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## Current status on researches of Meniere's disease: a review

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### ABSTRACT

**Background:** Meniere's disease (MD) is a complex and multifactorial inner ear disease. The etiology of MD is unclear. Significant progress had been made in diagnosis and treatment. Complete cure for this disease is still impossible.

**Objectives:** This review covers the updated research results in MD in the past decades.

**Material and methods:** Recent publications were critically reviewed.

**Results:** The relationship between Endolymphatic hydrops and Meniere symptoms requires further study. Direct visualization of EH is achieved by special sequences of inner ear MRI. Appearance of EH could be observed in MD patients both in symptomatic and asymptomatic ears. Visualization of EH *in vivo* might make a great substantial improvement in diagnose of MD. The first goal of the management of MD is to reduce the attack frequency. Several safe and effective medical and surgical therapies are practiced to help patients to control vertigo and preserve hearing.

**Conclusions and significance:** There has been no major breakthrough in the pathogenesis research of MD in recent years. Visualization of EH *in vivo* might make a great substantial improvement in diagnose of MD. Clinicians still have few effective ways to alleviate the progress of the disease.

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## Introduction

Meniere's disease (MD) is a complex and multifactorial inner ear disease. The characteristic feature of this inner ear disorder is a combination of episodic vertigo with neurovegetative symptoms, sensorineural hearing loss, and tinnitus or aural fullness. Different hypotheses about the mechanism of MD had been proposed. But currently there is no universally accepted theory on the underlying pathophysiology of the disease. The controversy about the relationship between endolymphatic hydrops (EH) and MD has always existed, and the cause of Meniere's disease remains unclear. Two mainly worldwide used diagnostic criteria for MD are defined by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1995 and Barany society in 2015. The 2015 criteria excluded certain MD and possible MD. The simplification of the diagnostic criteria is conducive to a unified recognition of the disease internationally. The application of Magnetic Resonance Imaging (MRI) makes the visualization of EH possible for MD patients. The MRI may provide useful information for EH indicating possible MD if patient has characteristic symptom. Conservative or surgical therapy options should be offered to MD patients according to treatment history and the





severity of their symptoms. Conservative therapy should always be the first option for the newly diagnosed MD patients. In this review, we summarized the recent progress in the aspects of epidemiology, pathophysiology, diagnosis techniques and management.

## Histopathology and mechanism

### MD and EH

EH has been considered the hallmark of MD since the histopathological investigation was first reported. Displacement of Reissner's membrane and dilation of the scala media of the cochlea are histological marker of EH. In the early study of MD, it is generally considered that all patients with MD should exhibit EH, and all patients with EH should also exhibit MD symptoms. However, study on human temporal bone histopathology indicates that EH should be considered as a histologic marker for MD, but not a true pathological mechanism.

Other histological features have also been observed by temporal bone studies of MD patients. These studies include findings of ischemia of the *stria vascularis*, fibrous tissue

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proliferation in saccular, atrophy of the sac and loss of epithelial integrity, hypoplasia of the vestibular aqueduct, and spiral ganglion degeneration at the apex of the cochlea [1]. Recently, histopathological examination of vestibular nerve (VN) in MD patients revealed evidence of various types of chronic VN impairment, including the formation of corpora amylacea, axon atrophy, and severe damage to the myelin sheath. Density of corpora amylacea is positively correlated with the duration of disease, as well as the degree of hearing impairment [2].

### Genetic aspects

MD is considered a result of multiple genes interacting with environmental factors. Familial MD has been observed in 5–15% patients and shows a feature of autosomal dominant inheritance. Martin-Sierra found two rare missense mutations on DPT and SEMA3D genes by Whole Genome Sequencing in two Spanish MD families. Extracellular signal encoded by the genes is associated with the formation and maintenance of inner ear structures. They concluded that DPT and SEMA3D gene mutations might be associated with the pathogenesis of familial MD [3].

### Autoimmune aspects

Animal studies and human studies had provided evidences that endolymphatic sac has an immune function and the presence of autoantigens can damage inner ear by autoimmune reactions. Recently, an immune genotyping array study in bilateral MD identified the first locus, at 6p21.33. Signaling analysis predicted the pathway of TWEAK/Fn14, which is involved in the modulation of inflammation in several human autoimmune diseases, can induce an inflammatory response mediated by nuclear factor- $\kappa$ B in MD[4].

### Diagnosis

The diagnosis of Meniere's disease still relies mainly on detailed medical history and clinical symptoms, supplemented by auditory and vestibular function examinations. The earliest diagnostic criterion was proposed by AAO-HNS in 1995 in which the diagnosis of MD is divided into four grades: namely certain MD, definite MD, probable MD, possible MD. More recently, the diagnostic criterion proposed by the Barany Association in 2015 only divided MD into two types: definite MD and probable MD. The pathological biopsy of the inner ear that could not be performed was excluded as definite diagnosis criterion. In the 1995 AAO-HNS guidelines, MD was divided into four stages based on patient's pure tone hearing threshold. While the guideline proposed by Barany Society in 2015 did not adopt the classification of hearing threshold. Hearing threshold is an important reference factor in the selection of treatment strategies and in the evaluation of treatment efficacy in MD.

### EH observation

Because of the inability to perform inner ear biopsy on MD patients, direct visualization of EH has been an important goal for clinicians. In 2007, Nakashima first observed EH in patients by 3D fluid-attenuated inversion recovery (3D-FLAIR) MRI after intratympanic injection of gadolinium-based contrast agent. With recent technical developments in MRI, 3D real inversion recovery (3D-real IR), Rapid acquisition with relaxation enhancement (RARE), has made the visualization of EH more clearly. A subtraction of a positive endolymph image from a positive perilymph image which was termed a HYDROPS image (hybrid of the reversed image of the positive endolymphatic signal and native image of the positive perilymph signal) could demonstrate anatomic information of the various inner ear compartments in one image series. Different grading scale for evaluating the degree of EH has been proposed. A widely used three-stage grading system for hydrops in vestibule and the cochlea was proposed in 2009. In a more recent study, the authors proposed the inversion of the saccule to utricle ratio (SURI) on an oblique sagittal section as a marker of EH. They considered SURI a more reliable approach than conventional semi-quantitative methods for diagnosing MD [5].

The correlation between MRI image and audio-vestibular function test is still inconsistent. Quatre reported that the correlation between MRI and electrocochleography (EcochG), MRI and shift of distortion product otoacoustic emissions (DPOAEs) were not significant. While, EH was correlated with hearing loss [6].

EH observation *in vivo* patients also confirmed the theory that EH should be considered as a histologic marker for MD, but not a true pathological mechanism. EH is closely related to hearing loss but does not necessarily result in Ménière's symptoms. Appearance of EH could be observed in MD patients both in symptomatic and asymptomatic ears [7].

### Functional assessment

#### Cochlea function assessment

Clicks EcochG had been used for the diagnosis of EH since 1970s. EcochG shows a high average summing potential (SP) to action potential (AP) ratio in patients with EH. The click SP/AP ratio has been world-widely used as a diagnostic tool for MD and also become the basis of numerous publications. A new technique that can help to understand the low-frequency hearing loss in early stage of MD is called Auditory Nerve Overlapped Waveform (ANOW) [8]. ANOW originates in the apical half of the cochlear turn. Researchers believed that ANOW changes were more sensitive than traditional CAP thresholds in detecting apical turn hydrops.

#### Utricle and saccule function assessment

Vestibular-evoked myogenic potentials (VEMP) testing is a neurophysiological technique that can assess saccule and utricle function. Cervical VEMP (cVEMP) is believed to

assess saccular vestibular signals carried *via* the vestibulospinal tract. Furosemide-loading VEMP (FVEMP), that is a cVEMP rises 60 min after furosemide administration in patients with MD, can also be a useful tool in assessing saccule function. Seo found that recent and frequent vertigo attacks were closely related with the results of FVEMP, which indicated a consequence of membranous labyrinth rupture during vertigo attacks [9]. Ocular VEMP (oVEMP) can be used in utricle function assessment.

### Semicircular canal function assessment

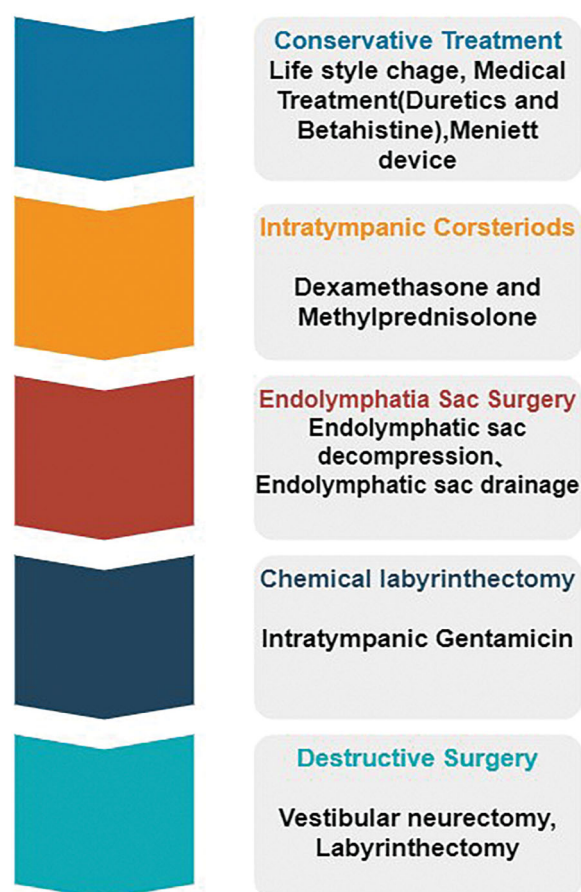
Caloric test and video-head impulse test (vHIT) can be used to examine the function of semicircular canals. Caloric test mainly assess the horizontal semicircular canal function while vHIT enables instrumental assessment of the vestibulo-ocular reflex in each of the 6 semicircular canals at high frequencies. It has been revealed that vHIT was almost normal in advanced MD patients while only 8% of caloric reflex test results were normal [10]. The contradiction between caloric test and vHIT could be explained as when the head turns in the plane of a semicircular canal, the ampulla neurons are stimulated and neurons in the contralateral canal are inhibited by reverse endolymphatic flow. This mechanism operates in vHIT, but not during caloric reflex testing.

### Management

Management of MD should be a combination of lifestyle and dietary changes, medical therapy, and psychological counseling. The first goal of the management of MD is to reduce the attack frequency. Secondly, vestibular function and auditory function preservation should also be considered. The modification of the lifestyle is important for MD Patients. High quality of sleep, decreasing stress, avoiding caffeine, alcohol and tobacco and adopting a low salt diet are recommended. Conservative treatment must first be considered and destructive treatment is preferred for patients with irreversible hearing loss [11] (Figure 1). Treatment of bilateral MD is difficult and the choice of treatment strategy should be extremely cautious. The possibility of developing into bilateral MD should be taken into consideration by clinical physicians at the beginning of unilateral involvement of the disease.

### Betahistine

Betahistine, a strong H3 antagonist that can increase cochlear blood flow, increases histamine turnover in the central nervous and vestibular system, and decreases vestibular input in the peripheral vestibular system. The minimum dose of 48 mg/d is effective. In patients with severe MD that low dose is ineffective, the dose of betahistine can be increased to 288~480mg/d. Betahistine is also effective to improve the recovery of static symptoms in MD patients with unilateral vestibular loss after unilateral vestibular neurectomy.



**Figure 1.** Treatment of MD should be a combination of lifestyle and dietary changes, medical therapy, and invasive therapy. Conservative treatment must first be considered and destructive treatment is preferred for patients with irreversible hearing loss.

### Diuretics

Hydrochlorothiazide, acetazolamide and chlorthalidone are most commonly used diuretics as treatments of MD. But a systematic review including 19 studies overall, of which 4 were randomized trials, revealed that the certainty of the evidence that whether diuretics could lead to a relief of symptoms is still very low [12]. It is commonly believed that diuretics are supposed to relieve vertigo and hearing loss by decreasing volume and pressure in endolymph. But Rosenbaum outlined the possibility that an abrupt lowering of blood pressure by diuretics can trigger an adverse sympathetic reaction and transmit misleading information to the cochlear vasopressin receptors. This eventually would lead to a permanent damage in inner ear [13].

### Intratympanic corticosteroids

When conservative and medical treatment failed in vertigo control, intratympanic corticosteroids are recommended as the second line treatment [11]. The rate of persistent tympanic membrane perforation following intratympanic steroid injection is low. Patients with a history of radiation to the head and neck may be at increased risk for persistent tympanic membrane perforation. The possible mechanisms of

corticosteroids in treating MD could be the effect of changes of fluid regulation, and ion regulation [14].

Both dexamethasone and methylprednisolone are acceptable by intratympanic injection. Either daily injection for consecutive days or weekly injection for consecutive weeks is proved to be effective. Several randomized, double-blind, placebo-controlled studies and systemic reviews have confirmed the significant improvements in vertigo control with intratympanic corticosteroids injection [15]. However there still lacks an international consensus on ideal frequency and dose of intratympanic corticosteroids injection. Also, controversy still exists regarding the efficiency between intratympanic corticosteroids injection and oral medical therapy. Paragache compared application of intratympanic dexamethasone and conventional medical therapy with dietary control and oral betahistine. The result showed no difference in vertigo control and tinnitus.

### **Intratympanic gentamicin**

Intratympanic gentamicin (ITG), a chemical labyrinthine resection treatment, is recommended as a fourth line treatment in refractory MD [11]. The risk of hearing loss should not be ignored for its ototoxic effects. Mitochondrial mutation of the gene *MTRNR1* is not screened in most of the countries. This mutation exposes to a complete and definitive deafness after a single injection of gentamicin. Patients receiving ITG should be well informed before treatment. A double-blinded, randomized, placebo-controlled trial revealed that ITG can be an effective treatment for vertigo in MD. The potential risk of hearing loss exists, but the trials showed no difference in hearing level between pre-treatment and post-treatment [16]. Patel et al. [17] compared the effectiveness between ITG and intratympanic methylprednisolone in a randomized, double-blind trial. The result showed an 87% reduction in vertigo frequency in ITG group and 90% reduction in vertigo frequency in intratympanic methylprednisolone group. There is no significant statistical difference in vertigo control and hearing levels. Both intratympanic methylprednisolone and gentamicin are safe and effective therapeutic options for refractory MD.

### **Endolymphatic sac surgery**

Endolymphatic sac surgery (ELSS) is a preferred treatment for refractory MD patients in the early stage. Both vestibular function and hearing function can be well preserved. Endolymphatic sac decompression (ESD) surgery is widely accepted for its easy manipulation and less post-operative complications. Literatures have shown efficacy of ESD for the control of vertigo and hearing loss in 64.5–90% of patients [18]. The controversy on the effectiveness of ESD still exists because it is difficult to conduct a single-blind or double-blind trial in surgical treatment of MD. Some clinicians question its long-term efficacy and consider that vertigo control is achieved more due to a placebo effect than because of the procedure itself.

Recently, Saliba et al. [19] proposed endolymphatic duct blockage (EDB) surgery as a new surgical procedure for treating MD. They reported a 96.5% complete control of vertigo in EDB group and 37.5% in ESD group after 24 months follow-up. Hearing level was well preserved in both groups. The assessment of quality of life also showed a significant improvement.

### **Destructive surgery**

Labyrinthectomy and vestibular neurectomy (VN) are considered to have the highest possibility of vertigo control in intractable MD patients. VN could be considered when patients have poor but serviceable hearing. Labyrinthectomy is suitable for patients with severe to profound sensorineural hearing loss. Meningitis, cerebrospinal fluid leak and epidural hematoma are possible post-operative complications following VN. Yu [20] reported a 100% vertigo control both in labyrinthectomy group and VN group. The quality of life also improved in both groups. Generally, destructive surgery is less and less performed.

### **Summary**

There is no denying that the etiology of MD is still unclear and completely cure for this disease is still impossible. Visualization of EH *in vivo* might make a great substantial improvement in diagnosis of MD, but again MRI cannot be regarded as a golden standard for the MD diagnosis. Several safe and effective medical and surgical therapies are practiced to help patients to control vertigo and preserve hearing. However, there has been no major breakthrough in the pathogenesis research of MD in recent years.

### **Disclosure statement**

No potential conflict of interest was reported by the author(s).

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### **References**

- [1] Cureoglu S, da Costa Monsanto R, Paparella MM. Histopathology of Meniere's disease. *Oper Tech Otolaryngol Head Neck Surg.* 2016;27:194–204.
- [2] Wang P, Zhu H, Lu W, et al. Subcellular abnormalities of vestibular nerve morphology in patients with intractable Meniere's disease. *Front Neurol.* 2019;10:948
- [3] Martín-Sierra C, Gallego-Martinez A, Requena T, et al. Variable expressivity and genetic heterogeneity involving *DPT* and *SEMA3D* genes in autosomal dominant familial Meniere's disease. *Eur J Hum Genet.* 2017;25:200–207.
- [4] Frejo L, Requena T, Okawa S, et al. Regulation of Fn14 Receptor and NF- $\kappa$ B Underlies Inflammation in Meniere's Disease. *Front Immunol.* 2017;8:1739.
- [5] Attyé A, Eliezer M, Boudiaf N, et al. MRI of endolymphatic hydrops in patients with Meniere's disease: a case-controlled

- study with a simplified classification based on saccular morphology. *Eur Radiol.* 2017;27:3138–3146.
- [6] Quatre R, Attyé A, Karkas A, et al. Relationship between audio-vestibular functional tests and inner ear MRI in Meniere's disease. *Ear Hear.* 2019;40:168–176.
- [7] Liu Y, Jia H, Shi J, et al. Endolymphatic hydrops detected by 3-dimensional fluid-attenuated inversion recovery MRI following intratympanic injection of gadolinium in the asymptomatic contralateral ears of patients with unilateral Ménière's disease. *Med Sci Monit.* 2015;21:701–707.
- [8] Lichtenhan JT, Lee C, Dubaybo F, et al. The auditory nerve overlapped waveform (ANOW) detects small endolymphatic manipulations that may go undetected by conventional measurements. *Front Neurosci.* 2017;11:405.
- [9] Seo T, Shiraishi K, Kobayashi T, et al. Recent and frequent vertigo attacks produce negative findings on furosemide-loading vestibular evoked myogenic potential testing in Meniere's disease. *Front Neurol.* 2018;9:636.
- [10] Rubin F, Simon F, Verillaud B, et al. Comparison of video head impulse test and caloric reflex test in advanced unilateral definite Meniere's disease. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2018;135:167–169.
- [11] Nevoux J, Barbara M, Dornhoffer J, et al. International consensus (ICON) on treatment of Ménière's disease. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2018;135:S29–S32.
- [12] Crowson MG, Patki A, Tucci DL. A systematic review of diuretics in the medical management of Ménière's disease. *Otolaryngol Head Neck Surg.* 2016;154:824–834.
- [13] Rosenbaum A, Winter M. Are diuretics effective for Ménière's disease? *Medwave.* 2018;18:e7188.
- [14] Froehlich MH, Lambert PR. The physiologic role of corticosteroids in Ménière's disease: an update on glucocorticoid-mediated pathophysiology and corticosteroid inner ear distribution. *Otol. Neurotol.* 2020;41:271–276.
- [15] Lavigne P, Lavigne F, Saliba I. Intratympanic corticosteroids injections: a systematic review of literature. *Eur Arch Otorhinolaryngol.* 2016;273:2271–2278.
- [16] Postema RJ, Kingma CM, Wit HP, et al. Intratympanic gentamicin therapy for control of vertigo in unilateral Meniere's disease: a prospective, double-blind, randomized, placebo-controlled trial. *Acta Otolaryngol.* 2008;128:876–880.
- [17] Patel M, Agarwal K, Arshad Q, et al. Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: a randomised, double-blind, comparative effectiveness trial. *Lancet.* 2016;388:2753–2762.
- [18] Sood AJ, Lambert PR, Nguyen SA, et al. Endolymphatic sac surgery for Ménière's disease: a systematic review and meta-analysis. *Otol Neurotol.* 2014;35:1033–1045.
- [19] Saliba I, Gabra N, Alzahrani M, et al. Endolymphatic duct blockage: a randomized controlled trial of a novel surgical technique for Ménière's disease treatment. *Otolaryngol Head Neck Surg.* 2015;152:122–129.
- [20] Yu H, Yang J, Zhou X. The effect of surgical treatment on Meniere's Disease. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2019;33:501–504.