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The Link Between Allergy and Menière's Disease

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Abstract

Purpose of review—To examine evidence supporting the association of allergy and Menière's disease.

Recent findings—Animal studies have shown evidence that a provoked systemic immune challenge can result in an allergic reaction within the inner ear while pre-medication with leukotriene antagonists can prevent the development of endolymphatic hydrops. In human subjects, further data supports a heightened allergic response in patients with Menière's disease while pharmacological treatments that target histamine receptors help to control vertiginous symptoms. However, the relationship of migraine with a history of allergy and Menière's disease may confound this association.

Summary—Although the evidence of a causal association between allergy and Menière's disease is inconclusive, the inclusion of allergy control as part of the treatment plan for Menière's disease is low risk to the patient and should be considered for patients with indications that include history of seasonal or food allergy, past childhood or family history of allergy, bilateral Menière's symptoms, or a development of symptoms within a short time after exposure of food or inhaled allergen.

Keywords

Menière's disease; endolymphatic hydrops; allergy

Introduction

Menière's disease (MD) was first described by Prosper Menière in 1861. Although involvement of the inner ear is generally agreed upon, there is no accepted theory regarding the pathophysiology. Hypothesized mechanisms based on laboratory and histological evidence include the disruption of longitudinal flow or malabsorption within the endolymphatic duct leading to endolymphatic hydrops [1]. MD is generally characterized as idiopathic, although speculation for the cause of this disease has included infection, inflammation, autoimmune disorders as well as allergy [1]. This review will focus on the most recent literature discussing the contribution of allergy to the development of MD.

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Conflict of Interest: None

Menière's Disease

MD is characterized by a constellation of symptoms including fluctuating sensorineural hearing loss, episodic vertigo, tinnitus and aural pressure. The American Academy of Otolaryngology's (AAO) Committee on Hearing and Equilibrium published diagnostic guidelines in 1995, reproduced in Table 1 [2]. In addition to history and symptoms suggestive of MD, objective testing utilizing electrocochleography (ECochG) can be performed. ECochG examines the ratio of the summation potential (SP) of the hair cells to the action potential (AP) of the synchronized firing of the cochlear nerve. An SP/AP ratio ≥ 0.5 has been correlated with MD symptoms [3].

Pathogenesis of MD is unknown; however a theory of fluid disruption leading to hydropic distention of the endolymphatic sac has been postulated [1]. Initial treatment includes diuretics and low sodium diet. Progressively more invasive treatments to prevent hearing loss and ultimately control vestibular symptoms with sacrifice of hearing include intratympanic injection of steroids, intratympanic gentamicin injections, endolymphatic sac surgery, vestibular nerve section and labyrinthectomy [4].

Allergy

The association of allergy and MD first appeared in the literature in 1923 [5]. Two cases were described of patients with symptoms consistent with MD. Each were treated with epinephrine and symptoms resolved. Much of the current literature supporting this association has come from the work of Derebery. Among cross-sectional surveys, the prevalence of diagnosed allergy was three times higher in those with a history MD compared to the general population [6]. More specifically, of those with MD, 58% had a history of allergy and 41% with a positive skin test [6]. Patients with the disease have been shown to have a “heightened immune” reaction. Subjects with a history of MD had elevated IgE levels compared to control groups (43.3% of subjects vs. 19.5%) [7]. Savastano et al. found elevated immune complexes, interleukins, and autoantibodies in patients diagnosed with MD [8]. Additionally, disease severity was associated with elevated immune complexes as well as an elevated CD4:CD8 ratio [8].

Derebery and Berliner describe three theories relating allergy to MD that center on inflammation within the endolymphatic sac [9]. First, the endolymphatic sac contains a fenestrated blood supply that may allow antigen entry leading to mast cell degranulation and inflammation. A second proposed mechanism involves circulating immune complexes that enter endolymphatic sac circulation and the stria vascularis leading to inflammation and increased permeability as well as fluid balance disruption. A final theory pertains to a viral antigen-allergic interaction. Viruses have been shown to exacerbate allergic symptoms by enhancing histamine release and can damage epithelial surfaces as well as trigger T-cell migration to the endolymphatic sac [8].

Both inhalant and food allergies have been associated with MD. In Derebery's work, wheat (gliadin) was the most common food allergen in MD patients [6]. More recently, Di Beradino et al. performed a study to verify the incidence of gliadin IgE hypersensitivity in MD patients [10*]. Patients with MD not currently being pharmacologically treated were

recruited and compared to two control groups. One group consisted of healthy volunteers while a second control group consisted of patients with grass pollen rhinoconjunctivitis. Prick testing to common inhalant and food allergens including gliadin was performed. Mean wheal diameter was measured and compared against a histamine control. Of subjects with MD, 8 out of 33 were positive to gliadin at 20 minutes (early phase response) with the remaining 25 subjects showing a late phase positive response. Gliadin prick test was negative for both control groups.

With data to show that patients with MD develop a robust allergic response, Topuz et al. study illustrates an association with allergy exposure, subsequent allergic response, and the development of endolymphatic hydrops [11]. Subjects, recruited by phone, were classified as MD based upon audiogram and ECochG. Prick test for dietary and inhalant allergens was performed and ECochG was obtained 30-45 minutes after exposure. A second provocation phase was performed where patients were given a second exposure to the antigen with the greatest induration. After provocation, 62.5% of patients subjectively reported tinnitus and aural fullness while 12.5% experienced vertigo. Before prick test, 28.7% of ears had a SP/AP ≥0.5. Post-prick test and provocation, the number increased to 77.5% and 72.5% respectively. Interestingly, in normal ears, a similar finding was noted. This data provided evidence that with allergic exposure, there appears to be a temporal sequence leading to the development of the disease. The authors also concluded that antigen exposure triggered a histaminergic reaction, leading to inflammation in the endolymphatic sac and potentially manifesting as symptoms of MD.

To support the theory that the endolymphatic sac appears to be a target for allergic activity, histamine receptors have been found within the sac. In animal studies, Dagli et al. showed immunohistochemical evidence of H_1 and H_2 receptors and weakly immunoreactive H_3 receptors [12]. Although not approved for use in the United States, betahistine has been used extensively in Europe as a treatment for MD. Betahistine is a structural analog of histamine and acts as a weak H_1 receptor agonist and strong antagonist on H_3 receptors. Its mechanism is thought to decrease the release of histamine, dopamine, gamma aminobutyric acid, acetylcholine, norepinephrine and serotonin and improve microcirculation in the inner ear [12]. In a retrospective analysis, Lezius et al. examined patients with MD who received high dose (288-480 mg/day) of betahistine and found that with increasing dosage of the medication, the number of patients reporting vertiginous attacks was lower [13]. Most common side effects were gastrointestinal complaints, fatigue and altered taste. The authors concluded betahistine is a potent, safe and effective treatment for MD.

As another marker of allergy, Takeda et al. performed a study examining plasma arginine vasopressin (p-AVP) and endolymphatic volume [14**]. P-AVP has been known to be elevated during allergic insults while endolymphatic volume has been show to increase with rising p-AVP. In this study, guinea pigs were sensitized with an allergic antigen. Histological examinations were performed at various time points post-provocation. Cross sectional area of the scala media was used to assess changes in endolymphatic volume and compared to control animals injected with saline. In a second experiment, subjects received oral administration of pranlukast hydrate, a leukotriene antagonist. Histological exam included toluidine blue stain to assess for mast cells. In a third experiment, prior to antigen

exposure, subjects were given pranlukast and compared with subjects given saline. P-AVP was then measured in both groups.

In subjects exposed to antigen without pranlukast pre-medication, results showed evidence of endolymphatic hydrops in all turns of the cochlea. However, animals pre-medicated with pranlukast did not develop endolymphatic hydrops. Staining in the experimental group showed large cells stained with toluidine blue consistent with mast cells. P-AVP levels were elevated in the sensitized group; however, among those pre-medicated with pranlukast, levels were statistically lower. Not only did this provide evidence that a systemic immune challenge could provoke an allergic reaction in the inner ears, the authors showed evidence of a decreased immune response when pre-medicated with a leukotriene antagonist.

Research regarding treatment of allergy as it relates to MD in human subjects has been limited. Patients using allergy immunotherapy and food elimination treatments have reported improved symptoms including decreased severity and frequency of episodes, decreased tinnitus and vertigo as compared to controls [6]. In a prospective study, patients rated symptoms before and after treatment and noted decreased severity of symptoms [9]. Derebery and Berliner concluded by recommending allergy testing for patients with MD if indicated [9]. Such indications include history of seasonal or food allergy, past childhood or family history of allergy, bilateral Menière's symptoms, or a development of symptoms within a short time after exposure of food or inhaled allergen. No recent studies including randomized controlled studies have been performed.

Confounders

Bank et al. provide the most recent literature review summarizing the association of allergy and MD [15*]. Much of the literature is based on cross-sectional or observational data without analysis for potential confounders. One area that has been highlighted is the association of allergy with migraines and MD. Through survey data collection, Sen et al. found a significantly higher incidence of allergy and migraine in patients diagnosed with MD [16]. Moreover, the incidence of allergy in the MD-migraine group was significantly higher than in the group with MD alone.

In a more rigorous study, Radtke et al. recruited patients with MD as diagnosed by AAO criteria (Table 1) [17]. Individuals were age and sex matched to control subjects. All subjects then underwent a semi-structured interview exploring lifetime prevalence of migraine. Results showed a higher lifetime prevalence of migraine among those with MD as compared to controls (56% vs. 25%) [17]. Authors speculated the high prevalence may be secondary to patients having migrainous vertigo or potentially a true physiological link between MD and migraine.

These studies bring to light the possibility of migraine as a confounder in the association of allergy and MD. Mehle provides a recent comprehensive review examining the relationship of migraine and allergy [18*]. Both allergic rhinitis and migraine have known common mediators such as histamine and IgE while epidemiological studies have shown that among those with history of migraine, prevalence of co-morbid conditions such as allergic rhinitis, seasonal allergies and asthma is higher [18]. However in clinical application,

pharmacological treatment has been inconclusive. Few clinical trials have been performed and although anti-histamine therapy has showed promise for control of migraines, leukotriene antagonists have failed to perform better than placebo [18].

No known study to date has been published that examines the relationship between allergy and MD in the context of a multivariate analysis. With this is in mind, several authors have stated that allergy is likely not the cause of MD nor is it the sole contributor. An association may be plausible given the scientific evidence and reported control of symptoms with treatment of allergies. Prescribing allergy control as part of a MD treatment plan may not be unreasonable, given that allergy avoidance is low risk to the patient, particularly those with a history of inhalant or food allergies. If a significant allergy is identified, the use of immunotherapy may be weighed against potential side effects. Clearly, more rigorous designed studies should be performed to fully examine this relationship.

Conclusion

MD, although described greater than 150 years ago, is still considered an idiopathic disease. Continued research is needed to further understand the etiology to assist in treatment. An association between allergy and MD has been shown in cross-sectional and observational studies while animal studies have shown evidence of allergic activity within the inner ear. Further studies are needed to demonstrate this association via well-designed randomized trials with inclusion of potential confounders. However, given the low risk to patients, inclusion of allergy avoidance and immunotherapy should be considered as part of the treatment plan to help patients control MD symptoms.

Acknowledgements

None

Abbreviations

MD	Menière's disease
AAO	American Academy of Otolarynology
ECochG	electrocochleography
SP	summation potential
AP	action potential

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Key Points

- Animal studies have shown evidence that antigen exposure leads to an increase in allergic markers that can trigger development of endolymphatic hydrops.
- Pre-medication with leukotriene antagonists in animals can limit the development of an immune response within the inner ear.
- Supporting prior research, incidence of gliadin IgE hypersensitivity is greater in patients with Menière's Disease.
- The association of migraine with allergy co-morbidities and Menière's Disease needs to be explored as a potential confounder.

Table 1

Diagnosis of Meniere's Disease

Certain Meniere's Disease
Definitive Meniere's Disease plus histopathological confirmation
Definite Meniere's Disease
Two or more definitive spontaneous epsidoes of vertigo 20 minutes or longer
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other causes excluded
Probable Meniere's Disease
One definitive episode of vertigo
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other causes excluded
Possible Meniere's Disease
Episodic vertigo of the Meniere type without documented hearing loss, or
Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without defintive episodes
Other causes excluded

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