The Journal of Laryngology & Otology
June 2005, Vol. **119,** pp. 455–460

Co-morbidity of migraine and Ménière's disease – is allergy the link?

PURUSHOTHAM SEN, FRCS, CHRISTOS GEORGALAS, MRCS, DLO, MICHAEL PAPESCH, FRACS

Abstract

This study determined the prevalence of migraine and allergy in patients with Ménière's disease (MD) compared with age- and sex-matched controls. We tested the hypothesis that if migraine and MD is linked by allergy, then allergy should be more prevalent in patients with MD and migraine compared with MD patients without migraine.

A web-based questionnaire was used to recruit patients with MD (n = 108) while the control group consisted of patients attending the ENT clinic for other problems (n = 100).

The prevalence of migraine and allergy was significantly higher in patients with MD compared with age- and sex-matched controls ($p \geq 0.005$). In addition, the prevalence of allergy was significantly higher in patients who had both MD and migraine (30/42) than MD alone (26/66, $p = 0.002$). However, there was no link with any specific allergy types.

This study suggests that migraine and MD may be linked by an immunological determinant.

Key words: Ménière's Disease; Allergy; Migraine

Introduction

Ménière's disease (MD) is a clinical diagnosis based on the presence of the classic triad of episodic tinnitus, episodic vertigo and permanent hearing loss. In his original description of the syndrome, Prosper Ménière suggested an association of migraine and MD.1 Since then, many authors have noted paroxysmal headache as an independent symptom that can occur in patients with MD.2–4 Studies investigating the prevalence of migraine in MD have shown conflicting results.5–7 However, a recent well-designed prospective trial based on strict diagnostic criteria has clearly established an increased lifetime prevalence of migraine in MD.8 The association between MD and migraine has led many investigators to suggest that the two diseases may share a common pathway or that they may be part of the same disease process.9–12 In this study, we determined the prevalence of migraine in MD compared with an age- and sex-matched control. We then investigated whether the history of allergy is more common in patients who suffer from both MD and migraine than MD patients with no migraine.

Hypothesis

If migraine and MD have a common immunological link, the history of allergy may be more prevalent in patients who suffer from both MD and migraine than MD without migraine.

Materials and methods

A web-based questionnaire was designed to recruit patients with MD (see Appendix). The questionnaire was posted at many MD support websites. In addition, the organizers of some support groups placed this questionnaire in their regularly subscribed MD magazines. Patients then posted or emailed the completed forms to us. Patients were free to participate by completing the questionnaire. Institutional ethics committee approval was obtained.

As the control group, we interviewed age- and sex-matched patients who attended the ENT clinic on randomly selected days to assess prevalence of migraine and allergy in the non-MD population. Age was matched in blocks of five. Migraine was defined as a self-reported history of migraine. History of allergy included inhaled as well as food allergy.

Analysis

Data were entered into a computer database (Microsoft Access). Statistical analysis was performed with a statistical package (SPSS 9.0). Analysis of variance or t-tests were done where

From the Department of Otolaryngology and Head and Neck Surgery, Whipps Cross University Hospital, London, UK.
Local ethical committee approval (8 March 2001) from Redbridge and Waltham Forest LREC.
Accepted for publication: 13 January 2005.

TABLE I
AGE AND SEX DISTRIBUTION

	Ménière's disease (n = 108)	Control (n = 100)	P VALUE
Age (mean, SD)	(51, 13.95)	(49.7, 13.41)	0.478
Sex (male/female)	30/78	26/74	0.773

appropriate. The criterion for statistical significance was taken as $p \leq 0.05$ in two-tailed comparisons.

Results

A total of 120 patients replied to the website-based MD questionnaire. Twelve of the replies had to be discarded due to unclear data. One hundred non-MD ENT patients were recruited as controls.

Age and sex distribution

Both groups were age-and sex-matched. Age was matched in blocks of five. There was no significant difference between the two groups in respect of gender or age (Table I).

Prevalence of migraine in MD

The prevalence of migraine was significantly higher in the MD group (42/108 or 39 per cent) compared with the age- and sex-matched control group (18/100 or 18 per cent) $p = 0.001$ (Pearson's chi-square test). The odds ratio was 2.89 (95 per cent confidence interval [95 per cent CI] 1.52–5.49) (Figure 1).

Prevalence of allergy in MD

The prevalence of allergy was also higher in the MD group (56/108 or 51.9 per cent) compared with the age- and sex-matched controls (23 per cent) (Figure 2). The odds ratio was 3.60 (95per cent CI 1.98–6.56) $p < 0.001$ chi-square). Food allergy was present in 29/108 (26.9 per cent) MD patients while inhalation allergy was present in 27/108 (25 per cent).

Association between migraine and allergy

On subgroup analysis of the MD group, we found that history of allergy was significantly more prevalent in MD patients with migraine than MD without migraine.

In the MD group, 71 per cent of migraine sufferers gave a positive history of allergy, versus 39 per cent of non-migraine sufferers. Thus in patients with MD, it was almost twice more likely for a migraine sufferer to have a history of allergy than for a non-migraine sufferer (Figures 3 and 4). The odds ratio was 3.84 (95 per cent CI 1.67–8.83). The difference was highly significant ($p = 0.001$).

Interestingly, this link between allergy and migraine disappeared completely in the control group, where the presence of migraine did not predict a positive history of allergy (22.2 per cent of control patients with migraine had allergy and 23.2 per cent of non-migraine control patients had allergy) (odds ratio 0.94, 95 per cent CI 0.27–3.22, $p = 0.93$).

We also compared the co-existence of allergy and migraine in the MD group compared with the combination in the control group. Only four out of 100 in the control group had the combination, versus 30 out of 108 in the MD group – the difference being highly significant ($p < 0.001$, Fisher's exact test). The combination was more than nine times more prevalent in the MD group compared with the control group (odds ratio 9.23, 95 per cent CI 3.11–27.32).

Discussion

In our study we used a web-based questionnaire to recruit patients with MD. Web-based questionnaires form an important tool for research into topics such as MD where recruitment from a single institution is insufficient. Results obtained from web-based questionnaires are comparable with results obtained from standard 'paper and pencil' format surveys.[13] The web-based MD support groups are very well developed and organized and formed an invaluable source for the recruitment of our patients.[14] We have assumed that all patients who seek support or are enrolled with MD support groups suffer from MD.

Our study shows a significantly higher prevalence of migraine in MD compared with non-MD otolaryngology patients (39 per cent *vs* 18 per cent). Our result is similar to a recent institution-based

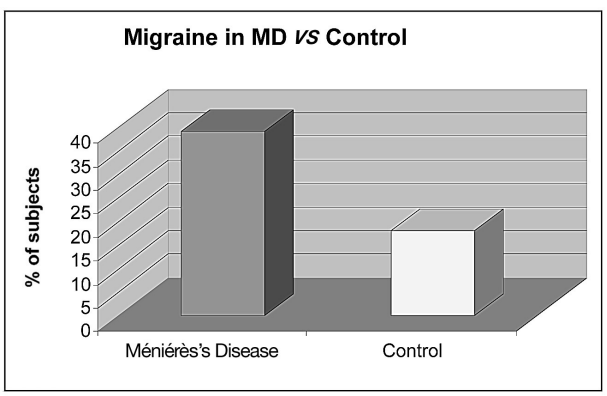

FIG. 1
Prevalence of migraine (odds ratio 2.89 [95 per cent CI: 1.52–5.49] $p = 0.001$).

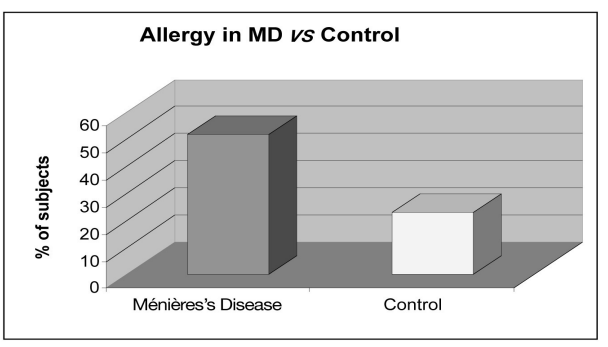

FIG. 2
Prevalence of allergy (odds ratio 3.60 [95% CI: 1.98–6.56] $p < 0.001$).

https://doi.org/10.1258/0022215054273133 Published online by Cambridge University Press

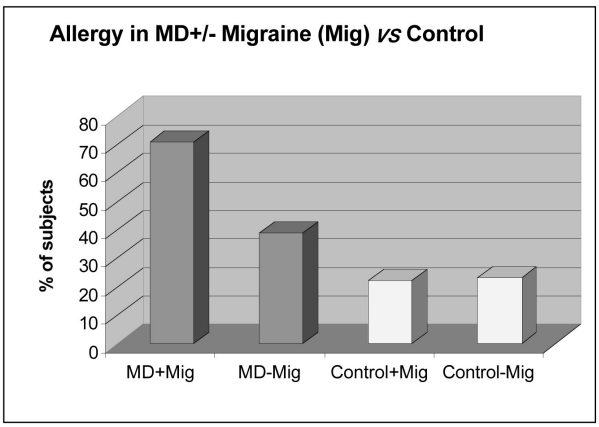

FIG. 3

Allergy in Ménière's disease +/- migraine (mig) vs control (odds ratio 3.84 [95 per cent CI: 1.67–8.83] $p = 0.001$).

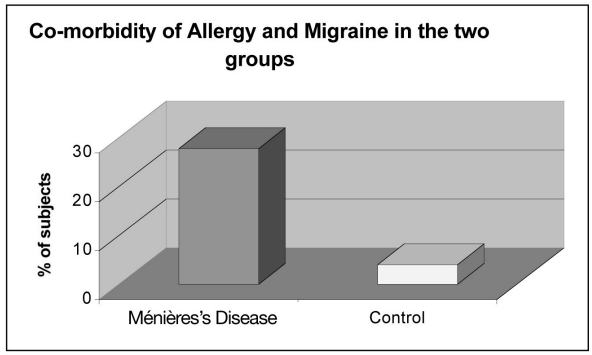

FIG. 4

Co-morbidity of allergy and migraine in the two groups (odds ratio 9.23 [95 per cent CI: 3.11–27.32] $p < 0.001$).

prospective study (56 per cent *vs* 25 per cent).[8] Twelve replies were discarded due to insufficient data. Even if they were all non-migraine sufferers, the prevalence of migraine would still be higher in the MD group compared with controls (42/120 vs 18/100, $p = 0.03$). It could be argued that we depended on self-reported migraine rather than on clinical diagnosis of migraine according to the International Headache Society criteria for the diagnosis of migraine.[15] However, our control population showed a prevalence rate of 18 per cent which is similar to the reported prevalence of migraine in population-based studies (11–18 per cent).[16–19] Therefore, we believe that the diagnosis of migraine was rather safe in both our control and our study patients.

A similarly increased prevalence of allergy of 52 per cent was found in our patients, compared with 23 per cent in the control group. Allergy is the most common immunological disorder in the general population with a prevalence of up to 20 per cent.[20] Co-morbidity of migraine and MD with atopic diseases is an important argument for a suspected common immune system dysfunction. Both migraine and MD appear in paroxysmal and recurrent fashion and a hypersensitive response could fit well with both. Based on these similarities it is understandable that both these diseases are linked to a hypersensitive immune system.

Gel and Coombs have initially identified four types of hypersensitivity reactions: type I (IgE mediated), II (humoral mediated), III (immune complex mediated) and IV (cell mediated). The antigens provoke different types of immunological reactions depending on its subtype.

Inhalant antigens largely cause type I hypersensitivity reaction mediated by IgE. It causes mast cell degranulation and release of mediators such as histamine that result in increased vascular permeability. Researchers have failed to find significant raised serum IgE levels in MD patients compared with controls.[21,22] However, 11.9 per cent with MD had raised IgE levels suggesting that in these patients, type I type allergy may play a role in initiation of the symptom complex.[22] Most of the clinical studies measuring total IgE levels in serum of migraine patients also correlated this with co-morbid atopy.[23–26] It may be that in atopic patients, increased IgE serum levels could be associated with the precipitation of both migraine and MD.

There is substantial evidence that histamine may be associated with migraine.[27–29] Histamine is a potent vasoactive compound and it may be a candidate mediator for vascular changes observed during migraine and MD. Antihistamines have been used as a treatment for MD.[30] As with all other treatment tried for MD, therapeutic efficacy of antihistamines also lies within the non-specific response bracket of 60–80 per cent.[31]

A type II reaction occurs when an immunoglobulin is directed against a cell constituent that acts as the antigen with subsequent complement activation. Yoo and colleagues have suggested autoimmunity to type II collagen may be of significance in MD.[32] However there is no evidence for a major role of type II hypersensitivity reactions in migraine.[33]

Type III hypersensitivity is characterized by expression of large amounts of circulating immune complexes (CIC) formed in response to circulating antigens. Several investigators have noted an association of CIC and MD[34–36] and it was noted that bilateral disease was more strongly associated with raised CIC compared with unilateral MD. In the inner ear the potential sites for CIC deposition include the stria vascularis and the endolymphatic sac and its surrounding capillaries. This is supported by the evidence of IgG deposits in the subepithelial area of the endolymphatic sac in patients with MD.[37,38]

Ménière's disease and migraine has not been associated directly with a type IV reaction but in migraine an aberrant cell mediated immunity has been reported in an earlier study.[39]

Food allergy can initiate all four types of hypersensitivity reactions. There are two types of food allergies: cyclic and fixed. Cyclic food allergy is more common and occurs several hours after ingesting the offending food. Fixed food allergy is rare and is often a type I IgE mediated reaction. Reports of clinical improvement to food elimination

https://doi.org/10.1258/0022215054273133 Published online by Cambridge University Press

diet in MD suggest an immuno-modulatory response of food allergens.[40–43] Similarly, 25 per cent of migraine sufferers report that their headache can be initiated by food.[44] However, the exact mechanism by which migraine and MD are linked to food allergy remains unclear.

- **Migraine and allergy are more prevalent in patients with Ménière's disease than age- and sex-matched controls**
- **Allergy is significantly more prevalent in patients with Ménière's disease and migraine than patients with Ménière's disease only**
- **This study suggests a possible immunological link between Ménière's disease and migraine**

Ménière's disease, migraine and allergy appear in a paroxysmal and recurrent fashion. Vascular changes play a role in all of these conditions: vasoconstriction followed by vasodilation of meningeal vessels, associated with plasma protein extravasation is implicated in the pathogenesis of migraine.[45] In MD, endolymphatic hydrops is associated with changes in the microvasculature of the cochlea including small ruptures of the membranous labyrinth.[46,47] Allergy, either through IgE (type I) or immunocomplexes (type III) is associated with vasodilation, the secretion of vasoactive peptides and extravasation with localized tissue oedema. It could account for these changes and serve as the common pathway for both migraine and MD.

Our study confirmed a much higher than expected association of allergy and migraine in MD sufferers. Although it does not prove a common pathophysiology or even a direct link, it provides an impetus for further study of this association.

It is possible that MD sufferers are a heterogeneous group, with different mechanisms leading to similar end-organ damage and clinical manifestations. Although the majority of patients with MD do not suffer from the combination of allergy and migraine, almost one in three presents with both, versus less than 4 per cent sharing the combination in the control group. Allergy is almost ubiquitous in MD patients with migraine and may well identify a highly distinct subgroup of patients. It would be interesting to note whether the common characteristics of these patients render them susceptible to similar interventions.

Conclusion

This study provides evidence of a link between migraine and MD. The higher prevalence of history of allergy in MD patients with migraine could suggest an immunological link between the two diseases. It is likely that both migraine and MD may have a multifactorial aetiology and that allergy may be a common triggering event that initiates various aspects of the symptom complex in predisposed individuals.

References

1 Ménière P. Pathologie auriculaire: memoires sur une lésion de l'oreille interne donnant lieu à des symptoms de congestion cérébrale apoplectiforme. [A report on lesions of the inner ear giving rise to symptoms of cerebral congestion of apoplectic type] *Gaz Med Paris* 1861;**16**:597–601
2 Atkinson M. Migraine and Ménière's disease. *Arch Otolaryngol* 1962;**75**:48–51
3 Hinchcliffe R. Headache and Ménière's disease. *Acta Otolaryngol* 1967;**63**:384–90
4 Dolowitz DA. Ménière's – an inner ear seizure. *Laryngoscope* 1979:**89**:67–77
5 Rassekh CH, Harker LA. The prevalence of migraine in Ménière's disease. *Laryngoscope* 1992;**102**:135–8
6 Stewart WF, Lipton RB, Celentano DD, Reed MD. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. *JAMA* 1992;**267**:64–9
7 Parker W. Ménière's disease. Etiologic considerations. *Acta Otolaryngol Head Neck Surg* 1995;**121**:377–82
8 Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H. Migraine and Ménière's disease: is there a link? *Neurology* 2002;**59**:1700–4
9 Lee H, Lopez I, Ishiyama A, Baloh RW. Can migraine damage the inner ear? *Arch Neurol* 2000;**57**:1631–4
10 William HL Jr. A review of the literature as to the physiologic dysfunction of Ménière's disease: a new hypothesis as to its fundamental cause. Laryngoscope 1965;75:1661–89
11 Gellhorn E. *Autonomic Imbalance and the Hypothalamus*. Minneapolis: University of Minnesota Press, 1957;300
12 Torok N. 'How I do it' – Otology and neurotology. A specific issue and its solution. Etiology as a guide in the management of Ménière's disease. *Laryngoscope* 1982;**92**:337–8
13 Davis RN. Web-based administration of a personality questionnaire: comparison with traditional methods. *Behav Res Methods Instrum Comput* 1999;**31**:572–7
14 Sen P, Papesch M. Ménière's disease patient information and support: which website? *J Laryngol Otol* 2003;**117**:780–3
15 Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;**8**(suppl):19–73
16 Goebel H, Petersen-Braun M, Soyka D. The epidemiology of headache in Germany: a nationwide survey of a representative sample on the basis of the headache classification of the International Headache Society. *Cephalalgia* 1994;**14**:97–106
17 O'Brien B, Goeree R, Streiner D. Prevalence of migraine headache in Canada: a population-based survey. *Int J Epidemiol* 1994;**23**:1020–6
18 Russel MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol* 1995;**24**:612–18
19 Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based study. *Neurology* 1999;**53**:537–42
20 Derebery MJ, Berliner KI. Prevalence of allergy in Ménière's disease. *Otolaryngol Head Neck Surg* 2000;**123**(1 Pt 1):69–75
21 Stahle J. Ménière's disease: allergy, immunology, psychosomatic, hypo- and hypertonus. *Arch Oto-Rhino-Laryngol* 1976;**212**:287–92
22 Hsu L, Zhu XN, Zhao YS. Immunoglobulin E and circulating immune complexes in endolymphatic hydrops. *Ann Otol Rhinol Laryngol* 1990;**99**(7 Pt 1):535–8
23 Bentley D, Katchburian A, Brostoff J. Abdominal migraine and food sensitivity in children. *Clin Allergy* 1984;**14**:499–500
24 Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double blind controlled trial of oligoantigenic diet treatment. *Lancet* 1983;**2**:865–9
25 Medina JL, Diamond S. Migraine and atopy. *Headache* 1976;**16**:271–4

https://doi.org/10.1258/0022215054273133 Published online by Cambridge University Press

26 Pradalier A, Weinman S, Launay JM, Baron JF, Dry J. Total IgE, specific IgE and prick-tests against foods in common migraine – a prospective study. *Cephalalgia* 1983;**3**:231–4
27 Lassen LH, Heinig JH, Oestergaard S, Olesen J. Histamine inhalation is a specific but insensitive laboratory test for migraine. *Cephalalgia* 1996;**16**:550–3
28 Lassen LH, Thomsen LL, Olesen J. Histamine induces migraine via the H1-receptor. Support for the NO hypothesis of migraine. *Neuroreport* 1995;**6**:1475–9
29 Lassen LH, Thomsen LL, Kruuse C, Iversen HK, Olesen J. Histamine-1 receptor blockade does not prevent nitroglycerin induced migraine. Support for the NO-hypothesis of migraine. *Eur J Clin Pharmacol* 1996;**49**:335–9
30 Hain TC, Uddin M. Pharmacological treatment of vertigo. *CNS Drugs* 2003;**17**:85–100
31 Ruckenstein MJ, Rutka JA, Hawke M. The treatment of Ménière's disease: Torok revisited. *Laryngoscope* 1991;**101**:211–18
32 Yoo TJ, Stuart JM, Kang AH, Townes AS, Tomoda K, Dixit S. Type II collagen autoimmunity in otosclerosis and Ménière's disease. *Science* 1982;**217**:1153–5
33 Kemper RH, Meijler WJ, Korf J, Ter Horst GJ. Migraine and function of the immune system: a meta-analysis of clinical literature published between 1966 and 1999. *Cephalalgia* 2001;**21**:549–57
34 Brookes GB. Circulating immune complexes in Ménière's disease. *Arch Otolaryngol Head Neck Surg* 1986;**112**:536–40
35 Derebery MJ. Allergic management of Ménière's disease: an outcome study. *Otolaryngol Head Neck Surg* 2000;**122**:174–82
36 Evans KL, Baldwin DL, Bainbridge D, Morrison AW. Immune status in patients with Ménière's disease. *Arch Otorhinolaryngol* 1988;**245**:287–92
37 Dornhoffer JL, Waner M, Arenberg IK, Montague D. Immunoperoxidase study of the endolymphatic sac in Ménière's disease. *Laryngoscope* 1993;**103**:1027–34
38 Futaki T, Nagao Y, Kikuchi S. Immunohistochemical analysis of the lateral wall of the endolymphatic sac in Ménière's patients. *Adv Otorhinolaryngol* 1988;**42**:129–34
39 Thonnard-Neumann E, Neckers LM. T-lymphocytes in migraine. *Ann Allergy* 1981;**47**(5 Pt 1):325–7
40 Shambaugh GE Jr, Wiet RJ. The diagnosis and evaluation of allergic disorders with food intolerance in Ménière's disease. *Otolaryngol Clin North Am* 1980;**13**:671–9
41 Derebery MJ. Allergic and immunologic aspects of Ménière's disease. *Otolaryngol Head Neck Surg* 1996;**114**:360–5
42 Derebery MJ, Valenzuela S. Ménière's syndrome and allergy. *Otolaryngol Clin North Am* 1992;**25**:213–24
43 Derebery MJ, Rao VS, Siglock TJ, Linthicum FH, Nelson RA. Ménière's disease: an immune complex-mediated illness. *Laryngoscope* 1991;**101**:225–9
44 Pradalier A, Launay JM. Immunological aspects of migraine. *Biomed Pharmacother* 1996;**50**:64–70
45 Moskowitz MA. Neurogenic inflammation in the pathophysiology and treatment of migraine. *Neurology* 1993;**43**:S16–20
46 Yazawa Y, Kitano H, Suzuki M, Tanaka H, Kitajima K. Studies of cochlear blood flow in guinea pigs with endolymphatic hydrops. *ORL J Otorhinolaryngol Relat Spec* 1998;**60**:4–11
47 Kimura RS, Schuknecht HF. Membranous hydrops in the inner ear of the guinea pig after obliteration of the endolymphatic sac. *Pract Otol Rhinol Laryngol* 1965;**27**:343–54

Address for correspondence:
Mr P Sen,
Department of Otolaryngology and Head and Neck Surgery,
Whipps Cross University Hospital,
Leytonstone,
London E11 1NR, UK.

Fax: 020 8535 6834
E-mail: senswathi@aol.com

Mr P Sen takes responsibility for the integrity of the content of the paper.
Competing interests: None declared

Appendix: Internet-based questionnaire used in this study[Q3]

Menieres Disease Internet Questionnaire

The ENT Department, Whipps Cross University Hospital, Whipps Cross Road

London, E11 INR.

Mr. P Sen FRCS & Mr. M Papesch FRACS Email: ent_info@yahoo.co.uk

Personal History

Age [ ] Age at onset of Meniere's Disease [ ] Sex [Male]

Main symptom [Vertigo] Second symptom [Vertigo]

Treatment [Medical]

Family History

Siblings with Meniere's: [Yes] Parents with Meniere's [Yes]

Grandparents with Meniere's [No Grandparent with Meniere's]

Do other illness run in your family [Yes] What are these illnesses?

[None]

If yes, do these family members also suffer from Meniere's? [Yes]

Migraine Headache History

Do you suffer from Migraine Headache? [Yes] Do any family members have migraine?

[Yes]

If family members suffer migraine, do they also have Meniere's? [Yes]

Allergy History

Do you suffer from any allergy? [Yes] If yes, please specify: [Food allergy]

Do any family members have allergies? [Yes] If yes, do they suffer also with Meniere's?

[Yes]

Siblings main symptom of Meniere's:

First [None] Second [None] Third [None]

Age at onset of Siblings Meniere's:

First [ ] Second [ ] Third [ ]

Were siblings with Meniere's living in same environment? [Yes]

Were siblings without Meniere's living in same environment? [Yes]

Comments or any further relevant family history:

[ ]

[Submit] [Reset]

Thank you for taking the time to fill in this questionnaire. Mr P Sen & Mr M Papesch

https://doi.org/10.1258/0022215054273133 Published online by Cambridge University Press