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A hypothetical proposal for association between migraine and Meniere's disease

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Abstract

Meniere's disease (MD) is a chronic condition affecting the inner ear whose precise etiology is currently unknown. We propose the hypothesis that MD is a migraine-related phenomenon which may have implications for future treatment options for both diseases. The association between MD and migraine is both an epidemiological and a mechanistic one, with up to 51% of individuals with MD experiencing migraine compared to 12% in the general population. The presence of endolymphatic hydrops in those with MD may be the factor that unites the two conditions, as hydropic inner ears have an impaired ability to maintain homeostasis. Migraine headaches are theorized to cause aura and symptoms via spreading cortical depression that ultimately results in substance P release, alterations in blood flow, and neurogenic inflammation. Chronically hydropic inner ears are less able to auto-regulate against the changes induced by active migraine attacks and may ultimately manifest as MD. This same vulnerability to derangements in homeostasis may also explain the common triggering factors of both MD attacks and migraine headaches, including stress, weather, and diet. Similarly, it may explain the efficacy of common treatments for both diseases: current migraine treatments such as antihypertensives and anti-convulsants have shown promise in managing MD. Though the etiology of both MD and migraine is likely multifactorial, further exploration of the association between the two conditions may illuminate how to best manage them in the future. MD is likely a manifestation of cochleovestibular migraine, which occurs as a result of migraine related changes in both the cochlea and vestibule.

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Keywords

migraine headache; Meniere's disease; cochleovestibular migraine; endolymphatic hydrops; association

INTRODUCTION

Meniere's disease (MD) is a chronic illness first described by Prosper Meniere over 150 years ago that is characterized by a triad of episodic hearing loss, vertigo, and aural symptoms including aural fullness and tinnitus. The condition, which primarily affects the inner ear, causes "attacks" wherein patients experience fluctuating symptomatology lasting as short as 20 minutes or as long as 24 hours. Although diagnostic criteria for the condition classically reference the above triad of symptoms, sufferers may also experience nausea/vomiting, gait disturbance, and headache during these attacks (1). Eventually, the affected ear may develop progressive and permanent loss of hearing. The prevalence of MD may be as high as 190 people per 100,000, representing over 600,000 sufferers in the United States alone; however, the precise etiology of the disease is not yet known (2).

It was not until 1937, over 70 years after the first descriptions of the disease, that a pathologic correlate of MD was found. By analyzing temporal bone specimens during autopsy, researchers were able to identify endolymphatic hydrops (EH) as a potential marker of MD (3). Endolymph is a potassium-rich fluid contained within the inner ear that plays a crucial role in both hearing and balance; when there is too much endolymph fluid due to over-production or under-resorption, it is referred to as EH. EH can be broadly divided into categories based on etiology and presence of symptoms: there exist congenital, acquired, and idiopathic forms of EH, and each of these can be symptomatic or asymptomatic (4). Known causes of EH include congenital malformations, trauma, surgery, infection, and neoplastic processes, but it can also be idiopathic, where there is no known cause or inciting event (5-8). Recent studies have confirmed the association between idiopathic EH and MD (4, 9-12). Rauch *et al.* performed a blinded study of temporal bones and found that all specimens with a clinical diagnosis of MD had idiopathic EH; however, there were 6 specimens with idiopathic EH who had no MD diagnosis (11). They concluded that their "... results challenge the dogma that endolymphatic hydrops per se generates the symptoms of Meniere's syndrome" (11). It appears that although sufferers of MD will in all cases have at least one ear with hydrops, not every individual with EH experiences the symptoms of MD. This finding has led to the conclusion that there must be another factor at play that induces those with EH to develop MD.

Multiple hypotheses have been proposed to explain this outlying factor. Membrane rupture causing contamination of perilymph with potassium-rich endolymph, mechanical damage by EH, and vascular phenomena have all at times been theorized to cause MD (3, 4, 13). Recent evidence has refuted the hypothesis that potassium intoxication of perilymph might explain MD, as well as the theory that EH alone is responsible for MD (10, 14, 15). This has led to recent popularization of the theory that MD may be related to vascular or ischemic conditions that affect perfusion of the inner ear during attacks. One such condition is

migraine headaches, which appear to have a partly vascular component to their manifestation and have been found in close association with MD (16-19). In this paper, we propose that MD is indeed related to the phenomenon that is migraine, and that treatments traditionally used for migraine headache can be applied to effectively treat MD as well.

HYPOTHESIS

Our hypothesis posits that MD is in fact a migraine-related phenomenon, with both conditions united by a common unknown, though potentially vasculogenic or related to spreading cortical depression, pathophysiology or risk factor that can predispose to development of both diseases. This common risk factor can cause those with otherwise asymptomatic EH to develop MD and potentially progressive hearing loss. This theory helps explain the significant association of MD with migraine and the similarity of triggering factors in both diseases. Furthermore, it can help explain the efficacy of current treatments for MD as well as provide a steppingstone for future management and treatment options.

EVALUATION OF THE HYPOTHESIS

An epidemiological and mechanistic association between Meniere's disease and migraine

Though not every individual with MD will experience migraine and not every individual with migraine will develop MD, there is a significant association of MD with migraine headaches. The association of migraine with MD dates to MD's origins in 1861, when Prosper Meniere first described the condition. In addition to the triad of symptoms used to characterize MD, Meniere also described migraine headaches and migraine auras occurring in the very same patient population he used to elucidate the symptoms of MD (20). Though the prevalence of migraine symptoms in this historical population is not known, recent studies have further explored this connection and determined that up to 51% of MD sufferers also suffer from migraine headaches (21) and that up to 45% of MD patients experience migraine symptoms during an attack (17). Familial clustering of migraine and MD has also been found, supporting a relationship between the two diagnoses (22).

In addition, migraine is associated with inner ear pathologies, including vertigo, tinnitus, and even sudden sensorineural hearing loss (23). Two disease entities – vestibular migraine and cochlear migraine – have been proposed that illustrate the interplay between migraine and inner ear symptoms. Vestibular migraine encompasses migraine and vertigo symptoms, and cochlear migraine encompasses migraine and auditory symptoms (24, 25). When experienced together, they form a symptom complex we term cochleovestibular migraine that is similar in presentation to MD (25).

The connection is not merely an epidemiological one but a mechanistic one as well. As part of a migraine attack, spreading cortical depression causes release of neuropeptides and cytokines including calcitonin gene-related peptide and substance P from the trigeminal ganglion, leading to vasodilation, increased vascular permeability, and extravasation of plasma (26-28). This contributes to the neurogenic inflammation and pain that occurs during the headache phase of a migraine. Innervation of the cochlea and cochlear blood vessels by trigeminal nerve fibers has been previously demonstrated, supporting the notion that

vascular effects of migraine can extend to affect the inner ear as well (29-31). To add another layer of complexity, the response of inner ears with EH to substance P differs from that of non-hydronic inner ears. Specifically, chronically hydronic inner ears appear to lose their ability to autoregulate their vasculature and blood flow, making them more vulnerable to other stress factors such as those detailed below (32-35). This could potentially cause those with existing neuropeptide and vasomotor dysfunction in the trigeminal nerve, such as in migraine, to manifest MD. In fact, individuals with concurrent migraine and MD appear to have a younger age of onset of MD and are more likely to experience bilateral hearing loss and aural fullness (36).

Specific case studies have also demonstrated a link between migraine and inner ear pathologies. In one case, migraine-associated vascular changes may have caused inner ear ischemia and EH, ultimately resulting in sensorineural hearing loss and MD-like symptoms (37). In another, an individual with migraine-associated hearing loss was found to have severe bilateral EH (38). Both migraine and MD have also been found in association with drop attacks, though the prevalence of drop attacks is rare in both conditions and sometimes is associated with neither (39, 40). Vascular factors that play a role in migraine may indeed predispose to earlier development of MD and manifestation of more inner ear symptoms.

Meniere's disease and migraine share similar triggers

In addition to the epidemiologic and mechanistic association of MD and migraine, both conditions also share common triggering factors, including stress, weather changes, and dietary intake. Multiple studies have found an association between stress levels and migraine occurrence, which may be related to the observed ability of steroids to increase the frequency of spreading cortical depression events in the presence of certain genetic mutations (41-43). This can be extrapolated to provide an explanation for why physiologic stressors such as acute illness, poor sleep quality, and new onset pain disorders, among other things, can provoke or worsen migraine and MD. Fluctuations in estrogen may also contribute to spreading cortical depression and thus both migraine and MD symptoms. Vestibular migraine in particular has a similar age of onset as MD in the fifth decade of life, and both migraine and vestibular migraine occur more frequently in women (44, 45). Sudden decreases in estrogen level, such as those that can occur peri-menopause, can provoke migraine, and certain female mice in the presence of estrogen have been observed to have faster and more frequent cortical spreading depression events (46, 47). Weather effects including low atmospheric pressure, high temperatures, low humidity, and increased light intensity during summer months have also been linked to increased migraine frequency (48-51). Finally, caffeine has been reported to trigger migraine as well. Similarly, stress and low atmospheric pressure have been linked to MD attacks (52-54), and caffeine consumption was associated with a lower age of onset of MD (55). To further unite the two diagnoses, strong odors and visual motion such as driving or watching television have been identified as triggers for both migraine and MD (21, 56). While alcohol and sodium restriction have traditionally been recommended in the management of MD and have shown some efficacy (57), there have yet to be studies critically evaluating the effect of these specific dietary changes on MD. Some studies have failed to show a link between dietary sodium intake and migraine occurrence, and rather the effect may be from lack of sufficient water intake or

from nitrites, glutamate, or tyramine that may be found in high-sodium-content foods (42, 58, 59).

In fact, both tyramine and caffeine are known vasoconstrictors and hypertensive agents that may be one of the factors to which hydroptic inner ears are more susceptible (60). Caffeine promotes vasoconstriction and decreased blood flow that normally is compensated for by adenosine receptors (61). With Long term use, however, the impaired autoregulation of blood flow in hydroptic ears may prevent adaptation and allow for easier provocation of both migraine and MD. This may also explain why fermented, tyramine-containing alcohol could worsen both conditions, and how abstaining from fermented alcohol and caffeine may improve symptomatology.

Treatments traditionally reserved for migraine may help treat Meniere's disease

Current migraine treatment options, including both medical and surgical treatments, have shown success in treating MD and inner ear symptomatology. Anti-hypertensive drugs including calcium channel blockers and beta blockers are options for prophylactic treatment of migraine (62, 63). Other anti-hypertensive diuretics such as carbonic anhydrase inhibitors and hydrochlorothiazide can be used as treatment options for MD, though evidence for efficacy varies (57, 64, 65). This may represent the commonality of vascular factors in both migraine and MD. Furthermore, by controlling diet for compounds that promote migraine, particularly caffeine, glutamate, and tyramine, and for dehydration, migraine and MD symptoms can be reduced (66). Tricyclic antidepressants (e.g., nortriptyline) and anti-convulsants such as topiramate have been successfully used to manage MD symptoms as well, most likely through a variety of mechanisms including neuromodulation and inhibition of certain subtypes of carbonic anhydrase enzymes (67, 68). Oral and parenteral steroids, which may help prevent spreading cortical depression and the release of inflammatory mediators that can affect the inner ear, have also been used to manage both acute migraine and MD (19, 69, 70).

Surgical treatment options such as tympanostomy tubes may alleviate both MD attacks and inner ear manifestations of migraine by preventing changes in barometric pressure from triggering acute events. This treatment has already shown some ability to alleviate vertigo symptoms in MD and remains effective for approximately 47% of patients (71-73). Interestingly, the percentage of migraine sufferers who report weather as a trigger also falls within the 40-60% range (48, 74, 75). Though the mechanism is not completely understood, changes in barometric pressure have been demonstrated to provoke neuropathic pain in rats (76). If the inner ear is lesioned, changes in pressure no longer worsen neuropathic pain (77). This suggests that the inner ear is profoundly affected by changes in atmospheric pressure, which are sensed at the tympanic membrane, and may instigate migraine and MD attacks, particularly in those with EH who are already more susceptible to perturbations in homeostasis. Removal of the tympanic membrane's ability to sense pressure by placing a tympanostomy tube can allow for elimination of barometric pressure changes as a trigger for both conditions.

Migraine's association with inner ear symptoms may also explain why treatments traditionally used for migraine have shown effectiveness when applied to inner ear

pathologies: migraine prophylactic medications have been successfully used to treat aural fullness, poststapedectomy-vertigo, and mal de débarquement syndrome (78-80).

DISCUSSION AND CONCLUSION

The association between MD and migraine headache suggests an underlying factor that unites them both; however, the precise etiology is not yet fully known. Evidence continues to emerge exploring various contributing factors of both MD and migraine, including spreading cortical depression, vasculopathies, neuropeptide derangements, hormonal interactions, calcium channelopathies, and salt metabolism (19, 81, 82). Though the true cause may be multifactorial, it is likely that the underlying triggers cause both MD and migraine depending on the individual, and in the case of MD, those with existing EH may be more susceptible. Rather than existing as separate conditions, MD and migraine inner ear disorder may instead exist on a continuum (Figure 1). At one end are patients with purely vestibular symptoms (e.g., vertigo, motion sensitivity, imbalance), termed vestibular migraine. At the other end of the spectrum are patients who have purely cochlear symptoms (e.g., fluctuating hearing loss, aural pressure, tinnitus, hyperacusis). The patients who have the combination of both symptoms are patients with cochleovestibular migraine, or Meniere's disease.

As of yet, there is no definitive cure for MD, but treatments traditionally used for migraine have shown promise in improving quality of life (67). Through further exploration of the association between migraine and MD, it may be possible to find more effective treatments and management techniques. Subsequent studies evaluating the treatment efficacy of dietary changes, the precise link between migraine, cortical depression, and inner ear pathologies, and, eventually, the pathophysiology of migraine itself may better illuminate the relationship between MD and migraine, potentially revealing how to best manage and cure MD in the future.

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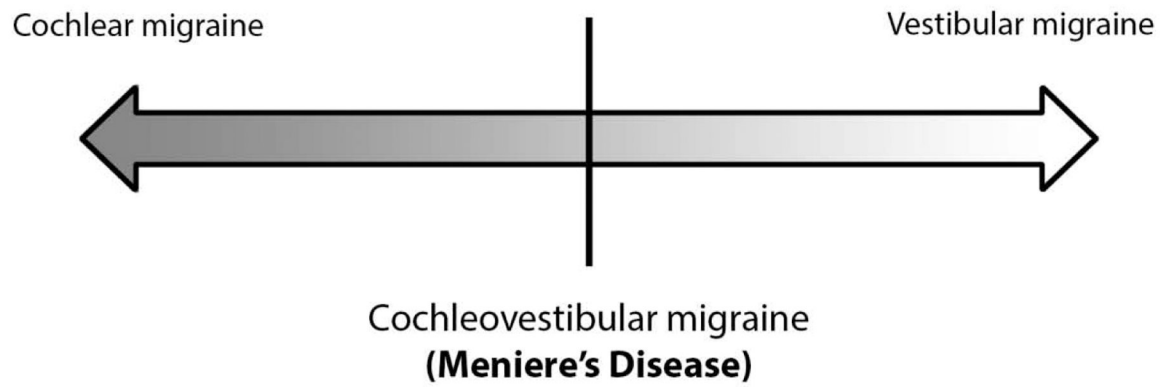


Figure 1.

Spectrum of migraine inner ear disease. Meniere's disease most resembles a combination of symptoms from both cochlear and vestibular migraine and may exist on a continuum with the two conditions.