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Evaluation of Serum Immunoreactivity to Common Indigenous Iranian Inhalation and Food Allergens in Patients with Meniere's Disease

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ABSTRACT

Background: A few studies investigated the relationship between allergy and Meniere disease considering complete allergen panel. We aimed to evaluate the serum immunoreactivity in patients with Meniere's disease (MD) compared with healthy people according to common indigenous Iranian inhalation and food allergens.

Methods: Thirty-nine patients with MD referred to Rasoul Akram Hospital (Tehran, Iran) were evaluated and compared with a 41 membered control group. A panel of common inhalation and food allergens (using an immunoblotting method), as well as total immunoglobulin E (IgE) level (using the sandwich enzyme-linked immunosorbent assay method), were checked on the patients' serum.

Results: The mean total IgE level was 193.85 ± 175.43 IU/ml in the patients with MD and 117.61 ± 138.05 IU/ml in the control group, which was significantly higher than the other subjects in the control group (P = .016). There was a significant difference between the two groups regarding inhalation allergens such as; sweet vernal grass, cultivated rye, cultivated oat, Russian thistle, goosefoot, and rough pigweed (P = .01–0.038). Patients with MD reported more reactive to food allergens such as; rye flour, hazelnut, pepper, citrus mix 2, potato, strawberry, and celery allergens. There was a significant relationship between Meniere and serum immunoreactivity to inhalation and food allergens (both P = .001).

Conclusion: Serum total IgE level in patients with MD (in both inhalation and food allergens groups) was higher than the control group, and there was a relationship between MD and immunoreactivity to common indigenous inhalation and food allergens of Iran.

KEYWORDS
Allergy; immune response; inhalation allergen; Iran; meniere; food allergen

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Introduction

Meniere's disease (MD), also known as idiopathic endolymphatic hydrops, is an inner ear disease characterized by symptoms including sudden spontaneous attacks of dizziness, sensory nervous hearing loss, tinnitus, and ear fullness. The prevalence of this condition varies from 7.5 to 157 cases per 100,000 people. MD is more common in the fourth to sixth decades of life, and only 3% of patients occur in childhood (da Costa et al. 2002; Meyerhoff et al. 1978)

Although inner ear involvement is evident in this disease, no acceptable assumptions have been made so far on the pathogenesis of this disease. The cause of MD is multifactorial, and anatomical and genetic factors play a role in the disease. Although this disease is considered idiopathic, it can be affected by factors such as hormonal changes, stress, infection, inflammation, autoimmune deficiency, and allergies (Horner and Cazals 2003; Paparella and Djalilian 2002; Weinreich and Agrawal 2014). It has been shown that autoimmune diseases are more prevalent in MD patients, in comparison with the general population. Additionally, the risk is also higher for those patients with concurrent migraine (Gazquez et al. 2011).

As a disease with episodes of recurrent vertigo, fluctuating sensorineural hearing loss, aural pressure, and tinnitus, there are various subgroups for the disease such as classic MD, delayed MD, familial MD, and comorbid MD, besides diseases such as the vestibular migraine (VM), which should be differentiated precisely. Recent studies on a large group of MD and VM patients have revealed that cytokines play considerable role on the pathogenesis of the diseases. Among them, the IL-1b, TNF-alpha, IL-6, CCL2, CCL22, and CXCL1 are shown to be different among MD patients, significantly (Flook et al. 2019; Frejo et al. 2018, 2017).

The relationship between MD and allergy was first reported in 1923. In a cross-sectional study, not only the prevalence of MD in patients with confirmed allergy was three times higher than in the general population, but also a remarkable point in that study was that 58% of MD patients had a history of allergic diseases and 41% had positive skin tests (Derebery 2000). Evidence suggests that patients with MD have severe immune responses. The results of another study showed that the serum of MD patients had elevated levels of serum total IgE compared with the general population (Keles et al. 2004). In this study, we examined the serum immunoreactivity in patients with MD compared with healthy people according to common indigenous Iranian inhalation and food allergens. To the best of our knowledge, this study was the first in Iran to assess the association of this disease with common indigenous allergens in Iran. It is noteworthy that the allergen panel for this study was more complete than what has been used in previous studies.

Methods and materials

Study design and patient enrollment

Among four main groups of MD (definite, certain, probable, possible), the study population consisted of patients with definite MD who were referred to Rasoul Akram Hospital (Tehran, Iran), whose disease was confirmed by an otolaryngologist according to 1995 AAO-HNS standards. The control group consisted of patients without MD (aged between 24 and 45). All MD patients (the case group, aged between 27 and 52) (n = 39) and the control group (n = 41) were selected from Feb 2018 until March 2019 according to inclusion criteria. The inclusion criteria were as follows: patients aged between 24 and 45 years with

definite MD diagnosis (two or more definitive spontaneous episodes of vertigo lasting at least 20 minutes along with audiometrically documented hearing loss on at least one occasion and tinnitus or aural fullness in the suspected ear), without the history of hormonal or immunosuppressive therapy or no plan for taking immunosuppressive therapy. Known patients of autoimmune or neoplastic diseases were excluded from the study. A board consisting of an otolaryngologist and an allergist who were fluent in both Persian and English extracted core questions from the European Community Respiratory Health Survey 2 (ECHRS) screening questionnaire. This questionnaire consisted of seven questions about asthma and allergy history. This questionnaire was previously analyzed in an Iranian population (Fazlollahi et al. 2018).

Ethical approval

The basic principles of the Helsinki Declaration (the ethics of medical research on humans) and the Ethics Committee of Iran University of Medical Sciences were observed throughout the study (IR.IUMS.FMD.REC.1397.117). Written informed consent was obtained from all participants prior to the study.

Measurements

Ten-milliliter peripheral blood samples in the absence of anticoagulant agents were collected from the study groups according to the standard sampling principles. After serum isolation, the sera were frozen at −70°C in standard conditions until the tests were performed. Immunoblotting was used to study the serum specific IgE immunoreactivity to common Iranian inhalation and food allergens (Euroimmune, Lübeck, Germany) of the case and control groups. The list of allergens used in each panel is shown in Tables 2 and 3. The tests were performed according to manufacturer's instructions. Briefly, the serum samples were added separately onto each inhalation and food allergen-coated strips. Then, the strips were incubated on a horizontal shaker at room temperature. After washing, horseradish peroxidase (HRP)-conjugated anti-human IgE was poured separately onto each strip. Following incubation and washing, 3′-diaminobenzidine (DAB) substrate was added onto each strip. Quantification of each specific IgE was done using a scanner and special software. Finally, the test results were scored from 0 (negative) to 6 (highest reactivity). Sandwich ELISA was used for assessing total IgE levels in the study groups (Padtan Elm, Tehran, Iran). The normal value of the serum total IgE in adults for this kit was below 182 IU/ml.

Statistical analysis

Statistical analysis of the continuous variables with normal distribution was expressed as mean ± standard deviation (SD), and categorical variables were defined as proportions or ratios. Baseline characteristics of study participants were compared using independent t, Mann–Whitney U, Fisher's exact or Chi-squared tests where appropriate. All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., NY). A P-value <0.05 was considered statistically significant. In the case of controlling confounders, multinominal logistic regression was performed, which is described accordingly.

Results

Baseline demographic and clinical characteristics of both groups

Eighty participants with a mean age of 34.95 years were included in this case-control study. 52.5% were female. Mean age of onset of MD and duration of MD were 41.57 ± 7.39 and 3.2 ± 1.2 in case group, respectively. All of MD cases had unilateral involvement. There was no significant difference between age, sex, place of residence, history of migraine disease and autoimmune disease or drug-induced autoimmunity, and socioeconomic status between both groups. A ECHRS 2 Screening Questionnaire was used to investigate the allergy and asthma history of the groups. Neither the case group nor the control group patients scored more than one in any question. However, the result of zero and one scores are presented in Table 1. There was no statistically significant difference between the groups except for the history of hay fever in the past 12 months (P = .01). Also, there are no statistically significant differences between the two groups in the history of allergy and MD in their families. The history of sneezing, runny nose, and blocked nose was more frequent in patients with MD (P = .03, 0.01, and 0.03, respectively).

Comparative effects of common indigenous Iranian inhalation allergens in both groups

The frequency distribution of susceptible individuals and the results of the Mann–Whitney U test for common indigenous inhalation allergens in Iran were investigated in the patient and control groups. The mean sensibility grades of sweet vernal grass, cultivated rye, mugwort, goosefoot, Russian thistle, rough pigweed, tree mix 4, and honey bee venom respiratory allergens were significantly higher in the case group (P = .007–0.050). There was no significant difference between the case and control groups for other inhalation allergens (Table 2).

Table 1. Baseline demographic and clinical characteristics. ECRHS II questions are presented as the number of patients with a positive response.

Variables	Patient group (n = 39)	Control group (n = 41)	P value
Age [a]	37 ± 7.77	33 ± 6.39	0.06
Sex (female/male) [b]	18/21	24/17	0.37
Family history of Allergy	5(12.8%)	1(2.4%)	0.07
Family history of Meniere's Disease	(2.6%)	0 (0%)	0.49
History of Migraine disease	3 (7.7%)	1 (2.4%)	0.48
History of autoimmune disease or drug-induced autoimmunity	1 (0%)	0 (0%)	0.49
Question 1 [b]	2 (5.1%)	1 (2.4%)	0.48
Question 1.1 [b]	1 (2.6%)	0 (0%)	0.49
Question 1.2 [b]	1 (2.6%)	0 (0%)	0.49
Question 2 [b]	2 (5.1%)	1 (2.4%)	0.48
Question 3 [b]	3 (7.7%)	1 (2.4%)	0.29
Question 4 [b]	5 (12.8%)	2 (4.9%)	0.20
Question 5 [b]	5 (12.8%)	4 (9.8%)	0.47
Question 6 [b]	2 (5.1%)	1 (2.4%)	0.48
Question 7 [b]	14 (35.9%)	4 (9.8%)	0.01

a: According to the Mann-Whitney U test
b: According to Fisher's exact test

Table 2. The frequency distribution of susceptible individuals and the mean of common Iranian indigenous inhalation allergens in both groups.

	Patient group (n = 39)		Control group (n = 41)		
Inhalation allergen	Mean± SD	N (%)	Mean± SD	N (%)	P value [a]
Cat	0.28 ± 0.93	4 (10)	0.10 ± 0.50	2 (5)	0.354
Sweet Vernal Grass	0.78 ± 1.40	12 (30)	0.15 ± 0.58	3 (7.5)	0.007
Orchard Grass	0.73 ± 1.47	9 (22.5)	0.25 ± 0.74	5 (12.5)	0.146
Cultivated Rye	0.55 ± 1.08	10 (25)	0.15 ± 0.48	4 (10)	0.050
Cultivated Oat	0.80 ± 1.47	11 (27.5)	0.25 ± 0.74	5 (12.5)	0.054
Meadow Foxtail	0.88 ± 1.50	12 (30)	0.33 ± 0.92	6 (15)	0.064
Mugwort	0.30 ± 0.88	7 (17.5)	0.03 ± 0.16	1 (2.5)	0.021
English Plantain	0.25 ± 0.54	8 (20)	0.08 ± 0.23	3 (7.5)	0.080
Goosefoot	0.65 ± 1.02	14 (35)	0.23 ± 0.62	6 (15)	0.022
Russian Thistle	1.38 ± 1.79	18 (45)	0.63 ± 1.13	8 (20)	0.007
Rough Pigweed	1.40 ± 1.90	18 (45)	0.63 ± 1.13	9 (22.5)	0.020
Fire bush	0.33 ± 0.73	8 (20)	0.13 ± 0.52	3 (7.5)	0.088
Rose	0.35 ± 0.80	8 (20)	0.13 ± 0.46	3 (7.5)	0.090
Box Elder	0.33 ± 0.65	9 (22.5)	0.13 ± 0.46	3 (7.5)	0.056
White Ash	0.63 ± 1.03	14 (35)	0.35 ± 0.95	7 (17.5)	0.065
White Pine	0.18 ± 0.55	5 (12.5)	0.10 ± 0.38	3 (7.5)	0.934
Mulberry Tree	0.20 ± 0.69	4 (10)	0.03 ± 0.16	1 (2.5)	0.145
Tree Mix4	0.60 ± 1.15	13 (32.5)	0.23 ± 0.62	6 (15)	0.048
Tree_Mix6	0.37 ± 0.87	9 (22.5)	0.20 ± 0.56	6 (15)	0.307
Honey Bee Venom	0.25 ± 0.74	6 (15)	0.03 ± 0.16	1 (2.5)	0.040
Cockroach German	0.28 ± 0.71	7 (17.5)	0.40 ± 0.13	4 (10)	0.281
House Dust	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Dermatophgoides Pter	-	0 (0)	0.03 ± 0.16	1 (2.5)	0.329
Dermatophgoides Farinae	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Penicillium Notatum	0.03 ± 0.16	1 (2.5)	0.03 ± 0.16	1 (2.5)	0.972
Caldosporium Herbarum	-	0 (0)	0.03 ± 0.16	1 (2.5)	0.329
Aspergillus Fumigatus	-	0 (0)	-	0 (0)	1.000
Alternaria Alternata	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.972

a: According to Mann-Whitney U test

Comparative effects of common indigenous Iranian food allergens in both groups

Table 3 shows the distribution of serum reactivity to common food allergens of the study groups. Among the studied allergens, rye flour, hazelnut, pepper, citrus mix 2, potato, strawberry, and celery immunoreactivity were significantly higher in cases compared to the controls, based on quantitative studies. (P = .037, 0.019, 0.005, 0.019, 0.037, 0.037, and 0.037, respectively). As there were too many patients, insensitive for some of the allergens, a qualitative study was also performed. For that purpose, the reactivity score of zero was considered as "not sensitive," and any score higher than zero was considered "sensitive." The same results were obtained from this qualitative study, as demonstrated in Table 3, which were not different statistically significant, except for rye flour, hazelnut, strawberry, citrus mix 2, potato, pepper, and celery reactivity (P = .019, 0.037, 0.019, 0.037, 0.005, and 0.037, respectively).

Comparative effects of total IgE levels and the mean of inhalation and food allergen scores in both groups

The mean total IgE level was 193.85 ± 175.43 in MD group and 117.61 ± 138.05 IU/ml in the control group (P = .016). However, there was no significant relationship between

Table 3. The frequency distribution of susceptible individuals and the mean of common food allergens in both groups.

	Patient group (n = 39)		Control group (n = 41)		
Inhalation allergen	Mean± SD	N (%)	Mean± SD	N (%)	P-value [a]
Egg white	-	0 (0)	-	0 (0)	1.000
Egg yolk	-	0 (0)	-	0 (0)	1.000
Cow milk	0.05 ± 0.22	2 (5)	-	0 (0)	0.144
Casein	-	0 (0)	-	0 (0)	1.000
Wheat flour	0.13 ± 0.40	4 (10.3)	0.02 ± 0.15	1 (2.4)	0.148
Rye flour	0.13 ± 0.40	4 (10.3)	-	0 (0)	0.037
Rice	0.10 ± 0.38	3 (7.6)	-	0 (0)	0.072
Grain mix2	0.13 ± 0.40	4 (10.3)	0.10 ± 0.30	4 (9.7)	0.912
Peanut	0.15 ± 0.43	5 (12.8)	0.07 ± 0.26	3 (7.3)	0.400
Soybean	0.08 ± 0.35	2 (5.1)	-	0 (0)	0.145
Hazelnut	0.18 ± 0.50	5 (12.8)	-	0 (0)	0.019
Almund	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Pistachio	-	0 (0)	-	0 (0)	1.000
Walnut	-	0 (0)	-	0 (0)	1.000
Gluten	-	0 (0)	-	0 (0)	1.000
Strawberry	0.13 ± 0.40	4 (10.3)	-	0 (0)	0.037
Apple	0.03 ± 0.16	1 (2.5)	0.02 ± 0.15	1 (2.4)	0.972
Grape	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Kiwi	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Banana	-	0 (0)	-	0 (0)	1.000
Mango	0.05 ± 0.22	2 (5.1)	-	0 (0)	0.144
Peach	0.13 ± 0.38	4 (10.3)	0.02 ± 0.15	1 (2.4)	0.148
Cherry	0.10 ± 0.38	3 (7.6)	0.05 ± 0.21	2 (4.8)	0.590
Melon	0.08 ± 0.27	3 (7.6)	-	0 (0)	0.072
Citrus mix2	0.15 ± 0.43	5 (12.8)	-	0 (0)	0.019
Tomato	0.08 ± 0.27	3 (7.6)	-	0 (0)	0.072
Potato	0.13 ± 0.40	4 (10.3)	-	0 (0)	0.037
Pepper	0.18 ± 0.38	7 (17.9)	-	0 (0)	0.005
Garlic	0.28 ± 0.72	6 (15.3)	0.05 ± 0.21	2 (4.8)	0.104
Celery	0.18 ± 0.55	4 (10.3)	-	0 (0)	0.037
Eggplant	0.08 ± 0.27	3 (7.6)	-	0 (0)	0.072
Chicken	0.21 ± 0.80	3 (7.6)	0.02 ± 0.15	1 (2.5)	0.273
Meat mix5	0.05 ± 0.22	2 (5.1)	-	0 (0)	0.144
Shrimo prawn	0.03 ± 0.16	1 (2.5)	-	0 (0)	0.305
Sea food mix3	0.38 ± 0.87	8 (20.5)	0.63 ± 1.29	11 (2.6)	0.458

a: According to the Mann-Whitney U test

IgE level and food or inhalation allergens in patients as compared to the controls (247.53 ± 204.88 vs. 135.11 ± 144.45 IU/ml, p-value = 0.092 for food allergens, and 165.92 ± 180.31 vs. 150.28 ± 154.03 IU/ml, p-value = 0.706 for inhalation allergens). To control the correlation between allergen sensitivity and MD, gradings were merged so that multinominal regression modeling would be possible. Grade 0 was considered "not sensitive," and all others were considered "sensitive." Multinominal regression was performed to investigate the effects of covariates on the result. Neither the total IgE level (Chi-Squared = 1.2, $P = .24$) nor its qualitative positiveness (Chi-Squared = 0.02, $P = .89$) were statistically significant in the analysis for inhalation allergen study. Also, the IgE serum level was not a statistically significant cofactor in food allergen study (Chi-squared = 2.19, $P = .139$). As patients had heterogeneous responses to the ECHRS 2 questionnaire, the results could not be controlled for its questions and the questionnaire responses were just compared, as discussed above.

Discussion

Our finding showed that there was a higher serum IgE level in patients with MD, as well as the existence of a relation between MD and serum immunoreactivity to inhalation and food allergens. It seems that symptoms of MD, such as vertigo, hearing loss, and tinnitus, are related to the sudden entrance of extra fluid to endolymphatic sac resulting in potassium intoxication of the auditory and vestibular nerves. According to the various studies, different causes including endolymph production or reabsorption, allergy, abnormal ion hemostasis, viral infections, and production of circulating immune complexes (CICs) are among the pathophysiologies of MD (Banks et al. 2012; Cass and Ambrose 2019; Couloigner et al. 2004; Derebery and Berliner 2010; Guo et al. 2018; Lopez-Escamez et al. 2018). Based on previous studies, three things are the main causes of the role of allergy in the accumulation of fluid in the endolymphatic sac. The first possible cause of MD is abnormalities in the endolymphatic sac by a viral antigen/allergic interaction that stimulates excess fluid production in the endolymphatic sac, as reported in Shambaugh and Wiet's study (Shambaugh and Wiet 1980). A second cause could be the production of circulating immune complexes such as IgM and IgG that brings on inflammatory responses by deposition in the blood vessels of the endolymphatic leading to the release of chemotactic factors that make the migration of macrophages into the region and result in the release of tissue-damaging enzymes; an increased amount of CICs in patients with MD has been shown in previous studies (Hahn et al. 2019). The last potential cause is systemic inhalants produce some vasodilators, such as histamine, serotonin, or bradykinin, by mast cell activation, and this could vasodilate blood vessels of the interosseous sac and increase fluid in the endolymphatic sac leading to symptoms of MD. One study showed that meclizine, an antihistamine, could treat episodes of vertigo in MD by blocking the vasodilating effects of histamine, leading to decrease fluid in the endolymphatic sac (Moller et al. 2016). In another study, Møller et al. investigated the histamine H1 receptor that is expressed in the human endolymphatic sac's epithelial lining and the histamine H3 receptor that is expressed in the sub-epithelial capillary network. That investigation found the usage of betahistine in inner ear disease and in the treatment of vertiginous episodes of MD, through the potential molecular mechanisms involved in histamine receptor intervention (Moller et al. 2016; Rosenbaum and Winter 2017). In another study in line with our findings, Derebery et al. showed that a classic IgE mediated type I hypersensitivity reaction by inhalant reactions plays a role in the production of endolymphatic hydrops (Derebery 2000). However, the association of different genes on the occurrence and the progression of the disease is being reported recently. Among them, an HLA-related gene (MICA-STR) and the ACE (I/D) polymorphism have reported to have strong associations with the hearing loss progression in MD patients (Gazquez et al. 2012; Mohseni et al. 2020).

Over the years, various studies have been conducted to investigate the effects of various types of inhalation allergens, as well as the treatment of MD based on anti-allergic treatments (Lezius et al. 2011). Animal studies suggest that a systemic immune challenge can yield to allergic reactions in the inner-ear, too (Weinreich and Agrawal 2014). In addition, Derebery et al., in a similar study, showed that 59.2% of patients with MD had allergies to inhalation allergens as compared to 42.7% for the control group, and 37.1% of patients with MD had a positive blood or skin tests. Besides, 31.2% of these people reported a history of allergies. Their results were similar to our finding that showed patients with MD had

allergies to inhalation allergens (Derebery 2000). The results of another study conducted by Derebery et al. in California showed that 41.6% of patients with MD had allergies to inhalation allergens. Also, they showed that 40.3% of patients with MD had an allergy to food allergens with the highest rate of the positive test for wheat, soy, milk, corn, egg and yeast. Moreover, they showed an increase in the level of circulating immune complexes, such as IgM and IgG, that indicated an immunologic response leading to form symptoms of MD (Derebery et al. 1991). The findings of that study were consistent with the present study. In another study, Keles et al. examined allergens and cytokines in patients with MD. In that study, they showed that the higher overall level of IgE and its specific level of immunoglobulin were investigated for allergens such as fruit, egg-white, cow's milk, corn flour, beef, and rice and 67.3% of MD's patients had a history of allergy (Keles et al. 2004). Besides the inhalatory and food allergens, a study on 58 adults with MD has shown that 82.7% of these patients respond positive to gliadin skin prick test. This number was zero for the rest of the healthy subjects in this study (Di Berardino and Cesarani 2012).

In a study by Savastano et al. that was carried out on 200 Italian patients with MD, non-specific serologic tests were compared with those of 50 subjects in a control group. The results of that study showed that patients with severe MD disability resulted in significantly increased values of CIC, C3, CD4/CD8 ratios, and early T-activation. That study showed that auto-antibodies tested positive in the same way in three sub-groups of patients with MD considering the phase of the disease, according to Pearson and Brackmann classification (PBc), and concluded that immunological factors play an important role in the pathogenesis of MD. Although the factors studied in that study were different from our present study, the results obtained from that study also suggested the potential significance of allergy and immunology in MD (Savastano et al. 2007).

This study evaluates the association of serum immunoreactivity to common inhalation and food allergens. In spite of the findings of this paper, the causality cannot be determined, and more variables should be assessed to find out the indications of allergy tests in MD patients. It is recommended that further prospective studies be conducted in MD patients considering their symptoms in one side or both side with a larger sample size focusing on specific IgE for each antigen, assessing prick test, and other immune-related antibodies involved in the pathogenesis of the disease, such as IgG, IgA, interleukins, and CD4. Studies with more accurately controlled cases for allergic diseases and migraine disease can also clarify any potential confounder for these findings.

Conclusion

We found that the serum IgE level in patients with MD was significantly higher than the control group and that there was a relationship between MD and serum immunoreactivity to common inhalation and food allergens. However, larger sample sizes are needed in the future studies, due to the high variances in the total IgE level of the patients. We concluded that inhalant and food allergens might play a role in MD. Maybe serum immune-reactivity in MD patients is a trigger for immune response in endolymph before the commencement of other clinical manifestations of allergy.

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Declaration of interest

The authors declare that they have no competing interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability

All data generated or analyzed during this study are included in this submitted article.

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