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Is Allergy Related to Meniere's Disease?

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Abstract Meniere's disease (MD) is characterized by episodic rotational vertigo, fluctuating sensorineural hearing loss, aural pressure, and tinnitus. The cause of MD is thought to be multifactorial, with anatomic and genetic contributions. Allergy is thought to be one of the possible extrinsic factors that, when combined with underlying intrinsic factors, may lead to MD. We review the epidemiologic associations of MD and allergy and review the recent literature on the association of allergy and MD.

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Introduction

Meniere's disease (MD) is characterized by episodic rotational vertigo, fluctuating sensorineural hearing loss, aural pressure, and tinnitus. Prosper Meniere first associated dizziness with the inner ear in 1861. Since his series of publications [1–3] in the *Gazette Medicale de Paris* in 1861, the pathophysiology and management of MD has remained controversial. The medical condition can be divided into two subcategories. When the cause is unknown, it is referred to as Meniere's disease. It is called Meniere's syndrome when it is secondary to a number of established inner ear disorders (eg, autoimmune vasculitis, syphilis, mumps, or trauma).

The true incidence and prevalence of MD in any population are difficult to ascertain [4]; the literature reports a prevalence of 17 to 218 per 100,000 [4–8], and incidence ranges from 4.3 to 15.3 per 100,000, depending on the geographical location [4, 9, 10]. It is more common in the fourth to sixth decade of life, with only 3 % of cases seen in the pediatric population [11]. The female-to-male ratio is 1.3 to 1 [4]. MD is sporadic in the majority of cases, but in 10 % to 20 % of patients, MD is familial with an autosomal dominant inheritance [12].

The cause of MD is thought to be multifactorial, with anatomic and genetic contributions. Allergy is thought to be one of the possible extrinsic factor that, when combined with underlying intrinsic factors, may lead to MD. The role of allergy and MD was first described by Duke [13] in 1923. Since then, role of allergy has been investigated in patients with unilateral and bilateral MD. Derebery et al. [14–21, 22••] have made a noteworthy contribution in investigation into allergy and MD. In this article, we

review MD in the context of allergy and highlight the literature on this topic published over the past year.

Clinical Presentation of Meniere's Disease

The diagnosis of MD can be difficult, especially in the early stages, when all symptoms are not present. There is no gold standard diagnostic test. The clinical picture of MD includes intermittent episodes of vertigo lasting minutes to hours, fluctuating sensorineural hearing loss, aural fullness or pressure, and tinnitus. The fluctuating nature of the symptoms is the characteristic feature of MD. Acute MD can occur in clusters, with 6 to 11 clusters per year [23]. Episodes have been observed to occur with increasing frequency over the first few years. Later, in association with a sustained deterioration in hearing, the episodes tend to decrease and may cease completely. This temporal fluctuating time course can make diagnosis difficult. To assist in diagnosis, in 1995, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) established a specific set of criteria for the diagnosis of MD (Table 1).

Pathophysiology of Meniere's Disease

Despite MD first being described more than 150 years ago, the etiology and pathophysiology remain unknown. In 1938, Hallpike and Cairns [24] and Yamakawa [25] showed the presence of endolymphatic hydrops in patients with MD. The endolymphatic hydrops represents increased volume within the sac, resulting in distention of the structures surrounding the endolymphatic sac. Postmortem histopathological studies looking at temporal bones in patients with MD also supported this finding [26, 27]. Endolymphatic hydrops is considered the distinguishing pathological finding in patients with MD. However, endolymphatic hydrops is not necessarily associated with the symptoms and signs of MD [28]. Endolymphatic hydrops has been observed in the asymptomatic contralateral ear [29, 30]. In 2005, a temporal bone study looking at MD patients suggested that the endolymphatic hydrops should be considered a histologic marker for Meniere's syndrome rather than being directly responsible for its symptoms. Developing evidence suggests that MD appears to be initiated by cytochemical abnormalities located within the spiral ligament, and stria vascularis. These cells play an important role in maintaining cochlear homeostasis. The trigger for the cytochemical abnormalities remains elusive [28, 31••, 32].

Allergy and Meniere's Disease

Associations of Allergy and Meniere's Disease

Allergy is the fifth most prevalent chronic disease in the United States among all age groups. It affects an estimated 50 million Americans. The prevalence of allergic rhinitis (AR) in America is estimated to be 14 % [33]. This is twice as common as the estimated prevalence of asthma [34]. Since 1923, both inhalant and food allergies have been linked to MD symptoms [13]; however, it is difficult to prove the relationship, as the onset of symptoms due to the insult may be delayed, and causes of MD are multifactorial [35]. MD patients report higher rates of allergy history and positive skin test or in vitro tests than control patients with other otologic diseases, and compared with the general public [20].

A few studies have looked at the association of MD and allergy (Table 2). In a large study, Derebery and Berliner [18] investigated the prevalence of allergy in MD. In a survey of 734 patients with MD, concurrent allergic disease was found in 41 %. A more recent survey by Derebery et al. [16] described an allergy history in 58 % of MD patients and skin test positivity in 41 %. This figure is almost three times that of the general population [18].

The notion of the unified airway, in which an allergic response in one part of the airway can evoke a response in other areas of the airway is generally well-accepted [36].

Table 1 American Academy of Otolaryngology-Head and Neck Surgery criteria for diagnosis of Meniere's disease (1995)

Criteria
1. Recurrent spontaneous and episodic vertigo. A definitive spell of vertigo lasting at least 20 min, often prostrating, accompanied by disequilibrium that can last several days; and usually causing nausea or vomiting, or both but no loss of consciousness. Horizontal rotatory nystagmus is always present
2. Hearing loss (not necessarily fluctuating)
3. Either aural fullness, tinnitus or both
Certain Meniere's disease: definite disease with histopathological confirmation
Definite Meniere's disease: ≥2 definitive episodes of vertigo with hearing loss, plus tinnitus, aural fullness, or both
Probable Meniere's disease: only 1 definitive episode of vertigo and the other symptoms and signs
Possible Meniere's disease: definitive vertigo with no associated hearing loss or hearing loss with nondefinitive disequilibrium

Table 2 Studies demonstrating an epidemiologic association between allergy status and MD

Study	*n*	Outcome or OR for patients with:
Derebery [19] (2000)	906	Airborne allergy and MD, 2.00 (59.2 %/42 %)
		Food allergy and MD, 2.02 (40.3 %/25 %)
		Positive skin test or blood test MD, 2.06 (37 %/22.2 %)
Berardino and Cesarani [38•] (2012)	109	56.9 % of MD patients had positive gliadin prick test
		None of the 50 control patients tested positive
Keles et al. [39] (2004)	92	MD and elevated IgE OR, 2.91 (41.3 %/19.5 %)
		MD and history of allergy, 3.87 (67.3 %/34.7 %)
Savastano et al. [55] (2007)	250	56.5 % of MD had elevated CIC (113 of 200) vs none in the 50-patient control group
Singh et al. [40] (2011)	50	100 % of AR patients had sensorineural hearing loss, compared with none of the 20 in the control group
Karabulut et al. [41] (2011)	89	Hearing loss in AR patients with positive skin test vs AR with negative skin test
		OR, 0.23 (39.6 %/74.1 %)
Sen et al. [45] (2005)	208	Migraine and MD vs control OR, 2.89 (39 %/18 %)
		Allergy and MD vs control OR, 3.60 (51.9 %/23 %)

AR allergic rhinitis; *CIC* circulating immune complex; *MD* Meniere's disease

Likewise, in allergy-susceptible patients, an allergic response can evoke responses in distal sites. This likely occurs via an integration of neurological, immunologic, and allergic responses involved in inflammation. People with AR may have asthma, nasal polyposis, otitis media, or chronic rhinosinusitis [36]. People with asthma and AR have a higher prevalence of food allergies, the estimated prevalence of which in America is 3.5 % to 6 %.[37].

Derebery and Berliner [18] in 2000 reported wheat as the most common food allergen found in patients with MD (68.2 %). Gliadin is considered the major cause of IgE-mediated hypersensitivity in people with wheat allergy. In 2012, Di Berardino et al. [38•] investigated the incidence of gliadin IgE hypersensitivity in patients affected by MD. This study compared 58 patients with MD, 25 healthy controls, and 25 patients with proven grass pollen rhinoconjunctivitis. In 48 of the 58 MD patients (82.7 %) a positive skin prick test for 1 or more allergens was found. A total of 33 MD patients proved to be sensitive to gliadin, and 20 of those patients were monosensitized and 13 showed a positive prick test to other allergens. What makes this study interesting is that only 8 of 33 MD patients were positive to gliadin prick test at 20 minutes. The other 25 showed a late-response reaction; 13 were positive at 6 hours, 11 at 12 hours, and 1 at 24 hours. The prick test for gliadin was negative in all healthy volunteers and in all patients with grass pollen rhinoconjunctivitis.

Interestingly, in 2004, Keles et al. [39] investigated the role of allergy in the pathogenesis of MD by observing the cytokine profiles, allergic parameters, and lymphocyte subsets in 92 patients. A total of 46 patients with MD were recruited to the study. The control group included 46 non-MD patients from the same age groups, same region, and same socioeconomic background. Lymphocyte subsets were measured, including CD4, CD8, and CD23 antibodies, interferon-γ, interleukin-4, total serum IgE, and antigen-specific IgE to regionally important tree pollen, fungi, and various foods. This study found a positive correlation between CD23 and IgE, CD8 and IgE, CD4/CD8 and IgE, and CD23 and CD8. The results showed total IgEs were above normal values in 19 of 46 patients with MD, compared with 9 of 46 in the control group. A total of 31 of the 46 MD patients had a history of allergy, compared with 16 of 46 in the control group.

In 2011, two studies investigated hearing in patients with AR. Singh et al. [40] assessed the otological and audiological status of patients with AR. Thirty AR patients and 20 controls underwent audiological investigation. All the AR patients had sensorineural hearing loss (not conductive) and otoacoustic emission abnormalities when compared with controls. However, a prospective study by Karabulut et al. [41] evaluated hearing in 58 AR patients with a positive skin prick test and a control group of 31 AR patients with a negative skin prick test. The test showed that the AR patients had better hearing at 8,000 Hz than those in the control group [41]. Additional research is needed to determine the clinical value of audiometry and otoacoustic emission testing in AR.

Allergic reactions are considered to be one of the many causes of migraines. Numerous studies have reported an association between migraines and allergies [42–44]. Sen et al. [45] compared 108 patients with MD with 100 non-Meniere's controls from an ear, nose, and throat clinic using a Web-based survey for patients to complete. They found that the incidences of both allergy and migraine were significantly higher in the Meniere's group and that the incidence of allergy in the MD migraine group was

significantly higher than that in the group with MD alone. The study is somewhat limited by the fact that both allergy and migraine diagnoses were self-reported. However, as Derebery [22••] observed, both the MD patients and the non-MD patients were asked the same questions.

Proposed Effects of Allergy on Meniere's Disease Pathophysiology

The exact function of the inner ear is not known. It is thought to play a role in fluid homeostasis and immune activity. In 2011, Friis et al. [46] reviewed the genes expressed in the endolymphatic sac in the rat and performed a functional characterization based on measured mRNA abundance compared with the dura. Among the different functional groups of genes, they showed genes involved in protection, antioxidant activity, and inflammatory response, which is consistent with previous studies supporting the idea that the endolymphatic sac is involved in immune-mediated reactions [47]. Many studies have shown the inner ear's capability to produce cellular and humoral responses. The endolymphatic sac can produce its own local antibody response and process antigens [47–49]. Destruction of the endolymphatic sac results in decreased antigen response and antibody production. Yoo et al. [50] demonstrated induction of endolymphatic hydrops in guinea pigs by immunizing them with native bovine type II collagen.

Derebery and Berliner [21] outlined three proposed mechanisms by which allergy can produce MD symptoms. The first mechanism, the endolymphatic sac, could be a target organ of the allergic reaction. Studies have shown that mast cells are located in the perisaccular connective tissue [51]. The antigen enters the endolymphatic sac and causes an IgE-mediated degranulation of mast cells. This produces a local inflammatory response that impairs the endolymphatic sac's filtering function, and a buildup of toxic metabolic products results, interfering with hair cell function. Histamine and other vasoactive mediators released in an allergic response elsewhere may also exert an effect on the well-vascularized fenestrated blood vessels of the endolymphatic sac, thereby affecting reabsorption.

The second mechanism proposed is deposition of circulating immune complexes (CICs). These CICs are deposited and accumulate in the fenestrated blood vessels of the endolymphatic sac and stria vascularis. This results in inflammation and an increased permeability of the leaky capillaries that surround the endolymphatic sac. The inflammation interferes with the capability of the endolymphatic sac's homeostasis function. Several studies demonstrated an increase in circulating immune complexes: 21 % to 96 % of patients with MD compared with controls [14, 52–54]. Savastano et al. [55] looked at nonspecific immunologic determinations in 200 patients with MD. In the 200 MD patients, 113 had high CIC values, compared with no increase in CIC values in the control group. In the Derebery et al. [14] study in 1991, 50 % of patients with increased CIC level had evidence of alimentary or inhaled allergies [55].

The third mechanism is the viral antigen–allergic interaction. This mechanism suggests that a viral insult can antigenically stimulate Waldeyer's ring, with T-cell homing to the endolymphatic sac, causing a low-grade inflammatory response. This impairs absorption of the endolymphatic sac but does not produce symptoms. Then, later in life, an unknown trigger in the system stimulates excessive fluid production. Derebery and Berliner [21] referenced how viruses are capable of exacerbating allergic symptoms by a variety of means, including causing histamine release, thought to be mediated by interferon. They can also damage epithelial surfaces, enhancing antigen entry and increasing responsiveness of target organs to histamine. Derebery [22••] noted heat shock protein 70 (HSP70), an antibody frequently seen increased in both MD and autoimmune inner ear disease, is often upregulated in viral infections. In contrast, Hornibrook and colleagues in [56] tested the claim that a significant proportion of patients with MD have antibodies to HSP70 antigen, which may lead to defective endolymphatic sac function and vertigo attacks. Serum samples were taken from 80 patients with AAO-HNS diagnosis of "certain" MD and 80 sex- and age-matched controls. In the MD group, 14 of 80 patients tested positive or equivocal for HSP70. Of the 80 controls, 10 tested positive or equivocal. They concluded that patients with clinically "certain" MD do not have a significantly raised incidence of HSP70 antibodies.

Treatment Implications

Derebery [19] looked at the effect of allergen immunotherapy and elimination of suspected food allergens in MD patients. A total of 137 patients were studied. These patients had MD and had been advised to consider allergy treatment. A total of 113 patients with MD received allergy treatment, and 24 MD patients elected not to have allergy treatment. These patients served as the control group. The 113 patients treated with allergen immunotherapy

Table 3 Study demonstrating an association between allergy treatment and Meniere's disease

Study	*n*	Outcome
Derebery [19] (2000)	137	113 patients accepted treatment; all 113 reported improvement of symptoms after treatment of allergy

and diet showed a significant improvement from pretreatment to post-treatment in both allergy and Meniere's symptoms [19]. Derebery and Berliner [21] then conducted a prospective study in which 68 patients completed a questionnaire rating their symptoms before and at an average of 23 months after treatment. Severity of vertigo, tinnitus, and unsteadiness decreased significantly. The frequency of vertigo and frequency and unsteadiness, and the ratings on AAO-HNS disability scale improved [21]. In Derebery's clinical experience, patients who have both MD and allergy benefit from immunotherapy and/or dietary avoidance of reactive food allergens. The symptoms of MD are generally better controlled, with fewer vertigo attacks and more stable hearing (Table 3) [21].

Conclusions

Despite being first described more than 150 years ago, the cause of MD remains elusive. The association of allergy and MD is well-documented. At the present time, it is generally accepted that the cause of MD is likely to be multifactorial, consisting of an underlying genetic predisposition, combined with an extrinsic insult. Allergy may well be involved in the final common inflammatory pathway in a select subpopulation of patients with MD.

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