Menière's disease: Clinical aspects, diagnostic tests and interventions

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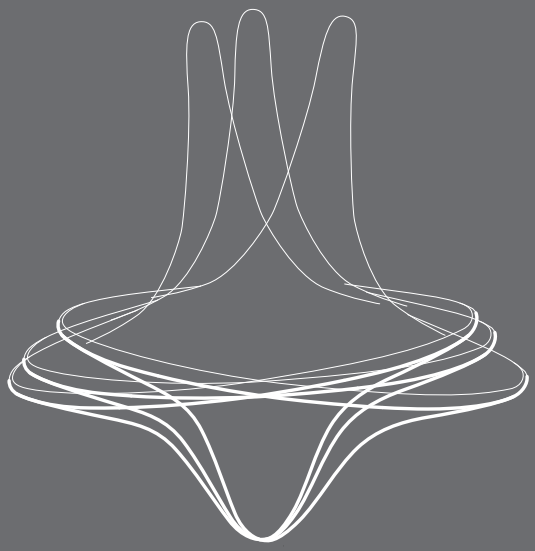

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GENERAL INTRODUCTION, THESIS OUTLINE AND RESEARCH QUESTIONS

Historical perspective

In 1861, Prosper Menière (1779-1862) published five papers that are now widely known as the primary reference for the concept of 'Menière's Disease' (MD) [1]. In these papers in the 'Gazette Médicinale de Paris', he described patients who suffered from a triad of symptoms: recurring spontaneous attacks of vertigo accompanied by hearing loss and tinnitus. He described that the attacks of vertigo were often accompanied by symptoms of nausea and vomiting and that the loss of hearing and tinnitus increased in severity over time [2].
Prior to the pioneering work of Menière, it was generally accepted that the central nervous system was entirely responsible for symptoms of vertigo [3]. Vertigo was lumped together with other central nervous disorders known as the 'symptomatology of apoplectiform cerebral congestion'. At that time, it was believed that the inner ear was composed of several parts that were all involved in mediating different aspects of sound [4]. Although the establishment of a relationship between the vestibular apparatus and the maintenance of head positions and balance was already accomplished by Flourens in 1824 [5], it was not applied in human science until Menière's remarks were published.

Definition of MD

Over time, there have been many different definitions of MD. All methods to define MD have been symptom-based [6]. The diagnostic criteria describe the type and character of vertigo, the amount of associated hearing loss, the presence of tinnitus and/or aural fullness and in all cases other causes are excluded. In 1972, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) first defined MD as an inner ear disease of the membranous part of the labyrinth with characteristic symptoms and a correlation with endolymphatic hydrops [7] (see section Pathophysiology). The criteria have been updated three times, in 1985, in 1995 and in 2015 [8,9, 10]. The latest set of diagnostic criteria was jointly formulated by the Classification Committee of the Bárány Society, the Japan Society of Equilibrium Research, the European Academy of Otology and Neurotology, the AAO-HNS and the Korean Balance Society to facilitate future collaborative studies [10]. However, as these international diagnostic criteria were only published recently and previous research widely used the AAO-HNS 1995 diagnostic guidelines, the latter set of criteria will be used in the current thesis. The AAO-HNS 1995 diagnostic criteria are shown in **Table 1**.

TABLE 1. The American Academy of Otolaryngology –Head and Neck Surgery criteria as published in 1995 [9].

Certain MD	Definite MD	Histopathological confirmation	
Definite MD	Two or more definitive spontaneous episodes of vertigo 20 minutes or longer	Audiometrically documented hearing loss on at least one occasion	Tinnitus or aural fullness in the treated ear
Probable MD	One definitive episode of vertigo	Audiometrically documented hearing loss on at least one occasion	Tinnitus or aural fullness in the treated ear
Possible MD	Episodic vertigo of the Menière type without documented hearing loss	Sensorineural hearing loss, fluctuated or fixed, with disequilibrium but without definitive episodes	

Pathophysiology

As mentioned in the *Historical perspective section*, the papers published by Prosper Menière were the first to describe a relationship between the maintenance of balance and the inner ear. The inner ear structures that convey information about balance are found in the petrous part of the temporal bone (see **Figure 1**) [11].

The bony labyrinth is located inside the temporal bone. It consists of a series of cavities: the three semicircular canals, the vestibule and the cochlea. The bony structures protect the membranous part of the labyrinth which is divided into a perilymphatic and an endolymphatic compartment. The membranous labyrinth consists of three semicircular ducts, two otolith organs, the utricle and saccule, and the cochlear duct. The semicircular ducts and the otolith organs convey information on balance whereas the cochlear duct is the organ of hearing.

Although the pathogenesis of MD is currently still unknown, it is generally accepted that the origin of the disease lies within the endolymphatic system of the membranous labyrinth. In 1938, two independent researchers performed autopsy on human temporal bone which revealed hydrops of the endolymphatic system [13,14]. Idiopathic endolymphatic hydrops is thought to be caused by either an over-production or an under-absorption of endolymph. The classical theory hypothesises that endolymphatic hydrops eventually causes Reissner's membrane to rupture (Menière crisis) [14]. Subsequently, potassium-rich endolymph escapes

into the sodium- rich perilymph leading to neurotoxic effects on the hair cells, causing loss of hearing and vestibular function.

Idiopathic endolymphatic hydrops is believed to be the etiological substrate of MD. A recent review reported that it is almost certain that in patients with unilateral 'definite' MD, at least one temporal bone shows endolymphatic hydrops [15]. Moreover, hydrops was also found in asymptomatic contralateral ears in patients with unilateral MD [16,17]. Therefore, endolymphatic hydrops may be regarded as a necessary histopathological finding, at least in definite unilateral MD.

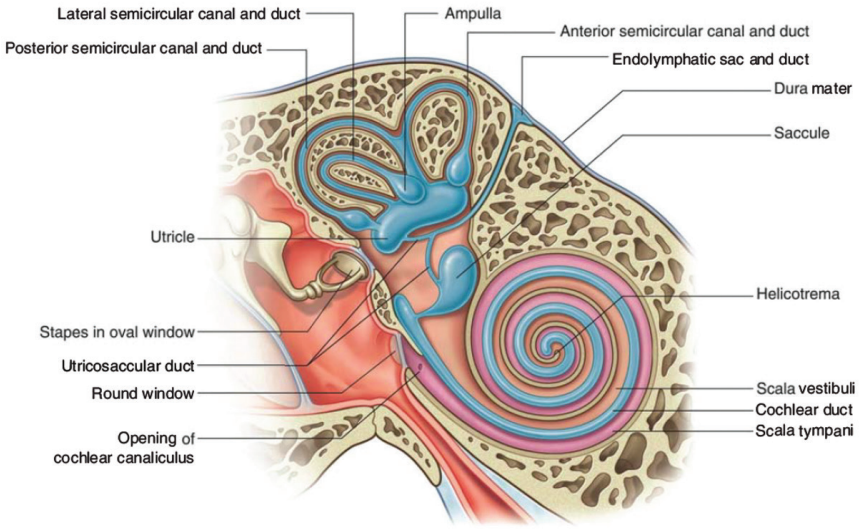

Figure 1. The labyrinth – Gray's anatomy for students [12].

Prevalence of MD

Although the cardinal symptoms of MD are spontaneous attacks of vertigo spells, hearing loss and tinnitus, in the presence of aural fullness, there is a great variety in the presenting symptoms. Symptoms do not necessarily manifest themselves simultaneously and there may be a delay of several years between the first symptoms and the definitive diagnosis [18,19]. When reviewing the literature on the prevalence of MD, rates from 3.5 per 100.000 to 513 per 100.000 inhabitants have been reported [20-22]. The wide range of values is most likely to be due to the inconsistency in defining and redefining the diagnosis over time, differences in study methods, (retrospective and prospective designs) and difficulty in distinguishing MD from related conditions (e.g. vestibular migraine (VM)). In general, these factors complicate the summation of epidemiological aspects of MD [23-25]. Based on research in the Netherlands, the prevalence has been estimated at 0.6 to 1.0 per 1000 inhabitants, cumulating in 15.000 MD patients [19,26].

Age of onset of disease

In reviewing the literature regarding the age of onset, it is safe to say that MD generally develops in middle age [27]. The peak incidence in onset of the disease lies in the fourth and fifth decade of life [28], but even onset later in life, during the sixth and seventh decade, is not an uncommon finding [29].

Recently, a Japanese survey reported a progressive increase in the age of onset of MD which was explained by the increase of the working elderly population. It was proposed that work-related stress might contribute to the development of MD [30,31]. In **Chapter 2** we will evaluate the age of onset of MD patients who visited a tertiary dizziness centre in the Netherlands. In addition, it will investigate whether a shift towards a later age of onset is also present in the Dutch MD population similar to the Japanese population.

Clinical course of MD

Understanding the natural history of MD is of paramount value to develop treatment strategies and time the follow-up moments of the efficacy and effectiveness of treatment modalities. However, the incapacitating character of the disease makes it difficult to abstain from treatment and patients tend to consult more than one physician which often results in different forms of treatment [32]. Any treatment, such as lifestyle changes or dietary modifications, may alter the natural course of the disease, even though a beneficial effect of the specific treatment has not been established [33]. As a result, there is limited information regarding the natural course of the disease [34], which inhibits the interpretation of treatment effects in the absence of a placebo. Nonetheless, the next section will attempt to provide information on the clinical course of each symptom of MD. Results should be interpreted with caution as the course of symptoms was assessed in various MD populations, different study design and in presence of various forms of therapy.

Vertigo symptoms

Episodes of spontaneous vertigo spells may be considered as the hallmark of the disease and are often experienced as debilitating. The AAO-HNS has defined that a definitive spell of MD occurs spontaneously, causes rotational vertigo which lasts at least 20 minutes (commonly several hours) and is accompanied by disequilibrium that may persist for several days [9]. Generally, it is accompanied by nausea and vomiting. In addition, hearing loss and tinnitus tend to worsen with the onset of vertigo.

A recent large prospective study (n=510) analysed the frequency and duration of definitive spells in patients who met the diagnostic criteria for 'definite' MD [35] and who received pharmacological treatment (administration of betahistine dihydrochloride or diuretic agents) or dietary modifications. The results indicated that two phases might exist in the course of the disease. In phase 1, the initial high frequency of vertigo rapidly declines over

the first 8 years. In Phase 2, covering years 9 to 20, vertigo attacks gradually decrease. The mean frequency of vertigo spells related to the duration of disease are shown in **Figure 2**.

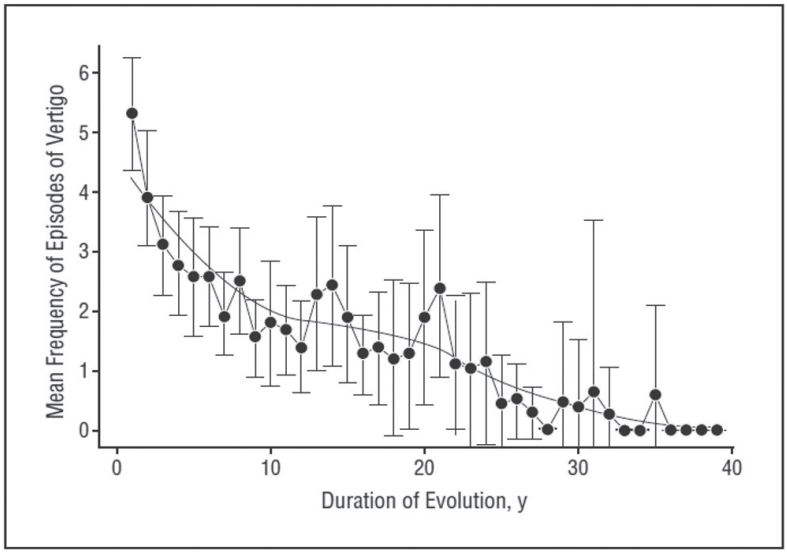

Figure 2. Mean frequency of episodes of vertigo per year of MD evolution. Bars indicate 95% intervals [34].

Previous studies demonstrated that MD can be associated with other diseases causing dizziness, such as Benign Paroxysmal Positional Vertigo (BPPV)[36-38] and psychological distress [39,40]. However, these studies [36-40] assessed the prevalence of a single comorbidity within MD populations. To date, it is still unknown which causes of dizziness most commonly coincide alongside MD. In **Chapter 3** we will quantify the prevalence of second causes of dizziness alongside MD including a reply to a letter to the editor (**Chapter 4**).

Auditory symptoms

In MD, sensorineural hearing deteriorates over the years [41-43]. It typically starts with an up-sloping low-frequency hearing loss and ends with a flat sensorineural hearing loss. Moreover, profound hearing loss (> 50 dB) is a rare finding [43]. A study in Sweden showed that 82% of the patients had a hearing loss of less than 30 dB [43]. After a follow-up of 21 years or more, the hearing further deteriorated but stabilized at a level around 50 dB which is illustrated in **Figure 3**.

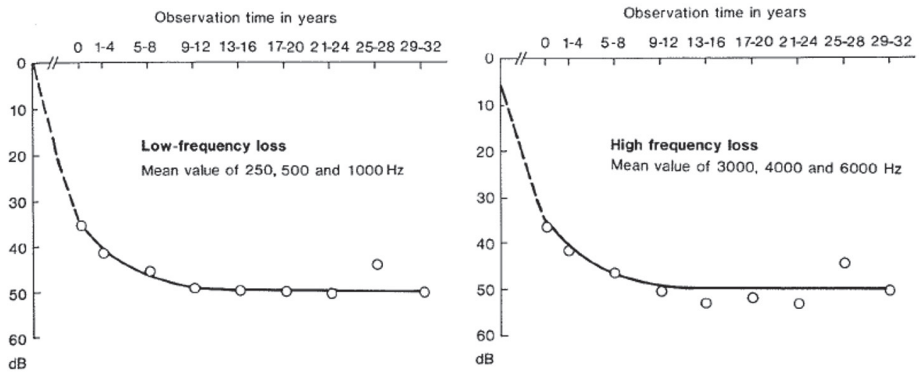

Figure 3. Hearing profile in 161 patients with Meniere's disease [43].

Tinnitus commonly involves a low-frequency type and it has been reported in up to 67% of the patients and was reported as the most incapacitating symptom in the triad of symptoms of MD [44]. A retrospective study [45] found that tinnitus increased when hearing deteriorated, and that patients with an early onset of disease and a bilateral form of MD experienced tinnitus more intensively. Aural fullness is another symptom that, similar to tinnitus, is experienced in two thirds of the MD patients [46]. In a retrospective cohort study, tinnitus, hyperacusis and balance problems were considered to be significant predictors of aural fullness [46].

Balance problems

Whilst treatment of MD is directed at reducing vertigo spells, hearing loss and tinnitus, problems with balance become more prevalent with the progression of disease [47,48]. To date, little attention has been focussed on symptoms of disequilibrium and unsteadiness in patients with MD. However, there has been increasing interest in the value of exercises for patients with balance disorders, known as vestibular rehabilitation (VR) [49].

VR includes Brandt-Daroff exercises, Cawthorne-Cooksey exercises, viewing exercises or balance exercises. By stimulating the vestibular system VR aims to improve the visual-vestibular interaction, to increase the static and the dynamic postural stability and to positively affect the quality of life by reducing complaints of imbalance, dizziness and anxiety [50]. The clinical recovery is thought to be based on three aspects. First, there is compensation/habituation, which is a central process and refers to the reduction in symptoms produced by specific movement and occurs through repetitive exposure to the movement. Secondly, there is adaptation, which is the recovery of the dynamic vestibulo-

ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input. Last, there is substitution, which is the use of other strategies to replace the lost function [51,52]. The effect of VR on MD will be evaluated in **Chapter 8** based on a systematic review of current literature.

Diagnostic assessment

As true today as it was in Prosper Menière's time, detailed history taking remains the first and most important diagnostic tool for MD as at present no 'gold standard' test exists. In order to limit the number of differential diagnoses, differentiation between vertigo and dizziness may be of clinical use.

Vertigo, according to the AAO-HNS [9] definition of vertigo spells in MD, involves a spinning sensation or illusory motion of the self or the environment. Dizziness, on the other hand, is less specific and is described by sensations of light-headedness, giddiness, wooziness or impending faint.

In addition to the distinction between dizziness and vertigo, the type of presentation may be of help to further differentiate between the cause of the complaints. The type of presentation can be divided into 1) a single acute episode of vertigo (not applicable to patients with MD by definition), 2) recurrent or episodic vertigo, 3) positional vertigo or 4) chronic sensations of dizziness or unsteadiness [53].

Diseases which manifest themselves with recurrent and spontaneous attacks of vertigo may particularly present diagnostic challenges when diagnosing MD due to similarity in medical history.

The most common cause of recurrent spontaneous vertigo is vestibular migraine (VM) (migrainous vertigo or migraine-associated vertigo) which affects about 30-50% of all patients with migraine [54,55]. Although complaints of vertigo and migraine commonly coincide, the Bárány Society only recently established a set of diagnostic criteria for VM which were added into the International Classification of Headache Disorders [56, 57].

Next to VM, there is a subgroup of patients who have attacks of recurrent vertigo without migrainous symptoms or cochlear features also known as benign recurrent vertigo. In 1981, Leliever and Barber were the first to describe this clinical syndrome as Recurrent Vestibulopathy (RV) [58]. RV, now renamed as 'Benign Recurrent Vertigo' (BRV), is characterised by recurrent spontaneous attacks of vertigo lasting for minutes to hours without any additional neurological or cochlear symptoms. Since additional symptoms are absent during attacks in RV, it may be regarded as a separate entity. However, previous studies claimed that RV might be related to either vestibular migraine or MD [59,60]. In **Chapter 5** the clinical characteristics of MD, VM and BRV will be explored and it will be assessed whether clinical symptoms exist to discern between these disorders.

Excluding differentials

Additional diagnostic assessments are important to increase or decrease the likelihood of the diagnosis and to exclude differentials. Excluding differentials should be based on prevalence rates.

In case laboratory evaluation is performed, one aims to rule out thyroid disorders, syphilis, anaemia, leukaemia, diabetes mellitus, immune or genetic disorders [61] whereas Magnetic Resonance Imaging (MRI) of the brain or the cerebellopontine angle is advised to eliminate central pathology, most importantly acoustic neuromas [62].

Vestibular function

The function of the vestibular system is generally assessed by the caloric test. In MD, the caloric test may reveal unilateral vestibular hypofunction [63], yet test results may fluctuate over time and normal results can be found as well [64-66]. Recently, the video-head impulse test (vHIT) was introduced [67] which assesses the vestibulo-ocular reflex based on unpredictable passive, high frequency head rotations. Little is known about the diagnostic accuracy of the vHIT in determining vestibular hypofunction when caloric testing is considered the reference standard. This will be the focus of **Chapter 6**. In previous research with the vHIT and MD, normal test results were found at least in the early stages of the disease [68,69]. The vHIT test results in later stages of the disease will be evaluated in **Chapter 7**.

Therapy

The main aim of treatment in MD is to reduce the frequency and intensity of the vertigo attacks and at the same time to preserve hearing and vestibular function [70]. Psychological suffering and reduced quality of life are linked to MD since disabling vertigo attacks can occur without warning [71,72]. Therefore, an effective prophylactic treatment is necessary to improve the quality of life of MD patients. Current pharmacological treatment options include betahistine, diuretics, oral steroids or intratympanic application of corticosteroids, and intratympanic gentamicin [73]. However, evidence in terms of reducing vertigo complaints has never been conclusive [74-76], except for intratympanic gentamicin treatment [77].

Of these pharmacological treatment options, betahistine is most commonly used, especially in Europe [78]. Betahistine has been available since 1968 and it is estimated that over 130 million people worldwide have used the drug [79]. Although it is thought to be specifically effective as medical treatment in MD, a Cochrane review [74] conducted in 2001 stated that there was no evidence of a benefit from the use of betahistine in this population. However, many studies have been performed since, and reassessment of the effect of betahistine in treating MD is therefore now warranted since it is still widely prescribed as first line

treatment for MD. **Chapter 9** describes the results of a systematic review examining the potential beneficial effect of betahistine for MD.

Non-pharmacological treatment includes positive pressure therapy (the Meniett device), ablative surgery such as vestibular nerve section, labyrinthectomy, endolymphatic sac surgery and VR [70,73,81]. Similar to the pharmacological treatment modalities, high quality evidence is also lacking for non-pharmacological therapies [80,81]. Since so many treatments exist without conclusive results, it may be hard for clinicians to select the best available treatment and to advise patients. **Chapter 10** portrays a protocol for an umbrella systematic review to summarise the body of evidence regarding treatment modalities in MD. In **Chapter 11** the results of this umbrella systematic review will be presented.

THESIS OUTLINE

The aims of this thesis are to explore the clinical aspects, to evaluate diagnostic tests and to systematically review the evidence for the effect of interventions for Menière's disease (MD). Part I describes the age of onset, second causes of dizziness in MD patients and compares clinical symptoms in patients with MD, Vestibular Migraine and Benign Recurrent Vertigo. Part II evaluates the diagnostic value and aspects of the vHIT in MD. Lastly, part III systematically summarizes the effect of treatment for MD based on current available literature. The main outcomes of the studies performed are summarized in the general discussion. Based on these outcomes, implications for clinical practice are stated and directions for future research are provided. The aim of this thesis is to answer the following research questions:

Part I.

Evaluation of clinical aspects of MD

- What is the age of onset in patients with MD in a specialized dizziness clinic in the Netherlands and is there a shift in age of onset (**Chapter 2**)?
- Which other causes of dizziness are prevalent alongside MD and do differences exist in specific age groups (**Chapter 3** and **Chapter 4**)?
- What are the clinical characteristics of patients with Benign Recurrent Vertigo, Vestibular Migraine and MD and can distinctive clinical symptoms be identified (**Chapter 5**)?

Part II.

Evaluations of diagnostic tests for MD

- What is the diagnostic value of the vHIT in determining vestibular hypofunction when compared to the caloric test in dizzy patients (**Chapter 6**)?
- Are vHIT test results in patients with MD more often normal in the early stage of the disease than at later stages (**Chapter 7**)?

Part III.

Evaluation of interventions for MD

- What is the effect of vestibular rehabilitation in patients with MD (**Chapter 8**)?
- What is the effect of betahistine in patients with MD (**Chapter 9**)?
- What is the most effective treatment for MD? (**Chapter 10** and **11**)?

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