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Review

European Position Statement on Diagnosis, and Treatment of Meniere's Disease*

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Meniere Disease keeps challenges in its diagnosis and treatment since was defined by Prosper Meniere at the beginning of 19th Century. Several classifications and definition were made until now and speculations still exist on its etiology. As the etiology remains speculative the treatment models remain in discussion also.

The European Academy of Otology and Neurotology Vertigo Guidelines Study Group intended to work on the diagnosis and treatment of Meniere's disease and created the European Positional Statement Document also by resuming the consensus studies on it.

The new techniques on diagnosis are emphasized as well as the treatment models for each stage of the disease are clarified by disregarding the dilemmas on its treatment. The conservative, noninvasive and invasive therapeutic models are highlighted.

KEYWORDS: Meniere's disease, treatment, betahistine, neurectomy, intratympanic treatment, diuretics, enedolymphatic sac surgery, intratympanic gadolinium, videohead impulse test

INTRODUCTION

Meniere's disease (MD) is a heterogeneous group of disorders defined by three core symptoms: episodic vertigo, tinnitus, and sensorineural hearing loss. The relevance of defining the diagnosis and treatment of MD could not be significantly achieved, as there still appear many arguments and few randomized double-blind prospective studies in this regard. The definition and classification have showed several revisions as the proposal made by the Barany Society in 2015 has received a significant support.

The working group on vertigo guidelines established by the European Academy of Otology and Neurotology (EAONO) Otologic Guidelines began studying on MD in 2011, and the group members met several times to discuss and offer the EAONO consensus on the diagnosis and treatment of MD. A comprehensive literature search was performed using PubMed and Embase as well to conclude this review.

The evidence has been low in many aspects of diagnosis and treatment options in MD and because of this the EAONO working group needed to make this review for a better clarification.

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Meniere's disease is characterized by episodic vertigo, low frequency fluctuating sensorineural hearing loss, tinnitus, and fullness on the affected side. Gait problems, postural instability, and drop attacks may accompany.

There has been the consensus with the published temporal bone studies that Meniere's disease has signs of endolymphatic hydrops. However, saccular endolymphatic hydrops can be found also in 10% of normal subjects and in 40% patients with >45 dB sensorineuaral hearing loss without any vestibular symptom [2].

Gurkov et al [3] categorizes endolymphatic hydrops as "primary hydropic ear disease" (PHED) and secondary hydropic ear disease (SHED). The primary disease is still assumed to be idiopathic and covers the whole inner ear. The term "secondary hydropic ear disease" describes the conditions that cause hydrops of the inner ear secondarily (such as endolymphatic sac tumors). This needs to be defined by imaging techniques.

In contrast to the AAO-HNS criteria published in 1972, 1985, and 1995, Barany Society in collaboration with AAO-HNS, the Japan Society for Equilibrium Research, the EAONO, and the Korean Balance Society published the criteria for the diagnosis of Meniere's disease. The Definite Meniere's disease is characterized with episodic vertigo and fluctuating low to medium frequency sensorineural hearing loss, fullness, and tinnitus being manifested at least with two episodes. The duration is mentioned to be between 20 min to 12 hours. Hearing loss in close temporal relationship to the episodes should also be considered [1].

Meniere's disease showed comorbidities with several disorders including autoimmune diseases and migraine [4, 5]. Several lines of evidence support that genetic factors contribute to phenotype variations [6]. Some patients (as high as 10%) may have first and second-degree relatives confirming the familial aggregation [6, 7]. Most of these families show an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity [8, 9].

The Ménière's Disease Consortium (a European multicenter initiative to collect clinical data and biological samples) have conducted 2 large epidemiological studies using cluster analyses and it has identifed 5 subtypes of MD disease in patients with uni or bilateral involvement [10,11]. In unilateral MD, group 1 was the clinical variant most frequently observed (53%) and it included patients without a familial history of MD, migraine, or autoimmune comorbidity; MD type 2 was termed delayed MD and was found in 8% of cases and characterized by SNHL which antedated the vertigo episodes; familial MD or type 3 (13%) included all familial cases of MD; MD type 4 (15%) was associated with migraine with or without aura, and MD type 5 (11%) was defined by a concurrent autoimmune disorder [11].Moreover, the allelic variant rs4947296 is associated with bilateral MD and it has been found in 18% of patients with a comorbid autoimmune disorder [12]. When this advanced diagnosis can be achieved, MD should be treated according to its subtype characterization.

Assessment

Low to medium frequency sensorineural hearing loss as mentioned above is the most significant finding of MD. Therefore, an audiologic evaluation following a relevant history taking is mandatory for diagnosis of MD. Recurring and fluctuant characteristics of the hearing loss pattern is important to mention. The bedside eye movement evaluation represents a fundamental diagnostic step both in the first stage and during the follow-up.

Vestibular test battery

The methods to assess MD have now been enriched with new laboratory techniques. Videonystagmography (VNG) replaced electronystagmography, as it gave the opportunity of realtime observation of nystagmus with its third dimension. Caloric tests are still applicable.

Video head impulse tests are based on analyzing the vestibulo-ocular reflex with two parameters; gain and presence of overt/covert saccades. It is significantly the parameter of peripheral disease and can give access for evaluation of all semicircular canals indivdually. Video head impulse tests and caloric tests by VNG are the tests not competing but but are complementary to each other possibly because they test different frequency parts of the vestibular function [13].

Vestibular evoked myogenic potentials (VEMPs) help evaluate the function of the utricule and saccule as well as the superior and inferior vestibular nerves. VEMPs are the reflexes rising as a response obtained through the sternocleidomastoid and orbital muscles due to high intense acoustic stimuli. These can either be applied as bone conduction or air conduction to stimulate the otolith organs. Today VEMPs are rather used for monitoring the ototlith function and the effect of intratympanic gentamicin applications [14].

Electrocochleography was supposed to be the most specific test to diagnose Meniere's disease for a long time. As it detects the summating and action potentials (SPs and APs) arising from the cochlea and the nerve due to the click stimulations, the belief of elevation of the SP/AP ratio in hydrops populated this evaluation technique. There were difficulties in obtaining the evoked responses, as the ideal location was promontorium, which was not practical to put electrodes nearby the round window routinely in office-based conditions, and the response quality has been low with the tympanic membrane surface electrodes. Electrocochleography has lost its popularity over time [15].

Imaging

In 2007, Nakashima et al. [16] proposed 3 Tesla magnetic resonance imaging (MRI) evaluation of the inner ear following intratympanic gadolinium injection. Gadolinium that perfuses through the round window membrane allows the boundary between the endolymphatic space and the perilymphatic space to be distinguished.

MRI with intravenous (IV) administration of gadolinium has also been suggested. A delay of 4 hours is necessary following the injection of double dose of gadolinium. Both ears can be assessed but there is the risk of systemic toxicity due to the high dose of gadolinium [17].

While the T2-weighted images represent both perilymphatic and endolymphatic fluids, the bright signal on the 3D-FLAIR images represents only the perilymphatic fluid and internal dark signal represents the endolymphatic fluid [18].

In case the endolymphatic duct expands more than 33%, it should be argued as endolymphatic hydrops. However, the visualization of endolymphatic hydrops is not required to define MD and the MRI imaging should not be used to replace the diagnostic criteria of MD when also all definition criteria are fulfilled.

Firstline Management (Preventive)

A personalized approach for MD patients is strongly recommended. So, if a patient presents a comorbid condition such as allergy, migraine or autoimmune arthritis, they should be treated. The familial history of hearing loss and episodes of vertigo are also recommended, since genetic testing will identify the causal variant in 30% of familial cases, paving the way for gene therapy in few years.

Diet

The known adverse effects of caffeine and salt in MD is not clear. Low sodium diet and high water intake may prevent the release of vasopressin and help to maintain inner ear homeostasis [19, 20]. The AAO-HNS scale restricts caffeine in MD with the argument that caffeine can provoke modifications in the endolymph volume with its sympathomimetic action. The habitual consumption of caffeine varies due to the geography; hence, the relation of habitual intake of caffeine and Meniere's disease symptoms also differ. It is possible to assume that low amounts of caffeine, such as 100 mg/day, will not trigger Meniere's symptoms [21].

Betahistine

Betahistine is a weak histamine H1 agonist and a stronger H3 antagonist. This is the medication currently being used worldwide except for the USA. There have been remarkable studies about the efficacy of betahistine on reducing the vertigo episodes of MD, and some studies suggest its dosedependent effect in suppressing the frequency of vertigo attacks [22-25].

Furthermore, there are others, such as the Cochrane reviews, which support the positive effect of the medication on reducing the symptoms with good tolerance, also by arguing significant methodological limitations over the conducted studies; hence, larger studies for reaching to higher quality evidence on suggesting the use of betahistine [26].

A meta-analysis by Nauta [27] suggested the therapeutic benefit of betahistine in Meniere's disease.

The recently conducted multicenter study also known as BEMED suggested that two different doses (48 and 144 mg/day) of betahistine did not show any difference from placebo regarding the incidence of attacks and vestibular function [28].

The conflicting findings among different studies motivate further studies with well-defined inclusion and exclusion criteria and higher doses of betahistine to be accomplished. According to the clinical experience, the use of Betahistine 48 mg bid for 3-6 months to prevent Meniere's attacks can be advised.

Diuretics

The Cochrane report by Burgess & Kundu (2006) identified ten trials executed on diuretics' effect and among them two were placebo-controlled. As all were lacking the high quality of evidence, some studies have reported the efficacy of diuretics. The report concluded that there has been no good evidence of using diuretics in MD [29].

Diuretics are generally issued as first-line therapy for MD. The studies that support using diuretics have a low level of evidence [30]. The thiazide group diuretics can be a part of the medical treatment.

Secondline Management (Preventive)

In case medical treatments and refraining from excess of caffeine and salt does not control Meniere's episodes, a second-line treatment must be considered.

Intratympanic treatment has been very popular since the last two decades as being practical to apply even in the office setup.

Among the two available steroids derivatives, dexamethasone is practical to use due to better tolerance by the patients, as methylprednisolone creates burning sensation in the middle ear mucosa. The challenge with dexamethasone is its availability with low concentrations, such as 4 mg/mL.

The studies executed on application of intratympanic steroids for MD not show any homogeneity regarding the treatment protocols. Lavigne et al. [31] could only find one article being in favor of controlling tinnitus and vertigo in Meniere's disease. Being safe in terms of complications, such as hearing loss, has been the main advantage of using steroids. Individual based application of intratympanic dexamethasone can be favored.

Beyea et al. [32] reported that the effect of intratympanic dexamethasone application can have a shortterm control over the Meniere episodes as being effective in only 5% to avoid ablative surgery.

The Cochrane review by Westerberg [33] showed limited evidence to support the effectiveness of intratympanic steroids in MD treatment. Of note, the recent Oto-104 study with 12 mg dexamethasone can have the potential of discarding the disadvantages of intratympanic dexamethasone treatment regarding its low concentration [34].

Thirdline Management

Endolymphatic sac surgery was first defined by Portmann in 1927. There have been several discussions in favor and against this technique. The most remarkable argument against endolymphatic sac surgery was introduced by Jens Thomsen [35], which mentioned that the procedure has only a placebo effect.

The evidence level to support this surgery is low. Additionally, there are welldesigned randomized, double-blind, placebo-controlled studies for it [36].

The Cochrane review by Pullens et al. [37] over two randomized controlled studies showed that no significant effect could be achieved using the endolymphatic sac surgery, providing insufficient evidence for the beneficial effect.

Kitahara [38] proposed the injection of dexamethasone into the sac. As the endolymphatic sac is the only location for immune reactions in the temporal bone the hypothesis by Kitahara makes sense. In a retrospective study, Wick et al. suggested that endolymphatic sac shunt procedures may benefit from steroid instillation at the time of shunt placement [39].

Fourthline Management

Intratympanic Gentamicin Injection

Gentamicin is an aminoglycoside antibiotic having more vestibulotoxic than cochleotoxic effect. Its effect is mainly causing atrophy on type 1 vestibular cells as well as the neuroepithelium [40].

Although the intratympanic application of gentamicin poses the risk of hearing loss, many clinical studies have been designed to find out the lowest risk of its application with the maximum control of vertigo in MD. Hence, due to the toxic effect over the peripheral vestibular end-organ, dizziness and unsteadiness following the injection can be a minor problem that can be resolved by vestibular rehabilitation [41].

The intratympanic application of gentamicin has received more interest due to its strong effect over the Meniere episodes, that also beat the frequency of vestibular neurectomies.

The recommended application of gentamicin is one injection of 26.7 mg/mL concentration and scanning the vestibular physiological responses by the number of vertigo spells, a bedside evaluation, VEMPs, and video head impulse tests.

Fifthline Management

Advanced Surgery

Among the treatment techniques the only methods for MD that have gained high evidence are labyrinthectomy and vestibular neurectomy. Among these two, vestibular neurectomy is a selective technique issued to superior and inferior vestibular nerves and keeping the cochlear nerve safe. The efficiency of both techniques is good [42].

Vestibular neurectomy is believed to be the most efficient technique for drop attacks (Tumarkin's disorder) and for incapacitating Ménière' disease.

Labyrinthectomy is the oldest surgical method to treat MD, and today is limited to older patients. The technique can be associated with cochlear implantation within the same stage in case of profound bilateral hearing loss [43].

CONCLUSION

The definition of MD has reached a large international consensus, diagnosis and especially treatment still represent a debated topic. The main aim of this position paper is to identify a common path for medical professionals dealing with Meniere's disease diagnosis and treatment based on literature evidences and expert opinions.

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