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Ménière's disease and allergy: allergens and cytokines

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Abstract

The aim of this article is to evaluate the role of allergy in the pathogenesis of Ménière's disease by means of cytokine profiles, allergic parameters and lymphocyte subgroups. A total of 46 patients aged between 26–68 years diagnosed with Ménière's disease between 1993–2002 were recruited to this study. The control group consisted of 46 healthy volunteers who were from the same age group, living in the same region and possessing similar socioeconomic indicators. Lymphocyte subgroups were measured from the peripheral blood by employing Becton Dickinson (BD) monoclonal CD4, CD8, CD23 antibodies. IFN-γ, IL4, total IgE levels, and specific IgE levels pertaining to tree, fungus, fruit, egg-white, cow's milk, wheat flour, corn flour, beef, and rice allergens, in all seasons, were measured and compared in the patient and control groups.

In patient serum samples there were positive correlations between CD23 and IgE, CD8 and IgE, CD4/CD8 and IgE, and CD23 and CD8 ($p<0.01$). There were negative correlations between IL-4 and IFN-γ, IFN-γ and IgE, and a positive correlation between IL-4 and IgE. Total IgE levels were above the normal values in 19/46 (41.3 per cent) of the patient group, but the ratio was nine out of 46 (19.5 per cent) in the control group. A history of allergy was found in 31/46 (67.3 per cent) when the patients were questioned. The ratio of a history of allergy was 16/46 (34.7 per cent) in the control group. When specific IgE levels were evaluated the ratio of patients with all the panels negative was eight out of 46 (17.9 per cent), but it was 31/46 (67.3 per cent) in the control group.

This study found that the prevalence of allergy was higher in patients with Ménière's disease than in the control group. Thus the authors suggest that allergy should be taken into account when patients with this disease are treated.

Key words: Ménière's disease; Hypersensitivity; Cytokines; Lymphocyte subsets

Introduction

The underlying pathophysiological state in Ménière's disease is endolymphatic hydrops, which can be demonstrated, with certainty, by histopathological study of the temporal bones only after death. For clinical purposes, the presence of endolymphatic hydrops can be inferred during life by the presence of the following signs and symptoms: recurrent spontaneous vertigo, fluctuating hearing loss, aural fullness or pressure, and tinnitus.[1]

Since Prosper Ménière first described the symptom complex that bears his name, its aetiology has been ascribed to many possible causes: abnormalities in endolymph production or absorption; abnormal ion homeostasis; allergy, autoimmunity or inflammation or viral infection.[2–7]

Reference to the role of allergy in the development of Ménière's disease was made as early as 1923 by Duke.[8] However, allergy and immunology were then poorly understood. By the early 1970s, a number of reports in the otolaryngology literature documented an improvement in vertigo, tinnitus, and hearing after desensitization to inhalant allergens and an elimination diet for food allergies. Although it was acknowledged that these reported patients showed clinical improvement, the suggestion that this was due to immunomodulation was viewed with some scepticism because the inner ear was thought to be immunoprivileged.[9,10]

Given that the endolymphatic sac is immunologically active, proponents of the allergy theory speculate that a sudden influx of fluid into the endolymphatic sac secondary to an antigen produces the rupture of Reissner's membrane. As a result, influx of potassium and subsequent toxicity to the cochlear and vestibular nerves causes the symptoms. The cessation of absorption of endolymph in the sac or increased production of endolymph in the sac is thought to be a response of the endolymphatic sac to antigens.[11]

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A study made with rats in 1986 demonstrated that T helper (Th) cells could be allocated to two subsets, Th1 (type 1) and Th2 (type), according to their cytokine production.[12] The mechanisms by which CD4+ Th cells are responsible for both humoral and cell-mediated immunity remained unclear until evidence had been provided that repeated stimulation of murine CD4+ Th cells, with given antigens, resulted in the outgrowth of cells with polarized patterns of cytokine section (type 1 or Th1 and type 2 or Th2). Th1 cells activate cellular immunity by producing IL-2, IFN-γ and TNF-β. Therefore, they ensure defence against viral, bacterial, fungal and protozoal infections. The Th2 cells that stimulate humoral immunity produce IL-4, IL-5, IL-10 and IL-13. They also have roles in some helminthic infections with IgE and IgG responses.[13] It is not known clearly which factors initiate cell development as Th1 and Th2. But it was found that IL-12 and IL-4 are the two important cytokines that polarize the development of Th1 and Th2 cells inversely.[14] The natural immune responses at the beginning of an infection probably regulate the deviations in the predominance of Th1 and Th2 cells.

Th cells may be subdivided according to the lymphokine types they produce: Th0, Th1 and Th2. Th1 clones produce IFN-γ and IL-2, but not IL-4 or IL-5. However, Th2 cells produce IL-4, IL-5 and IL-13, but they do not produce IFN-γ and IL-2 cytokines. Th0 clone has the cytokine profile of both cells. Lymphokines secreted from Th1 cells activate the cellular immune system by stimulating the production of macrophages and causing B cells to produce IgM and IgG2.[14] IFN-γ and IL-12 cytokines change the Th polarization to Th1 while IL-4 changes it to Th2.

The divergent effects of Th1 and Th2 cells are also seen in their association with deleterious immune reactions in humans. In particular, autoimmune disorders associated with the destruction of host tissues, such as diabetes mellitus, multiple sclerosis, or inflammatory bowel disease, predominantly involve Th1 responses. By contrast, allergic disorders (e.g. seasonal rhinitis, asthma, and contact dermatitis) in which IgE, mast cells, and eosinophils play a prominent role are dominated by Th2 cells.

In this study, cytokine profiles in the serum samples of the patients diagnosed with Ménière's disease were evaluated to demonstrate the Th polarization. By comparing the allergic parameters and lymphocyte subgroups, the role of allergy in the pathogenesis of Ménière's disease was investigated.

Materials and Method

Forty-six patients aged between 26–68 years (average age 43.9 ± 11.54) diagnosed as having Ménière's disease, at the ENT Department of Firat University School of Medicine between 1993 and 2002, were recruited to this study. Adult patients meeting the American Academy of Otolaryngology Head and Neck Surgery criteria for the diagnosis of Ménière's disease were eligible for inclusion to this study. Patients with a history of thermal burns, diabetes mellitus, Alzheimer's disease, cancer, or recent influenza, fever, or ulcerative colitis were excluded. The control group consisted of 46 healthy volunteers who were from the same age group, living in the same region and possessing similar socioeconomic indicators to the patient group. The patient and the control groups were questioned for a history of allergies.

More than 10 ml of venous blood was drawn from all the patients and the controls and the samples were transferred to the Immunology Department's laboratories within half an hour. The blood samples were collected when the patients were not in an acute episode of Ménière's disease. Lymphocyte subgroups were measured from the peripheral blood by employing Becton Dickinson (BD) monoclonal CD4, CD8, CD23 antibodies and the BD FACScan flow cytometry method. Total IgE levels were measured in the serum by the ELISA technique (IgE; Int. Alfa Wassermann Diagnostic, Netherlands) and specific IgE levels were evaluated by ELISA technique (ELx 800, Bio-tek Instruments, USA) as recommended by the manufacturers (Clinotech Diagnostics and Pharmaceuticals, Netherlands). IFN-γ, IL-4, total IgE levels and specific IgE levels pertaining to all seasons, tree, fungus, fruit, egg-white, cow's milk, wheat flour, corn flour, beef and rice allergens were measured and compared for the patient and the control groups. Specific IgE levels between 0–3.5 IU/ml were negative, levels between 3.5–17.5 IU/ml were (+), levels between 17.5–50.00 IU/ml were (++), and levels above 55.0 IU/ml were (+++). Serum IFN-γ and IL-4 levels were evaluated using the ELISA technique (ELISA, BioSource, California, USA). The results were expressed as pg/ml.

Statistical analyses were performed using the SPSS 10.1© statistics programme. Pearson correlation, Student's *t*- and Mann-Whitney U tests, were used to determine differences between the groups. As a threshold, $p<0.05$ was accepted as statistically significant.

Results

Age, gender, allergic symptoms of the patient and the control groups and the demographic data pertaining to the affected ear are summarized in Tables I and II.

Table III demonstrates the lymphocyte subgroups CD4, CD8, CD4/CD8, CD23 and IFN-*y*, IL-4 levels in the peripheral blood samples of the patient and control groups.

The differences between the CD4, CD4/CD8, CD23, IFN-γ and IL4 levels of patient and the control groups were statistically significant ($p<0.05$).

In patient serum samples there were positive correlations between CD23 and IgE, CD8 and IgE, CD4/CD8 and IgE and CD23 and CD8 ($p<0.01$). There were negative correlations between IL-4 and IFN-γ, IFN-γ and IgE but a positive correlation between IL-4 and IgE. However, these correlations were not statistically significant. Total IgE levels of the patient group were above normal levels (0–150

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TABLE I

SGE AND GENDER OF THE PATIENT AND CONTROL GROUPS AND THE DEMOGRAPHICAL DATA OF THE AFFECTED EAR

Variables	Patient group (n = 46)	Control group (n = 46)
Age	43.9 ± 11.54	41.0 ± 10.46
Gender		
Male	21/46	23/46
Female	25/46	19/46
Affected		
Right	16/46	–
Left	28/46	–
Bilateral	2/46	–

TABLE III

THE RATIOS OF CD4, CD8, CD4/CD8, CD23 ANTIBODIES AND LEVELS OF IFN-γ AND IL-4 IN THE PERIPHERAL BLOOD SAMPLES OF THE PATIENT AND CONTROL GROUPS

	Patient group (n = 46)	Control group (n = 46)	*p* Value*
CD4	44.22 ± 8.86	39.49 ± 4.85	$p<0.05$
CD8	30.84 ± 7.20	32.92 ± 4.48	$p>0.05$
CD4/CD8	1.65 ± 0.71	1.22 ± 0.24	$p<0.05$
CD23	10.09 ± 3.96	6.82 ± 1.88	$p<0.05$
IFN-γ	8.34 ± 10.54	8.59 ± 1.92	$p>0.05$
IL4	6.35 ± 6.20	2.67 ± 0.65	$p<0.05$
IgE	267.10 ± 394.69	97.78 ± 87.34	$p<0.05$

* Student's *t* test

IU/ml) in 19/46 (41.3 per cent) of patients, but only nine out of 46 (19.5 per cent) in the control group. After questioning, a history of allergy was found in 31/46 (67.3 per cent) patients, and 16/46 (34.7 per cent) in the control group. When specific IgE levels were measured (all seasons, tree, fungus, fruit, egg white, cow's milk, wheat flour, corn flour, beef and rice), the number of patients having all the panels negative was eight out of 46 (17.9 per cent), but 31/46 (67.3 per cent) in the control group. Specific IgE levels of the patient and control groups are given in Table IV.

Discussion

Endolymphatic hydrops is the accumulation of the endolymph which fills the membranous labyrinth and the narrowing of the perilymphatic space through the enlargement of the endolymphatic space. It is suspected that the effect of immune, viral, allergic and metabolic causes can alter the balance between the cochlea that produces the endolymph and the sac that absorbs it.[16] In experiments carried out on animals, it is sufficient to have the obstruction of the endolymphatic duct for the development of endolymphatic hydrops. This can be achieved by mechanical obstruction.[17] Chemical fibrosis of the endolymphatic duct, viral infections of the endolymphatic sac and inflammations of immunological and allergic origin have all been reported to narrow the duct.[18]

Ménière's disease patients show seasonal or food-related increases in their symptoms. The treatment of allergy results in reductions in vertigo and Ménière's disease-related symptoms. In patients with vertigo, tinnitus, fullness of the ear, Ménière's disease and eustachian dysfunction, the relationship between the radio allegro sorbent test (RAST) and inhalant allergies has been investigated and IgE-mediated hypersensitivity has been found in 40 per cent of the individuals.[19] Derebery and Berliner[11] showed allergy in 37.1 per cent of the blood or skin tests of Ménière's disease patients and a history of allergy in 31.2 per cent of these patients. The same authors[19] questioned Ménière's disease patients and found inhalant allergy in 41.6 per cent and food allergy in 40.3 per cent. In the present study, total IgE was above normal levels in 41.3 per cent of the serum samples. After questioning a positive allergic history was found in 67.3 per cent of our patients. Following the elimination of allergy-inducing food sources from the diet for 72 hours, Derebery[10] performed a food allergy test on Ménière's disease patients and reported a 68.2 per cent wheat, 64.2 per cent soy, and more than 50 per cent milk, corn and egg allergy. In the same study, inhalant allergy was mostly to grass, weed and trees. In our study of Ménière's disease patients we have identified 82.6 per cent cow's milk, 69.5 per cent all seasons, 69.5 per cent beef, 65.2 per cent fungi, 56.5 per cent rice, 52.1 per cent egg white, 47.8 per cent wheat flour, 43.4 per cent fruit juice and 43.4 per cent corn flour allergy. In their Ménière's disease patients, Derebery and Berliner[11] identified

TABLE II

ALLERGIC SYMPTOMS OF THE PATIENT AND CONTROL GROUPS

Allergic history	Patient group n = 46	%	Control group n = 46	%
Nasal or sinus congestion	29	63.0	14	30.4
Itching	28	60.8	15	32.6
Nasal drainage	9	63.0	12	26.0
Sneezing	21	45.6	13	28.2
Smelling disorders	11	23.9	4	8.6
Eczema or allergic skin rushes	21	45.6	8	17.3
Frequent upper airway infections	30	65.2	16	34.7
Diarrhoea	9	19.5	4	8.6
Constipation	5	10.8	–	
Extreme fatigue	21	45.6	12	26.0
Food allergies	26	56.5	13	28.2
Drug allergies	21	45.6	9	19.5
Dust allergies	26	56.5	9	19.5

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TABLE IV

SPECIFIC IgE LEVELS OF THE PATIENT AND CONTROL GROUPS

Panels	Patient group (n = 46)				Control group (n = 46)			
Specific IgE levels*	n% (-)	n% (+)	n% (++)	n% (+++)	n% (-)	n% (+)	n% (++)	n% (+++)
All seasons	14(30.4)	6(13.0)	24(52.1)	2(4.3)	38(82.6)	4(8.6)	4(8.6)	–
Fungus	16(34.7)	8(17.3)	16(34.7)	6(13.0)	37(80.4)	5(10.8)	4(8.6)	–
Fruit	26(56.5)	14(30.4)	4(8.6)	2(4.3)	38(82.6)	4(8.6)	4(8.6)	–
Egg white	22(47.8)	20(43.4)	4(8.6)	–	35(76.0)	6(13.0)	5(10.8)	–
Cow's milk	8(17.3)	4(8.6)	22(47.8)	12(26.0)	35(76.0)	7(15.2)	4(8.6)	–
Wheat flour	24(52.1)	12(26.0)	8(17.3)	2(4.3)	39(84.7)	4(8.6)	3(6.5)	–
Corn flour	26(56.5)	12(26.0)	8(17.3)	–	38(82.6)	6(13.0)	2(4.3)	–
Beef	14(30.4)	24(52.1)	6(13.0)	2(4.3)	34(73.9)	8(17.3)	4(8.6)	–
Rice	20(43.4)	8(17.3)	14(30.4)	4(8.6)	40(86.9)	5(10.8)	1(2.1)	–

*Specific IgE levels between 0 –3.5 IU/ml were negative; levels between 3.5 –17.5 IU/ml were (+); levels between 17.5 –50.0 IU/ml were (++); and levels above 55.0 IU/ml were (+++).

wheat, milk, egg and soy allergies to be the most frequent through food provocation. In our study, cow's milk allergy was the most common one followed by all seasons, beef and fungi.

The pathophysiological link between allergy and Ménière's or middle-ear diseases has not yet been clarified. For the role of allergy in Ménière's disease, the endolymphatic sac is thought to be the target and the accumulation of the immune complexes circulating in the blood might hinder the filtering ability of the sac.[10,11] Recent studies showed respiratory viral infections in early childhood to be of potential importance for the enhanced allergic sensitization. Data from animal models provide support for the concept that enhanced allergic sensitization caused by increased uptake of allergen during infection may play a critical role, as well as T-cell-mediated immune responses to viral infection.[20]

CD23 is a type II integral membrane glycoprotein of 45 kDa. It comes from the C-type lectin superfamily. It is a low affinity receptor for IgE found in active B cells, follicular dentritic cells, monocytes and eosinophils. When B lymphocytes are cultured with IL-4 the expression of CD23 increases. The soluble CD23 molecule serves as an autocrine growth factor for B cells and is required for IgE isotype differentiation.[21] CD4 has a monomeric structure of 55–59 kDa. It functions as a helper molecule in signal transduction and the binding of the T cells to the MHC molecule found in antigen-presenting cells. The CD8 molecule is either a homodimer composed of alpha chains or a heterodimer of CD8 alpha and beta chains. The CD8 molecule enables both easy signal transduction and provides the binding to MHC class I molecules. The immune system tries to stabilize the size of the T-cell population against increases or decreases of CD4 and CD8 by maintaining a balance.[22] In the present study, the CD4/CD8 ratio of the patient group was higher than that of the control group. In the serum samples of the patients, there were positive correlations between CD4/CD8 and Ig E, CD23 and IgE, CD8 and IgE and CD8 and CD23 ($p<0.01$). It is well known that the frequent respiratory infections of viral origin encountered in early childhood result in an increased tendency for allergic sensitization. The changes in CD4/CD8 ratios of Ménière's disease patients when compared to controls can be related to frequent viral respiratory infections. This might create a predisposing factor for the development of allergy in such patients. The positive correlation between CD4/CD8 and IgE seems to support this suggestion.

The diagnostic tests used in routine laboratory practice for allergic diseases, can only identify the basic parameters of allergy in the organism through *in vitro* immunoglobulin measurements, *in vivo* skin tests and provocation tests. However, the interactions of the immune system that result in such alterations are not taken into account enough. The fact that allergic diseases are more common in developed countries with higher socio-economical levels resulted in an increased attention to T cells. The studies that have been conducted showed that T cells can be differentiated into two groups Th1 and Th2 and that the balance between these two different cell groups was definitive for the cellular and humoral immune response. This phenomenon, which is called Th polarization, has been helpful in clarifying the aetiopathogenesis of several diseases and the fact that this polarization could be guided through therapy brought about new treatment protocols. In order to identify which of the Th1 and Th2 cells dominate it is possible to make *in vivo* measurements of the related cytokines they produce. In the diagnosis and treatment of allergic diseases, in addition to the presence of a history of allergy, clinical signs and the identification of basic elements of allergy, the measurement of Th polarization will be an important part of future studies.

In Th polarization, Th2 cells stimulate allergy by increasing the synthesis of IL-4, IL5, IL-6, IL-13 and IgE, while Th1 cells play an inhibitory role through the synthesis of IFN-γ and IL-2. In this study, the levels of IL-4, IgE and CD23 were significantly higher in the serum samples of the patient groups than the control group ($p<0.05$). In the patients' serum samples there were negative correlations between IL-4 and IFN-γ, IFN-γ and IgE, and a positive correlation between IL-4 and IgE. However, these correlations were not found to be statistically significant.

In atopic patients, the T cells specific for allergens generally belong to the Th2 subgroup and they

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produce IL-4 and IL-3 that stimulate IgE production by B cells and have roles in IgE-controlled allergic diseases.[23] Many studies have shown that therapy could be effected by regulating these cytokines through triggering cytokine levels or cytokine antagonists. IFN-γ therapy was found to be effective in atopic dermatitis, but this treatment does not have established clinical protocols at the moment. In a study, IFN-γ therapy was recommended to patients who had eosinophil ratios of less than nine per cent and serum IgE levels of less than 1500 IU/ml.[24] Jung *et al.*[25] demonstrated that the decreased IFN-γ production in cultures prepared from T cells in atopic patients did not have any intrinsic or genetic basis. It was proven that the return of IL-2 and IFN-γ production to normal could improve the degenerated Th1 response on precursor T cell levels. With the use of recombinant IFN-γ in long-term therapy in patients with atopic dermatitis, an important decrease was observed in the parameters demonstrating clinical severity.[26] Terfenadine acting as a H1 blocker, was demonstrated to inhibit specifically the production of Th2 type cytokines (IL-4, IL-5) in human peripheral T cells. But it did not inhibit the Th1 cytokines such as IL-2 and IFN-γ.[27] Testa *et al.*[28] determined a clear-cut clinical improvement in patients with allergic rhinitis with the use of H2 blockers. They suggested that H2 blockers increased IFN-γ levels, but decreased IL-4 and total IgE levels. Further studies to be conducted will help in planning new treatment protocols by giving priority to the molecular basis of allergic diseases.

- **It is known that functional obstruction of endolymphatic flow or failure of absorption appears to occur in Meniere's disease and that genetic anomalies, viral infections, allergen stimulation and autoimmunity may have a role in the pathogenesis of this disease**
- **In respect of allergy there is an extensive literature, especially in respect of food allergy, in the possible management of patients with Ménière's disease**
- **The study examined a variety of cytokine profiles, allergic parameters and lymphocyte subgroups in 46 patients recruited over a nine-year period. The study was controlled with a similar age and sex matched group of healthy volunteers**
- **The results of this study show that the prevalence of allergy in patients with Ménière's disease when compared to a control group and such findings may have therapeutic significance**
- **It is still not clear from this paper whether allergy is implicit in the pathogenesis of this disease or whether markers of allergic disease are surrogate end-points in a disease with a complex aetiology**

In conclusion, this study was undertaken to clarify the Th1 and Th2 polarizations in allergy. In the light of such studies, it should be possible to design new treatments for allergies by suppressing the production of IL-4 and IL-1, or by blocking them with antibodies, or by administering IFN-γ and thereby ensuring the predominance of Th1 and decreasing the Th2 populations and the cytokine levels they secrete. The provocation of Th1 cell predominance can be obtained by the application of repetitive doses of BCG vaccine. Thus, a treatment method with the least interference to the intrinsic organization of the organism can be investigated.[29] In this study, the authors tried to underline the role of allergy in the aetiology of Ménière's disease. They suggest that further studies are needed to demonstrate the efficacy of IFN-γ application, H1-H2 blockers and inhibition of IL-4 production, or its blockage with antibodies, in the treatment of this disease.

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