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

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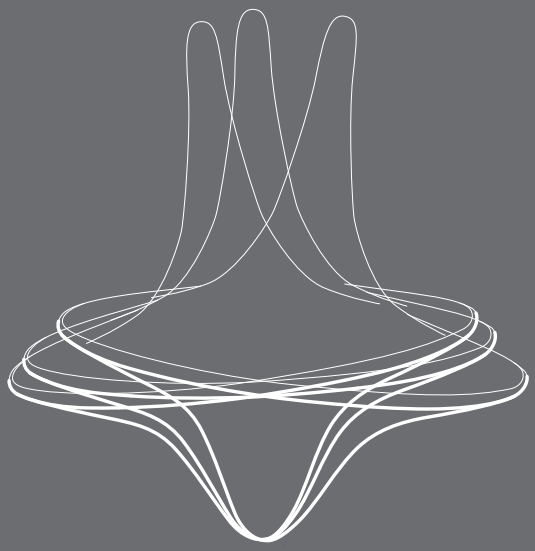

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TWO COMMON SECOND CAUSES OF DIZZINESS IN PATIENTS WITH MENIÈRE'S DISEASE

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ABSTRACT

Objective: There are no epidemiological studies quantifying the prevalence of second causes of dizziness in Menière's disease (MD). Therefore, we aimed to quantify which dizziness-inducing causes are prevalent alongside MD. Moreover, we analysed which second cause of dizziness was more common in a specific age group and if age was a risk factor.

Study design: Retrospective cohort study.

Setting: Tertiary referral center.

Methods: Data were retrospectively obtained from all MD patients who visited our clinic between January 2000 and December 2013. Workup included vestibular tests, pure tone audiometry, blood pressure monitoring, and the hyperventilation provocation test, the Nijmegen Questionnaire and the Hospital Anxiety and Depression Scale. The final causes of dizziness were based on consensus between an ENT-surgeon and a neurologist who were consulted simultaneously.

Results: We found that 143 (30%) of 469 MD patients suffered from a second cause of dizziness. The two most common causes were Psychological Distress (PD) (70%) and Benign Paroxysmal Positional Vertigo (BPPV) (18%). The mean age for MD patients with PD was 58.7±13.3 years compared to the mean age of 63.9±14.3 years for MD patients without PD (mean difference=-5.2 years, 95% CI:-8.3 to -2.2, p=0.001). MD patients younger than 60 of age had a 15% higher risk of suffering from psychological distress than those who were older than 60 (risk difference 15%, 95% CI 7.0%-22%). Age could not be identified as a risk factor for BPPV in older MD patients.

Conclusions: In 30% of the patients with MD a second cause of dizziness is present. PD most commonly coincides with MD, especially in younger patients. The second most common cause is BPPV.

Key words: Menière's disease, comorbidity, diagnoses, dizziness.

INTRODUCTION

Spontaneous episodes of vertigo accompanied by hearing loss, tinnitus and aural fullness are hallmark characteristics in patients suffering from Menière's Disease (MD). However, as clinical symptoms vary widely and most of these symptoms are subjective and not specific, the disease can present diagnostic challenges. In 1995, a set of criteria for the diagnosis of MD was established by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [1]. Taking into account that a reference diagnostic standard and a confirmatory test are still absent, a detailed medical history is essential. Therefore, MD is a clinical diagnosis. The diagnostic process is further complicated when multiple diagnoses causing dizziness coexist. During the first clinical visit and also during follow-up, coexisting causes may obscure the diagnosis MD and challenge the physician to clarify the origin of complaints.

While previous studies demonstrated that Benign Paroxysmal Positional Vertigo (BPPV) is associated with orthostatic hypotension [2], MD commonly coincides with BPPV [3-5] and psychological distress (PD) [6,7]. PD, unpleasant experiences of emotional or psychological nature such as anxiety or depression, is known to be prevalent in patients with chronic dizziness [8], especially in patients with MD [9].

However, the previously mentioned studies assessed the prevalence of a single diagnosis within MD populations. To date, it is unknown which second causes of dizziness are most common in patients with MD. In the present study, we aimed to quantify the prevalence of the second causes of dizziness in patients with MD who visited our tertiary dizziness clinic. In line with previous literature on general dizziness populations, PD tends to be more common in the younger dizzy patient [6,9] whereas BPPV becomes more prevalent at an older age [3]. However, as prevalence rates of PD and BPPV alongside MD are unknown, the second objective was to establish whether comparable age differences also existed in patients with these second causes of dizziness in presence of MD.

MATERIALS AND METHODS

We obtained records from all the MD patients in our database who had visited our centre between January 2000 and December 2013. Patients were included if they met the AAO-HNS 1995 criteria for 'definite' and 'possible' MD (see **Table 1)** [1]. Based on the medical information processed, we assessed if the selected MD patients suffered from two different types of dizziness, such as 'episodic vertigo' and 'positional vertigo' or 'episodic vertigo' and 'chronic sensations of light-headedness'. We analysed anonymous data on a second cause of dizziness based on the medical information as recorded in the electronic data handling system and in discharge letters.

All procedures were in accordance with the ethical standards and in line with the Helsinki declaration. All data were analysed anonymously. In all patients, the workup included vestibular tests (oculomotor, caloric, rotational and positional), pure tone audiometry, and blood pressure monitoring. In addition, the hyperventilation provocation test was performed and two questionnaires were filled in prior to the clinical visit.

TABLE 1. Criteria for Menière's disease published by the American Academy of Otolaryngology-Head and Neck Surgery in 1995[1].

Certain Menière's disease	Definitive Menière's disease
	Histopathological confirmation
Definitive Menière's disease	Two or more definitive spontaneous episodes of vertigo of 20 minutes or longer
	Audiometrically documented hearing loss on one occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Probable Menière's disease	One definitive spontaneous episode of vertigo of 20 minutes or longer
	Audiometrically documented hearing loss on one occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Possible Menière's disease	Episodic vertigo of the Menière type without hearing loss or,
	Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes
	Other causes excluded

The hyperventilation provocation test

During the hyperventilation provocation test (HVPT), hypocapnia was induced by having the patient overbreath intentionally for several minutes. Immediately following the HVPT, the patient was asked if any symptoms similar to what they had experienced before occurred during the test. The test was considered positive if such symptoms were present [10].

The Nijmegen questionnaire and Hospital Anxiety Depression Scale

Patients were asked to complete two questionnaires prior to the clinical visit: the Nijmegen Questionnaire (NQ) and the Hospital Anxiety and Depression Scale (HADS) (from 2012 onwards). The NQ is a valid method to screen for the hyperventilation syndrome (HVS) [11,12].The questionnaire consists of 16 items, which are graded as follows: 0=never

occurring, 1=rare, 2=sometimes, 3=often, 4=very often. A total score higher than 23 out of 64 is suggestive for a diagnosis of HVS.
The HADS is an instrument for screening for PD [13]. It has been shown to be a reliable and valid tool for evaluating patients in various disease populations [14]. The HADS contains 14 items: an anxiety subscale and a depression subscale, both consisting of 7 items. Items have the same answering options as the NQ. We considered the test results positive if a score of ≥ 8 on either subscale (anxiety or depression) was found in the presence of complaints of 'light-headedness' or 'giddiness' [13,15].

Definitions of the causes of dizziness

A positive test result for either the HVPT or the NQ was considered to be suggestive for HVS. HVS is defined as a syndrome characterized by various somatic symptoms which cause "physiologically inappropriate hyperventilation and are usually reproduced by voluntary hyperventilation" [16]. Symptoms of HVS have been proven to be correlated with increased levels of anxiety and depression [17,18]. Similarly, chronic vertigo disorders – including MD – are known to be associated with PD complaints [12,19]. As a result, MD patients with increased scores on the HVPT, the NQ or the HADS were clinically suspected of having PD. In line with the definition of the National Comprehensive Cancer Network, PD was considered a multifactorial unpleasant emotional experience of a psychological or social nature [20].

We used current available diagnostic criteria to confirm vestibular neuritis [21], vestibular migraine [22], and Benign Paroxysmal Positional Vertigo (BPPV) [23]. The diagnosis of BPPV was established by complaints of episodic vertigo with changes in head position and the presence of a characteristic nystagmus provoked by either the Dix-Hallpike manoeuvre or the supine roll test. The BPPV group also included patients with subjective BPPV. In these patients a diagnostic manoeuvre provokes vertigo, but not a nystagmus. Historical BPPV was diagnosed when a patient had typical complaints of positional vertigo but a negative Dix-Hallpike manoeuvre at the time of evaluation. Since subjective and historical BPPV are less clearly defined, these patients were excluded from analysis.
Conventional open bithermal loop caloric testing (33°C and 44°C) was used in both ears to elicit vestibular responses. The Jongkees formula [24] was applied to express the vestibular preponderance (VP) and directional preponderance (DP) in percentages, based on the velocity of the slow phase component of nystagmus evoked by each vestibular organ. Vestibular hypofunction was defined as a vestibular preponderance of 22% or more or a directional preponderance of 28% or more [25,26]. Caloric testing was also considered abnormal if the responses for all irrigations were below normal. The criterion for bilateral weakness was a V_{max} below 15°/s for each vestibular organ (V_{max} is the sum of the slow-phase velocity for irrigation warm water + slow phase velocity for irrigation cold water).

Orthostatic hypotension was defined as a reproducible fall in systolic blood pressure of 20 mmHg or diastolic blood pressure of 10 mmHg during the first 2 minutes standing. We diagnosed patients with a central vascular disorder on the basis of clinical history and abnormal findings on neurologic and MRI examinations. The clinical diagnoses were determined by an ENT-surgeon and a neurologist by means of simultaneous consultation.

Statistical analysis

By means of SPPS software (version 18), we calculated frequencies for categorical variables, including sex, type of MD and the second causes of dizziness. Means and standard deviations were calculated for age. MD patients with a common second cause were grouped and compared to patients without these causes. In the analysis of the BPPV group, we excluded patients with historical or subjective BPPV. Cut-offs for age were based on previous literature: young adults were defined as ≤ 60 years of age; old adults were defined as >70 years of age [27]. Differences were assessed by using the *t*-test and chi-square test. Absolute and relative risk ratios were calculated with the online software of Open Source Epidemiologic Statistics for Public Health (available at (www.openepi.com). A p level below 0.05 was considered significant.

RESULTS

The 469 MD patients included in this study consisted of slightly more women (n=254, 54%) than men. The mean age was 62.8±14.2 years. In 67% of cases (n=314) the diagnosis was 'definite' MD.

Second causes of dizziness

Table 2 shows the causes of dizziness of the included MD patients. The presence of another cause of dizziness was registered in 143 patients (30%). These patients comprised significantly more women (n=86, 64%) than men (n=49, 36%) (p=0.01). The mean ages for MD with a second cause of dizziness were comparable (62.2 ±14.1) to MD patients without (63.0 ± 14.2 years). As shown in **Figure 1**, the most common coexisting diagnoses were PD (n=102, 70%) and BPPV (n=24, 18%). In 15 (11%) patients in the BPPV group, a typical nystagmus was provoked by either the Dix-Hallpike manoeuvre or the supine roll test.

Age in MD patients with and without PD

MD patients with PD (n=102) were compared with MD patients without this diagnosis (n=367). The mean age for MD patients with PD was significantly lower (59.3±13.3 years) than in MD patients without PD (63.6±14.3 years) (mean difference=-4.2 years, 95% CI:-7.5 to -1.0, p=0.01). In line with **Table 3**, MD patients younger than 60 years of age had a

15.4% (95% CI: 11.5-20.3) higher risk of suffering from PD than patients above 60 years of age. This correlated with a relative risk ratio of 2.0 %(95% CI:1.4-2.8).

TABLE 2. Coexisting diagnoses in the MD population.

Diagnosis	**Number (%)**
No coexisting diagnosis	326 (69.5)
PD*	102 (21.7)
BPPV†	15 (3.2)
Orthostatic hypotension (incl. asymptomatic)	7 (1.5)
Vestibular migraine	5 (1.1)
Cardiovascular	3 (0.6)
Unknown central cause	1 (0.2)
Bilateral vestibular paralysis	1 (0.2)
Total	**469(100)**

*=Psychological distress; †= Benign Paroxysmal Positional Vertigo

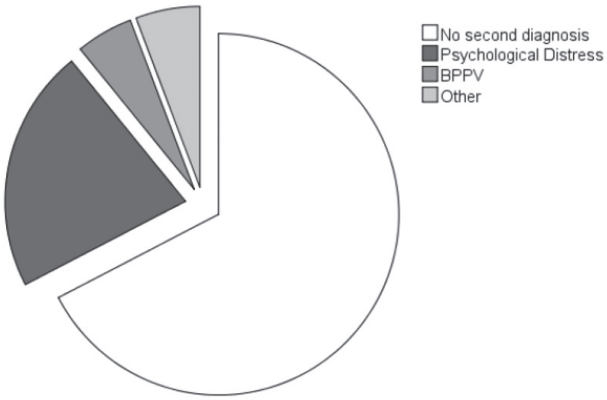

Figure 1. Most common second diagnoses in Menière's disease patients (N=469)

TABLE 3. Absolute and relative risks for young adult MD patients with psychological distress.

	MD with PD*	MD	Total
Age ≤60	61	142	203
Age >60	41	225	266
	102	367	469

*PD= Psychological Distress. MD patients younger than 60 year of age had a risk of 30.1% (95% CI:24.2%-36.7%) for psychological distress. This risk was 15.4% (95% CI:11.5%-20.3%) in older MD patients. The absolute risk difference was 14.6% (95% CI: 6.9%-22.3%). The relative risk ratio was 1.95 (95% CI:1.4%-2.8%).

Age in MD patients with and without BPPV

MD patients with proven BPPV had a mean age of 66.6±13.2 (n=15) whereas MD patients without BPPV were younger (62.6±14.2 (n=454); mean difference 4.0 years, 95% CI: -3.4 to 11.4, p=0.29). As displayed in **Table 4,** older age (> 70 years) was not found to be a significant risk factor in the development of BPPV in our MD population. The risk difference was 2.2 (95% CI: - 6.1.2 -1.6) and the relative risk ratio was 0.5 (95% CI:0.2-1.4).

TABLE 4. Absolute and relative risks for old adult MD patients to suffer from BPPV.

	MD with BPPV*	MD	Total
Age ≤70	8	313	321
Age >70	7	141	148
	15	454	469

*= Benign Paroxysmal Positional Vertigo, patients with historical or subjective BPPV were excluded. MD patients > 70 years had a risk of 4.7%(95% CI:2.1%-9.6%) to suffer from BPPV. This risk was 2.5% (95% CI:1.2%-49%) in MD patients ≤ 70 years. The absolute risk difference was 2.4% (95% CI: -6.1%-1.6%). The relative risk ratio was 0.6% (95% CI:0.2%-1.4%).

DISCUSSION

To date, there are no epidemiological studies quantifying the prevalence of second causes of dizziness in MD. In the present study, we aimed to determine the prevalence of secondary causes of dizziness in patients with MD. Additionally, we aimed to verify whether MD patients with PD were younger and if MD patients with BPPV were older than patients without these second causes of dizziness.

In our retrospective analysis of 469 MD patients, a second cause of dizziness was found in almost one third of the population. The two most second causes of dizziness were PD and BPPV. In line with our hypothesis, MD patients with PD were significantly younger and the

risk of PD comorbidity was 15% higher in younger MD patients. MD patients with BPPV were slightly, although not statistically significantly older than MD patients without BPPV. Our results on elevated anxiety and depression scores in MD patients were comparable to analyses of PD in the general population and in various disease populations. An analysis of the general German population revealed that the HADS scores were increased (≥8) for anxiety in 21% of the subjects and for depression in 23% [15]. In previous studies among patients with sarcoidosis (28) and systemic lupus erythematodes [29] elevated HADS scores for anxiety and depression ranged from 16% to 39%. In a study of patients with different types of vestibular peripheral vertigo, the prevalence rate of anxiety and depression in patients with MD was more or less the same as in patients with vestibular migraine [30]. Although high levels of anxiety and depression are commonly linked to MD [6,7,31], the presence of PD may be less distinctive for MD than previously thought.

No reports were found assessing age differences within MD populations based on PD. However, our finding is in line with previous literature in general dizziness populations that patients with both vertigo and PD tend to be younger than patients without these complaints [9].

The prevalence of BPPV in the general population lies between 10 to 64 per 100.000, with a lifetime prevalence of 2.4% [23,32]. Previous literature demonstrated an association between MD and BPPV [33,34]. Endolymphatic hydrops may damage the utricle, which may cause loosening of otoconia, resulting in BPPV [35]. In concordance with previous studies, we found a significantly higher prevalence of 5% BPPV in our MD population. However, previous research found BPPV prevalence rates up to 30% [2,3,34]. This discrepancy may be accounted for by the difference in study design. Taura *et al.* [33] prospectively registered BPPV-like vertigo episodes during a follow-up period of up to 30 months whereas we used a retrospective approach and assessment at a single clinical consultation. Therefore, we may have underestimated the BPPV prevalence in our population.

In our study, BPPV patients were older than MD patients without BPPV, but no statistical significance was found. This finding is unexpected, as previous reports show that BPPV becomes increasingly prevalent in older patients [2,23]. Since only 15 proven BPPV patients could be analysed in this subgroup, it might be due to chance that current results were found.

What emerges from the current study is the need to take PD and BPPV into account when considering therapy options in MD. Patients with PD alongside MD may benefit from psychological therapy. Although psychological interventions are generally not regarded as the key component of therapy in MD, cognitive behavioural therapy has been effective in treating vertigo and tinnitus [36]. When BPPV is encountered during follow-up, this can be treated effectively by canalith repositioning manoeuvres [11,35].

The scope of this study was limited in several ways. The most important potential limitation concerns the suspicion of PD based on the presence of HVS. Even though HVS was proven to be correlated with increased levels of PD, Hornsveld *et al.* [37] stated that the term HVS is best to be avoided in clinical practice. In addition, confirmation of a psychological disorder would require a structured clinical interview according to the DSM-IV-TR. We are aware that no complete psychological work-up was performed and we therefore not cannot calculate prevalence rates of anxiety and depression.

Moreover, the present study included patients who visited our centre between January 2000 and December 2013, whereas we did not use the HADS until 2012. Nonetheless, the number of patients who visited our dizziness centre increased substantially during the final two years of this study. Thirty percent (n=33) of the MD patients with PD were identified by increased levels on the HADS. In 10 patients PD was based on an elevated HADS score only. The remaining were identified by abnormality on the HADS and either the HVPT or the NQ. Due to this methodological inconsistency, it is likely that prevalence rates of PD would have differed in case we had used the HADS from 2000 onwards.

In MD, a second cause of dizziness is a common finding. In 30% of the patients we found a second cause of dizziness. The two most second causes are PD and BPPV which comprise 80% the patients with a second cause of dizziness. PD is especially common in younger MD patients, but the prevalence is comparable to various other disease populations. The current study emphasizes the need to take PD and BPPV into account when considering therapy options in MD.

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