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Migraine and Ménière's disease

Is there a link?

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Abstract—*Background:* A possible link between Ménière's disease (MD) and migraine was originally suggested by Prosper Ménière. Subsequent studies of the prevalence of migraine in MD produced conflicting results. *Objective:* To determine the lifetime prevalence of migraine in patients with MD compared to sex- and age-matched controls. *Methods:* The authors studied 78 patients (40 women, 38 men; age range 29 to 81 years) with idiopathic unilateral or bilateral MD according to the criteria of the American Academy of Otolaryngology. Diagnosis of migraine with and without aura was made via telephone interviews according to the criteria of the International Headache Society. Additional information was obtained concerning the concurrence of vertigo and migrainous symptoms during Ménière attacks. The authors interviewed sex- and age-matched orthopedic patients (n = 78) as controls. *Results:* The lifetime prevalence of migraine with and without aura was higher in the MD group (56%) compared to controls (25%; $p < 0.001$). Forty-five percent of the patients with MD always experienced at least one migrainous symptom (migrainous headache, photophobia, aura symptoms) with Ménière attacks. *Conclusions:* The lifetime prevalence of migraine is increased in patients with MD when strict diagnostic criteria for both conditions are applied. The frequent occurrence of migrainous symptoms during Ménière attacks suggests a pathophysiologic link between the two diseases. Alternatively, because migraine itself is a frequent cause of audio-vestibular symptoms, current diagnostic criteria may not differentiate between MD and migrainous vertigo.

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An association between Ménière's disease (MD) and migraine was suggested as early as 1861 by Prosper Ménière.[1] Since then, several authors have given anecdotal account of headaches as an additional symptom in typical Ménière attacks.[2,3] More recently, two studies have yielded conflicting results. A questionnaire-based survey found a lower lifetime prevalence of migraine in 46 patients with MD (22%) compared to a control group (33%); the difference, however, was not significant.[4] In contrast, a retrospective study of 85

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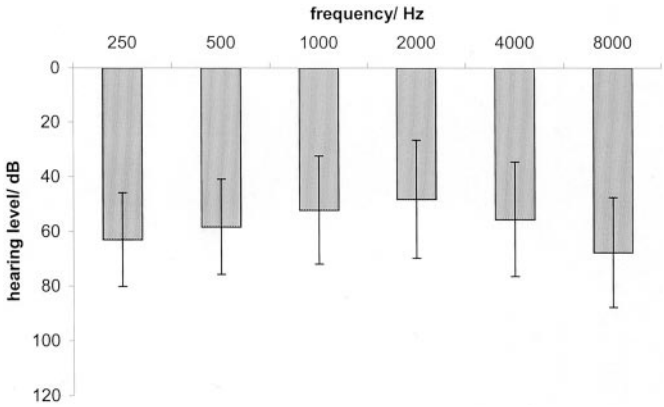

Figure. Hearing level (mean ± SD) in the more severely affected ear of 78 patients with Ménière's disease.

patients with MD found a lifetime prevalence of migraine of 43% for women and 19% for men,[5] which appears higher than migraine lifetime prevalences reported in previous population-based studies (6 to 17% for women and 1.5 to 6% for men).[6] However, methodologic shortcomings in both studies obscured the nature and magnitude of the association of migraine and MD (see Discussion). The aim of our prospective study was to determine the lifetime prevalence of migraine in patients with MD compared to an age- and sex-matched control group and to investigate the occurrence of migrainous symptoms during Ménière attacks.

Patients and methods. The study population consisted of 78 patients recruited out of 114 unselected patients with idiopathic MD seen between 1990 and 1999 at a neuro-otologic clinic for whom medical records were available. Diagnosis of unilateral or bilateral MD was based on the criteria of the American Academy of Otolaryngology (AAO) (1995)[7] and included the following:

1. A history of recurrent, spontaneous, rotational vertigo with at least two episodes lasting longer than 20 minutes.
2. Occurrence of tinnitus or aural fullness (or both) on the affected side.
3. Sensorineural hearing loss as documented by audiometric testing on at least one occasion according to the AAO regulations concerning magnitude of hearing loss and frequencies affected.
4. Exclusion of other causes for recurrent rotational vertigo.

As we specifically intended to study interrelations of MD and migraine, the diagnosis of migrainous vertigo was not excluded, as long as criteria 1 through 3 were met. Patients with secondary Ménière's syndrome (delayed endolymphatic hydrops) due to previous ear infection or trauma were excluded from this study.

All 114 patients were sent a letter to request consent to participation in the study. Thirteen letters were returned undelivered. Of the remaining 101 patients, 78 volunteered to participate, representing a response rate of 77%. There were 38 men and 40 women, aged 29 to 81 years (mean ± SD, 56 ± 12 years). Sixty-five patients had unilateral MD and 13 patients had bilateral MD. All patients had documented hearing loss in at least one ear according to the AAO criteria (figure). The average follow-up period after first onset of MD at the time of the interview was 10 ± 9 years. As a control group, we interviewed 78 unselected sex- and age-matched patients (age range 21 to 80 years, mean 56 ± 13 years) who underwent surgery for orthopedic problems or trauma. Orthopedic patients were chosen assuming that the causes for hospitalization were unrelated to either vertigo or migraine. Age was matched within blocks of 10 years and did not differ significantly between the two groups.

All participants underwent a semi-structured interview to establish the lifetime prevalence of migraine in patients with MD compared to the control group.

Diagnosis of migraine with and without aura was made according to the International Headache Society (IHS) classification (1988).[8] For this study, vestibulo-cochlear symptoms were not regarded as aura symptoms for the diagnosis of migraine with aura. In patients with MD, clinical features of MD according to the AAO criteria were confirmed in the interview. Patients were questioned in detail about the concurrence of headaches or other migrainous symptoms and Ménière attacks as well as the temporal sequence of symptoms during typical Ménière attacks. Phonophobia during MD attacks was not regarded as a migrainous symptom, because it was difficult to dis-

Table 1 *Lifetime prevalence of migraine in patients with Ménière disease (MD) compared to age- and sex-matched controls*

Migraine	MD, n = 78, prevalence in 100 (95% CI)	Controls, n = 78, prevalence in 100 (95% CI)*	*p* Value
Total migraine	56 (45–67)	25 (16–36)	<0.001
Men	37 (22–52)	8 (0–17)	<0.01
Women	75 (62–88)	43 (28–58)	<0.01
Without aura	34 (23–45)	15 (7–23)	<0.05
Men	24 (10–38)	5 (0–15)	NS*
Women	45 (30–60)	25 (12–38)	NS
With aura	22 (13–31)	10 (3–10)	<0.05
Men	13 (2–24)	3 (0–8)	NS
Women	30 (16–44)	18 (6–30)	NS

* Not significant ($p > 0.05$).

Table 2 *Reported symptoms during Ménière attacks in 78 patients, %*

Frequency	Hearing loss	Tinnitus	Aural fullness	Migrainous headaches	Photophobia	Aura symptoms	Nonmigrainous headaches
Always	37	42	37	14	46	1	1
Sometimes	17	30	31	14	6	9	5
Never	46	28	32	72	48	90	94

tinguish from distortion of sound often associated with Ménière attacks. Interviews were performed by two neurologists trained in neuro-otology and in the diagnosis of migraine according to IHS criteria.

Statistical methods. The prevalence of migraine in the Ménière group and in the age- and sex-matched control group was compared using the McNemar test. The paired *t*-test was used to verify comparability of groups for age after matching within blocks of 10 years, and to assess differences in age at onset for Ménière and migraine in the Ménière group. The results of all tests were considered significant at a 0.05 two-sided level of significance.

Results. *Prevalence of migraine.* The lifetime prevalence of migraine was significantly higher in the MD group compared to the age- and sex-matched control group: 44 out of 78 patients with MD (56%) had a history of migraine, compared to 20 out of 78 controls (25%, $p < 0.001$). An increased prevalence of migraine was found both for men and women with MD (table 1).

Concurrence of Ménière attacks and migrainous symptoms. Migrainous headaches during Ménière attacks were experienced by 22 out of 78 patients with MD (28%). In 11 of these 22 patients, Ménière attacks were always accompanied by migrainous headaches, whereas in the other half migraine headaches sometimes (i.e., more than 20% of attacks) concurred with the vertigo. Migrainous headaches usually preceded the onset of vertigo in six patients, whereas 16 had headaches during or following the vertigo. Photophobia during typical Ménière attacks occurred in 52% of patients with MD. Aura symptoms (scintillating scotomata, spreading sensory symptoms) during the attacks were reported by 10% of the patients (table 2). Ménière attacks were always accompanied by at least one migrainous symptom (migrainous headaches, photophobia, or aura symptoms) in 35 patients (45%) and sometimes in 9 patients (11%). Migrainous symptoms were identical with each attack in 32 patients and varied in 12 patients.

Onset of Ménière disease and migraine. Mean age at onset of MD (46 ± 12 years) was higher than age at onset of migraine (32 ± 17 years, $p < 0.001$). Onset of migraine preceded the first occurrence of Ménière attacks in 33 out of 44 patients by 1 to 38 years; in five patients, the onset of Ménière attacks and migrainous headaches was simultaneous. In the remaining six patients, migraine manifested later (by 2 to 23 years).

Discussion. Our study shows a significantly higher lifetime prevalence of migraine in patients with MD (56%) as compared to age-and sex-matched controls (25%). Of the original 114 unselected patients with MD for whom medical records were available, 13 never received our letter, so their nonresponse should not cause any bias. Even if the 23 patients who presumably received our letter but did not respond were all nonmigraineurs, the prevalence of migraine would still be significantly increased in the MD group compared to the controls (44/101 vs 20/78, $p = 0.013$). Therefore, we believe that our finding of an increased prevalence of migraine in patients with MD should apply to all patients with MD with typical presentation of the disease.

Only two previous studies have investigated the prevalence of migraine in MD. In a questionnaire survey, patients with unilateral MD were less commonly affected by migraine than were normal controls (22% vs 33%); the difference, however, was not significant.[4] These results must be taken with caution because the age and sex distribution of the groups was not specified and adjustment of these factors would undoubtedly affect the incidences of MD and migraine. A retrospective, uncontrolled case series found prevalences of migraine of 43% for women and 19% for men,[5] which are higher than prevalences reported in population-based studies of 6 to 17% for women and 1.5 to 6% for men.[6] Diagnosis of migraine in our study was based on the IHS classification of headaches, whereas these previous investigators applied distinct diagnostic criteria. A meta-analysis of 24 studies on migraine prevalence showed that case definition, in combination with sex and age distribution, accounts for the greatest proportion of data variance.[9] Thus, the differences between our results and those reported previously may be accounted for partly by differences in case definitions.

The lifetime prevalence of migraine found in our control group (25% overall; 43% for women and 8% for men) is slightly higher than lifetime prevalences reported from large population-based studies (11 to 18% overall; 15 to 33% for women and 7 to 13% for men).[10-14] An estimation of the expected lifetime prevalence of migraine in our control group, based on the age- and sex-specific lifetime prevalences from a recent large population-based study applying the IHS criteria,[14] results in 27% (35% for women and 19% for men), which is similar to our findings.

Migrainous headaches, photophobia, or aura are not normally considered to be features of typical Ménière attacks, although Ménière and others[1,5,15] have noted headaches as frequent accompaniments of the vertigo. In our study, 28% of all patients with MD had typical migrainous headaches always or

sometimes associated with Menière attacks and 45% of patients regularly experienced at least one migrainous symptom with their vertigo. The high prevalence of migraine in MD and the frequent occurrence of migrainous symptoms during Ménière attacks can be explained in two ways: either some of these patients actually have migrainous vertigo (MV) or there is a pathophysiologic link between MD and migraine.

Migraine is an increasingly recognized cause of recurrent vestibular symptoms. Features of MV include episodic vestibular symptoms lasting minutes to several days, an individual history or a family history of migraine, migrainous symptoms during the attack that may or may not involve headaches, and migraine-specific precipitants of the attack.[16-25] Apart from vertigo, fluctuating cochlear symptoms and hearing loss, key symptoms for the diagnosis of MD, have been stated to occur in migraine in 12%[25] to 38%[18] of cases. Vestibulo-cochlear symptoms have been reported in 78 out of 200 unselected migraineurs: 39% had vestibular symptoms only, 16% combined vestibular and cochlear symptoms, and 5% cochlear symptoms only. Likewise, in 80 patients investigated for vestibulo-cochlear symptoms related to migraine, 7.5% could be diagnosed with MD.[16] Therefore, a partial explanation for the high prevalence of migraine in MD and the frequent concurrence of MD and symptoms of migraine could be ambiguity in differential diagnosis so that some patients may fit the diagnostic categories of both MD and MV. Accordingly, it is possible that some of our patients with MD may have actually had MV. Especially in patients in whom the onset of migraine coincided with the onset of vertigo attacks or in patients who always experience migrainous symptoms during their attacks, a diagnosis of MV with vertigo attacks closely mimicking those of MD seems possible. However, even if we had not considered these patients (n = 13), assuming that they had MV alone, the prevalence of migraine in the remaining 65 patients with MD would still be higher than in the control group (31/65 vs 20/78; $p = 0.0061$).

Differential diagnosis of MD and MV is compromised by the lack of agreement on the classification of MV, although operational criteria have recently been proposed.[24] Also, specific vestibular testing including sinusoidal harmonic acceleration has been shown helpful for discriminating between MV and MD.[26] Despite problems of differential diagnosis, the substantial evidence for high prevalence of migraine in MD and of vestibulo-cochlear symptoms in MV raises the possibility of some common etiology.

The precise etiology of MD is unknown. Anatomic, genetic, immunologic, infectious, metabolic, and vascular causes have been proposed.[27-29] Histologic studies have given evidence for endolymphatic hydrops as the direct cause of the Ménière attack.[30] During the attack the perilymph becomes contaminated with potassium-rich endolymph, due to rupture or leakage of the distended endolymphatic membrane, resulting in an intoxication of vestibulo-cochlear hair cells.[31] Hydrops is thought to be the final common pathway of damage to the inner ear and can develop secondary to infection,[32] trauma,[33] or vascular impairment.[27]

There is clinical evidence that migraine can damage the inner ear, causing permanent hearing loss or impairment of vestibular function.[34-36] It has been suggested that endolymphatic hydrops may develop in an ear previously compromised by vasospasm due to a migrainous mechanism.[20] However, this would not fully explain why a large subgroup of patients with MD experience migrainous symptoms in association with Ménière attacks. For these patients, a common pathophysiologic mechanism generating both migraine symptoms and MD can be supposed, as has been discussed for MV.

The pathophysiology of MV is subject to speculation. For vestibular symptoms of longer duration, it has been proposed that neurotransmitters that modulate vestibular function (serotonin, noradrenalin, dopamine, and neuropeptides such as calcitonine-gene-related-peptide) are released during migraine attacks.[19] Transient changes in blood supply to the labyrinth could be responsible for the development of short-lasting vertigo, fulfilling the criteria of a migraine aura.[19,23] The insult of repetitive vascular challenges in migraine attacks could eventually lead to irreversible loss of cochlear and vestibular function.

Recently, channelopathies have been identified as the cause of various paroxysmal disorders such as hypokalemic paralysis, episodic ataxias, or familial hemiplegic migraine.[37] Accordingly, it has been suggested that in MV a defective ion channel with predominant expression in the brain and inner ear may lead to a local increase of extracellular potassium, causing both the spreading depression in migraine and a paroxysmal osmotic disequilibrium, resulting in endolymphatic hydrops and increase of perilymphatic potassium with consequent toxic effects on hair cells in the inner ear.[20]

Hypotheses that offer an explanation of the simultaneous occurrence of MD and migrainous features are variations of a vascular mechanism, abnormal release of neurotransmitters, and an ion channel disorder. The high incidence of migraine in patients with MD suggests the possibility of common pathophysiologic mechanisms whose existence could lead to new therapeutic options in the treatment of MD. It is possible that patients who have both MD and migraine would be relieved from their vertigo by antimigrainous medication. It would be worthwhile to explore this prospect further because, in many patients, MD responds poorly to current medical treatment.

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