct, which does not show enhancement, into the scala vestibuli. This enlargement partially blocks the scala vestibuli. (See Figure 1b).

 Grade II cochlear hydrops refers to a condition where the scala vestibuli is completely blocked by the excessively swollen cochlear duct, as shown in Figure 1c.

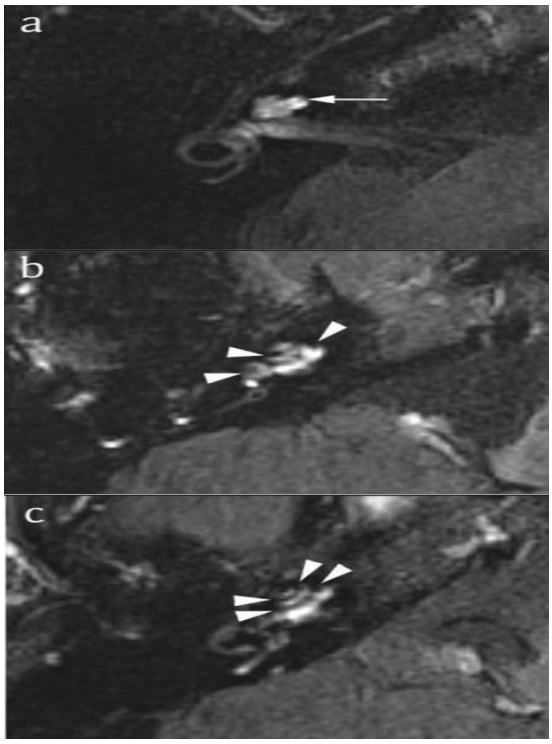


Figure 1: Cropped axial 3D-FLAIR image of the right ear, four hours after intravenous administration of a double dose of Gd, at the level of the mid turn of the cochlea. (a) Observe the distinct separation between the enhancing scala vestibuli and scala tympani (spaces filled with perilymph) with the non-enhancing cochlear duct or scala media (space filled with endolymph) evident as a thin hypo-intense line (arrowhead): indicating normal findings. (b) The non-enhancing dilated cochlear duct (arrowheads) is visible as a tiny non-enhancing protrusion into the enhancing scala vestibuli. The patient has cochlear hydrops classified as grade 1 according to the Baráth classification. (c) The expanded scala media or cochlear duct is displacing the scala vestibuli and can be observed as band-like areas of reduced intensity (arrowheads) in the middle and upper part of the cochlea. The patient has grade 2 cochlear hydrops as per the Baráth classification [21].

 Normal vestibule: The non-enhancing saccule and utricle can be clearly distinguished from the enhancing vestibule. The saccule, which is the smallest of the two structures, is situated in the anterior, inferior, and medial regions of the vestibule (Figure 2a).

 Low-grade vestibular hydrops refers to a condition where the saccule, which is typically the smallest of the vestibular sacs, has increased in size and is now equivalent to or greater than the utricle, but they have not merged together yet (Figure 2b).

 Grade I vestibular hydrops refers to the expansion of the endolymphatic space in the saccule, utricle, or both. The perilymphatic area surrounding the bone vestibule can still be seen around the edges.

 Grade II vestibular hydrops is characterized by significant distension of the saccule and utricle, with no apparent enhancement of the perilymphatic space surrounding them (Figure 2d).

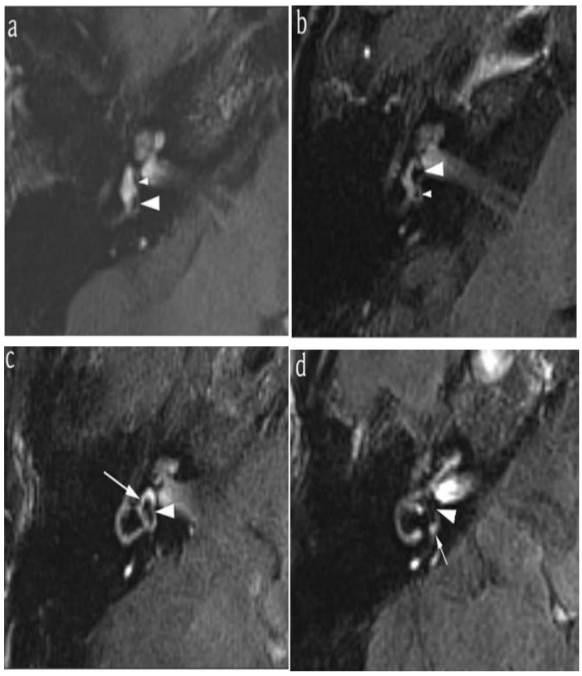


Figure 2: Cropped axial 3D FLAIR image of the right ear, four hours after intravenous administration of a double dose of Gd, at the level of the lower part of the vestibule. (a) The saccule (little arrowhead) and utricle (big arrowhead) may be easily distinguished. No evidence of vestibular hydrops is present. (b) In this instance, the saccule, which is typically the smaller of the two vestibular sacs, has

grown to be the same size as or larger than the utricle, but they have not yet merged together. According to the Baráth classification, which utilizes a three-stage grading system, this is considered to be within the normal range. Nevertheless, it is important to acknowledge that this is a relatively modest manifestation of vestibular hydrops, which can be classified as abnormal according to the four-stage grading system for vestibular hydrops. (c) The saccule and utricle have increased in size and merged together, although they are still surrounded by contrast enhancement in the perilymphatic area. Based on the Baráth classification, this is classified as grade 1 vestibular hydrops. However, when applying the four-stage grading method, this condition is classified as grade 2 vestibular hydrops. (d) Observe the expansion and merging of the saccule and utricle, without any contrasting structures around them (shown by the arrowhead). Only a small amount of contrast is apparent in the base of the posterior semicircular canal (arrow). According to the Baráth classification, which utilizes a three-stage grading system, this condition is classified as grade 2 vestibular hydrops. Applying the four-stage grading method, this condition is classified as grade 3 vestibular hydrops [21].

A more accurate technique for quantifying EH involves the utilization of Mimics software to create a three-dimensional model using inner ear MRI, allowing for the measurement of the endolymphatic hydrops index (EHI). This approach provides additional insights into the presence of endolymphatic hydrops in the superior and posterior semicircular canal, which are often overlooked by two-dimensional methods. The calculation of EHI is as follows:
The equation EHI is defined as the difference between the total volume and the perilymph volume, divided by the total volume .

The calculation of EHI in this study showed a strong correlation with many factors, including the stage of Meniere's illness, the ratio of Summating Potential to Action Potential in Echocochleography, low-frequency pure tone audiometry, and the Asymmetric Ratio of Vestibular Evoked Myogenic Potential .[22]
Magnetic Resonance Imaging (MRI) of enlarged vestibular aqueduct (EH) has provided valuable insights into the distinct impact on the cochlear and vestibular compartments. Furthermore, EH is frequently observed in the asymptomatic ears on the opposite side, with a significant occurrence rate of up to 65% [23][24]. According to a recent study, EH predominantly affected the cochleovestibular system, with vestibular EH being somewhat more prevalent than cochlear EH [23].

Intravenous (IV) versus intratympanic (IT) gadolinium injection

The benefit of IT delivery is that it produces higher concentrations of GBC, while using a much lower total dosage (approximately 1:1,000) compared to i.v. delivery. This leads to a greater contrast between the endolymph and perilymph in the inner ear fluid spaces, allowing for a clearer visualization. As a result, the observer can more accurately assess the extent of endolymphatic hydrops.[25]
Another benefit of IT administration of GAD is its utilization as an initial predictive tool for drug distribution to the inner ear, namely for the distribution of gentamicin and steroids following intratympanic administration. This aids in treatment and enhances the quality of patients' lives.[25]

In addition, the injection of IT (intrathecal) GBC (Gadolinium-based contrast) reduces the probability of systemic toxicity, but it may be linked to local irritation and toxicity [26][27]. However, the existing published data indicate a lack of ototoxicity throughout both short and long durations of observation [28][29][30].

Nevertheless, the approach is subject to certain limitations. It can thoroughly examine endolymphatic hydrops specifically on the side where gadolinium was administered. Consequently, patients requiring examination of both ears must receive two injections. Additionally, the IT application is unsuitable for patients with middle ear illness, since it hinders the absorption of contrast.

Another drawback of IT injection is the insufficient transfer of the gadolinium agent from the tympanic cavity to the perilymph space through the round window in certain patients. Additionally, the extent of the contrast effect of perilymph following intratympanic gadolinium injection may exhibit greater variations between individuals compared to IV injection.[25]

Mobile applications aiding in the diagnosis of MD

As mentioned before one important corner stone in the diagnosis of MD is fluctuating

hearing loss documented by at least two PTA, nowadays there are many mobile applications for smartphones acting as daily portable audiometry enabling patients to test their hearing level during and in between attacks thus helping physicians in diagnosis.
Another application helping in the diagnosis and follow up is an application that enables patients to record nystagmus during vertigo attacks therefore helping the physician to diagnose by knowing the direction and character of nystagmus.

Regeneration of hair cells after gentamycin injection

Hair cells (HCs) are the sensory cells in the inner ear that are responsible for the detection of sound and maintenance of balance [31]. Each hair cell is surrounded by non-sensory supporting cells (SCs) that act like glia cells and create the necessary conditions for hair cells to perform their function.[32]

Hair cells (HCs) and supporting cells (SCs) originate from a shared precursor during development after the completion of cell division. The determination of whether a precursor becomes an HC or a SC relies on the presence of the Atoh1 transcription factor and the Notch-Delta signaling pathway. The expression of the Atoh1 transcription factor guides the precursor cells towards the HC fate. Hair cells (HCs) exert lateral inhibition on neighboring cells by activating the Notch-Delta signaling pathway [34][35]. This signaling system suppresses the production of Atoh1, causing the inhibited cells to develop as supporting cells (SCs) .

Typically, in mammals, the utricular hair cells (HCs) are spread out over an epithelial sheet called the macula. Within the macula, there is a distinct band in the center known as the striola. The striola covers around 10-20% of the macula area and is specifically formed to fit the design of the macula. This observation was made using fluorescent protein in transgenic mice. The study revealed that the promoter responsible for the expression of proteolipid protein 1 (PLP1) is active in the extrastriolar areas, but not in the striola [36][37][38][39][40].

In contrast, stem cells (SCs) in reporter mice for Lgr5, a gene that is activated by Wnt signaling and stimulates cell growth, are found only in the striolar region during development [37][41][42]. Lgr5 is subsequently suppressed and is not present in the fully developed vestibular sensory epithelia of adult individuals [43, 44].
In mammalian vestibular organs, there are two types of hair cells: Type I and Type II. These two types differ in their shape, innervation patterns, and ion channel composition. Their physiological reactions vary in terms of rapidity .[38]
Post-mitotic stem cells (SCs) maintain the ability to re-enter the cell cycle, however this capability is no longer present by P5 [38]. The loss of this ability is caused by the development of dense actin bands at the adherens junctions around the necks of SCs. The bands are believed to make the adult sensory epithelia more rigid and stable. The thickness of these bands in mammals is one reason why regeneration responses are suppressed in the mature mammalian utricle [38]. There is no subsequent stem cell division in the mature tissue after experiencing a loss of hematopoietic cells. The regenerated hair cells in the vestibular sensory epithelia of adult animals are formed through the direct transformation of supporting cells, as established by Golub et al. [45].
Based on the prior introduction, there are now four ways being investigated for the regeneration of vestibular hair cells:

- The induction of SC conversion is a mechanism being studied to regenerate vestibular hair cells. Two approaches have been explored: viral-mediated transduction using the Atoh1 gene and pharmacological suppression of the Notch system.
- Studies conducted on mature mice [46] and humans [47] have demonstrated that adenoviral vectors can transport Atoh1 to utricle explants. These studies involved the use of aminoglycoside to remove hair cells, and both indicated the development of cells that expressed the myosin (myo)7a marker, which is characteristic of hair cells.

Transcriptomic analysis in both cases showed an increase in the expression of numerous genes that are typical of HC, while genes associated with SC were found to have decreased expression. Nevertheless, a considerable number of HC genes remained unexpressed, and morphological examinations revealed the absence of structured hair bundles .

 Notch signaling inhibition in adult mouse utricle explants has been found to cause supporting cell conversion. Conversely, in the vestibular region of humans, the suppression of Notch activation did not result in the production of cells that express myo7a.[47]

 After destroying hair cells in DTR mice, studies using cell fate mapping techniques have demonstrated that PLP1-expressing supporting cells (SCs) in both early post-natal and mature animals (P60) exclusively transform into Type II hair cells. These transformed cells are identified based on their appearance, specific molecular markers, and thorough electrophysiological evaluation .

 Activating Wnt signaling has been suggested as a potential mechanism for promoting the growth of Lgr5+SCs, which could lead to hair cell regeneration [37][48][49]. A combination of stimuli that seem to enhance the growth of Lgr5+ cells obtained from inner ear tissues, including those from primates and humans, and that encourages the development of daughter cells into hair cells has been documented [50]. Nevertheless, the stimulation of Wnt in mature utricles explants following hair cell loss did not result in the proliferation of supporting cells [51]. However, a limited quantity of stem cells that included mitotic markers were detected when both Wnt activation and inhibition of the Notch pathway were applied simultaneously.

Conflict-of-interest statement: The authors hereby declare that they have no competing interest.

Ethical approval: Ethical permission was taken from a local faculty of medicine research ethics committee (MUFMIRB) No:101/10/2022. In accordance with the protocol established by the committee, all of the patients gave their permission to retrieve their data for research following the confidentiality of their information was guaranteed. As a result, the study does not compromise the patient's health or safety in any way.

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