Inheritance of Ménière’s Disease in the Finnish Population

Tuomas Klockars, MD, PhD; Erna Kentala, MD, PhD

Objective: To study the inheritance of Ménière’s disease in the Finnish population.

Design: A detailed questionnaire was sent to patients with symptoms resembling Ménière’s disease previously examined at the Department of Otorhinolaryngology, Helsinki University Central Hospital, Finland.

Patients: The study population comprised 118 patients with symptoms resembling Ménière’s disease. The patients were divided into groups based on the diagnostic criteria by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery.

Main Outcome Measures: Relatives with Ménière’s disease, geographic distribution of birthplaces of grandparents, symptoms, vestibular findings, and audiologic and otoelectronic tests.

Results: Approximately 15% of the patients with definite Ménière’s disease were found to represent familial disease. The majority of these patients were female, and they had more severe and intense attacks compared with patients with sporadic Ménière’s disease. The mode of inheritance is autosomal dominant with incomplete penetrance.

Conclusions: A significant part of Ménière’s disease is inherited. The use of genetic isolates in which genetic homogeneity can be assumed might lead to the identification of gene defects leading to Ménière’s disease.

Arch Otolaryngol Head Neck Surg. 2007;133:73-77

MÉNIÈRE’S DISEASE IS AN IDIOPATHIC SYNDROME CHARACTERIZED BY TINNITUS, FLUCTUATING HEARING LOSS, AND REPEATED ATTACKS OF VERTIGO. DESPITE INTENSIVE RESEARCH, THE ETIOLOGY OF MÉNIÈRE’S DISEASE REMAINS UNKNOWN. THE DISEASE IS SUGGESTED TO BE OF MULTIFACTORIAL ORIGIN, COCHLEAR ENDOLYMPHATIC HYDROPS BEING THE PATHOPHYSIOLOGIC CONDITION CAUSING THE DISEASE. NUMEROUS CAUSES HAVE BEEN SUGGESTED, INCLUDING ALLERGY, VIRAL INFECTION, AUTOIMMUNE MECHANISMS, ALtered GLYCOPROTEIN METABOLISM, and HORMONAL LEVELS.

Although most cases of Ménière’s disease are likely to be sporadic, there are numerous reports of familial cases. Morrison described 41 families with more than 1 living member with Ménière’s disease. The mode of inheritance was found to be autosomal dominant, with penetrance being approximately 60%. Some family members only had partial syndrome, with vestibular symptoms predominating. Morrison was the first to report anticipation in Ménière’s disease, ie, an earlier age at onset and tendency to have more severe manifestation in successive generations. This finding was later supported by Fung et al and Oliveira et al. However, there are also families in which no anticipation is seen.

Despite reported familial cases, no causative genes have yet been reported for Ménière’s disease. A mutation in the inner ear–specific transcript gene COCH has been reported to cause Ménière’s disease–like symptoms with progressive hearing loss and a wide spectrum of vestibular involvement. Usami et al and Sanchez et al have excluded COCH mutations being causative for sporadic Ménière’s disease in restricted populations.

CME course available at www.archoto.com

No phenotypic difference between sporadic and familial cases has been reported, although in familial cases, the onset seems to be at a younger age and there are more affected female than male individuals. Data from various
studies indicate that 3% to 14% of Ménière’s disease is familial.9,16

In addition to familial cases, differences in the geographical distribution27,28 and in the incidence of Ménière’s disease in different races19 suggest that genetic factors are of significance.

Finland is one of the best-studied genetic isolates. The small number of original founders in addition to geographic isolation restricted the Finnish gene pool. In regional isolates, a small number of founders unavoidably resulted in consanguineous marriages.20 This random in-breeding increased the local incidence of inherited disorders, and in many diseases, regional clustering can still be observed.21 Strategies using these unique features have been efficiently used in disease gene mapping. Tracing the birthplaces of patients’ grandparents has revealed a founder effect in several diseases of the Finnish disease heritage.22

The prevalence of Ménière’s disease in Finland is estimated to be 43 to 513 per 100 000.18,23 Until today, there have been no reports, to our knowledge, of genetic studies or familial Ménière’s disease in the Finnish population. The aim of the present study was to evaluate characteristics and occurrence of familial Ménière’s disease.

METHODS

A questionnaire concerning family history and relatives with Ménière’s disease was sent to 243 patients with symptoms resembling Ménière’s disease. All the patients had been examined in our vestibular unit, and the hospital database had detailed information about symptoms (intensity, frequency, duration, nausea, and migraine); vestibular findings; results from audiologic and otoneurologic tests (electronystagmography, posturography, and saccadic and pursuit eye movements), imaging studies, and serologic tests; concurrent diseases; medica-tions; former head trauma; and use of tobacco and alcohol.

A total of 118 patients returned the questionnaire and were included in the study. The patients were aged from 34 to 80 years and 73% were female. The hospital records and database information were carefully analyzed. The patients were evaluated based on the diagnostic criteria of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery.24

- Certain Ménière’s disease
  - Definite Ménière’s disease and histopathologic confirmation

- Probable Ménière’s disease
  - One definite episode of vertigo
  - Audiometrically documented hearing loss on at least 1 occasion

- Possible Ménière’s disease
  - Episodic vertigo of the Ménière’s disease type without documented hearing loss, or
  - Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without definite episodes
  - Other causes excluded

Of the 54 patients with definite Ménière’s disease, 8 (15%) had a relative with definite Ménière’s disease compared with 1 (13%) of 8 patients with probable Ménière’s disease, 3 (14%) of 21 patients with possible Ménière’s disease, and 1 (4%) of 27 patients excluded as having Ménière’s disease. The 8 families with 2 or more patients with definite Ménière’s disease are referred to as having “inherited Ménière’s disease” hereafter in the text. The mode of inheritance was evaluated from the pedigrees presented in Figure 1. In 7 of the 8 pedigrees, the mode of inheritance seemed to be autosomal dominant with incomplete penetrance. One of the families was suggestive for recessive or autosomal dominant mode of inheritance, with incomplete penetrance (Figure 1, pedigree 5). The 8 families included 19 patients with definite Ménière’s disease and 12 relatives with symptoms resembling Ménière’s disease or partial syndrome but no diagnosis. Of the 19 affected individuals, 13 (68%) were female, and the corresponding value

Abbreviation: MD, Ménière’s disease.

<table>
<thead>
<tr>
<th>Diagnostic Distribution</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite MD</td>
<td>54</td>
</tr>
<tr>
<td>Inherited</td>
<td>8</td>
</tr>
<tr>
<td>Southwestern</td>
<td>12</td>
</tr>
<tr>
<td>Eastern</td>
<td>10</td>
</tr>
<tr>
<td>Probable MD</td>
<td>8</td>
</tr>
<tr>
<td>Possible MD</td>
<td>21</td>
</tr>
<tr>
<td>Excluded as having MD</td>
<td>21</td>
</tr>
<tr>
<td>Not enough information</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
</tr>
</tbody>
</table>

Table. Numbers and Distribution of Patients Included in the Study
was 9 (75%) of 12 patients for the relatives with Ménière’s disease–like symptoms. In 2 of 8 pedigrees, otosclerosis was inherited as an independent phenotype distinct from Ménière’s disease (Figure 1, pedigrees 6 and 7).

The analyses of the birthplace of parents or grandparents resulted in clustering to southwestern Finland and eastern Finland (Figure 2). Of the 54 patients with definite Ménière’s disease, 13 (24%) had ancestors in southwestern Finland (hereafter referred to as southwestern patients) and 10 (19%) had ancestors in eastern Finland (hereafter referred to as eastern patients). Of the southwestern and eastern patients, 4 and 5, respectively, had 3 or more grandparents originating from the specific region. One of the patients had a grandparent from both regions. None of the patients excluded as having Ménière’s disease had ancestors from these regions. For the 8 families with inherited Ménière’s disease, no founder effect or regional clustering could be identified (Figure 2).

The patients with definite Ménière’s disease were divided into 4 groups: inherited Ménière’s disease (n=8), southwestern patients (n=13), eastern patients (n=10), and remaining patients with definite Ménière’s disease (n=24) (Table). These groups were compared against each other and against other definite patients with Ménière’s disease for differences in symptoms (intensity, frequency, duration, nausea, and migraine); vestibular findings, results from audiologic and otoneurologic tests (electronystagmography, posturography, and saccadic and pursuit eye movements), imaging studies, and serologic tests; concurrent diseases; medications; former head trauma; and use of tobacco and alcohol.

The patients with inherited Ménière’s disease had more severe nausea (P = .001) compared with sporadic patients. Their attacks were more intense (P = .04) and lasted longer (P = .01). The southwestern patients had more postural instability (eyes open) compared with patients with definite Ménière’s disease (P = .04). There were no statistically significant differences between the eastern and southwestern or the eastern and other patients with definite Ménière’s disease.

**COMMENT**

Previous reports indicate that 3% to 14% of Ménière’s disease is genetic. In our study, 15% of the Finnish patients with definite Ménière’s disease had a relative with the same disease, suggesting that a significant part of Ménière’s disease is inherited. It is reported that some of the affected individuals with familial Ménière’s disease express only a partial syndrome. In our study, only families with 2 or more members with definite Ménière’s disease were considered as having inherited disease. Thus, it is likely that the proportion of dominant Ménière’s disease in the Finnish population is even higher than 15%.

In all but 1 of our pedigrees, autosomal dominant inheritance with incomplete penetrance seems to be the mode of inheritance. Interestingly, in 3 of the families, the mode of inheritance could represent maternal transmission (Figure 1, pedigrees 2, 6, and 8). The majority of the patients with familial Ménière’s disease were female. A similar finding has been previously reported by Morrison. However, in our material there also was a female preponderance in patients with sporadic Ménière’s disease. In previous studies, no true difference in prevalence between sexes has been proven. Kotimäki et al found a slight female preponderance (58%) in the Finnish population. Owing to the limited number of pa-
tients with familial Ménière’s disease, the significance of female preponderance remains unclear. However, based on our pedigrees and previous reports on familial Ménière’s disease, it seems likely that in female subjects, the genetic predisposition is stronger than in male subjects.

To our knowledge, no phenotypic difference between sporadic and familial cases has been previously reported.2–10 Our patients with inherited Ménière’s disease had more severe nausea and their Ménière’s disease attacks were more intense and lasted longer. No other statistically significant differences were found in comparison with patients with sporadic Ménière’s disease. Despite the observed phenotypic differences, it is impossible to recognize familial from sporadic Ménière’s disease based on clinical picture and audiologic or oto-neurologic tests.

In 2 of the 8 families, otosclerosis was inherited as an independent phenotype distinct from Ménière’s disease. Both otosclerosis and Ménière’s disease are of unknown etiology and likely represent numerous causes. An association between these diseases has been proposed on both a clinical and histopathologic basis. The causal relationship is controversial: it has been suggested that they may be 2 separate diseases that exist coincidentally or that endolymphatic hydrops is caused by the otosclerotic process, thus leading to Ménière’s disease.23 It is tempting to speculate that in the 2 families described herein, otosclerosis and Ménière’s disease represent different outcomes of the same mutation. The search for additional families and candidate gene analyses will hopefully reveal if this hypothesis is true. The 2 families are described in detail elsewhere (Klockars and Kentala20).

Of the 54 patients with definite Ménière’s disease, 22 had ancestors from 2 distinct regions in Finland (Figure 2). The observed regional clustering may indicate a genetic founder effect, which is seen in several inherited diseases in the Finnish population. If this is true, a significant proportion of Finnish patients with Ménière’s disease might have a recessive predisposition for developing Ménière’s disease. However, further genealogical and genetic studies will need to be performed.

There are 2 reports on the prevalence of Ménière’s disease in Finland.18,23 The results of these 2 studies are rather controversial: Kotimäki et al18 estimated the prevalence to be 43 per 100 000, whereas Havia and coauthors23 estimated the prevalence to be 513 per 100 000. It is likely that there is several explanations for the 10-fold difference, one of which could be the geographical distribution of the populations analyzed. Kotimäki et al18 based their calculation on hospital records covering 30% of the Finnish population, whereas the prevalence obtained by Havia and coauthors23 is based on a questionnaire sent to 5000 randomly selected individuals living in southern Finland. Controversially, Kotimäki and coauthors18 reported Ménière’s disease to be more prevalent in northern Finland. Regional clustering of patients with Ménière’s disease could partly explain the difference in prevalence, although methodological and diagnostic differences are the most likely explanations for the variation.

There are several reports on anticipation in Ménière’s disease.10–12 Anticipation is defined as a condition in which the disease increases in severity with each generation based on the varying number of nucleotide repeated expansions found in the different individuals. This phenomenon is supported by our pedigrees, but owing to the limited number of families, further studies are still needed to confirm the finding.

Despite reports of familial cases, no causative gene(s) have yet been reported for Ménière’s disease. We believe that inherited Ménière’s disease is likely to represent genetic heterogeneity causing difficulties in genetic linkage and mutation analyses. We conclude that the most efficient way to identify defective genes leading to Ménière’s disease is through the identification of families large enough for linkage studies or by using genetic isolates in which genetic homogeneity can be assumed. For this purpose, the Finnish families with Ménière’s disease and regional isolates described in this study might prove useful.

Submitted for Publication: April 19, 2006; accepted June 21, 2006.

Correspondence: Tuomas Klockars, MD, PhD, Department of Otorhinolaryngology, Kymenlaakso Central Hospital, Kotkantie 41, 48210 Kotka, Finland (tuomas.klockars@fimnet.fi).

Author Contributions: Drs Klockars and Kentala had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Klockars and Kentala. Acquisition of data: Klockars. Analysis and interpretation of data: Klockars and Kentala. Drafting of the manuscript: Klockars. Critical revision of the manuscript for important intellectual content: Klockars and Kentala. Statistical analysis: Kentala. Obtained funding: Klockars. Administrative, technical, and material support: Klockars and Kentala. Study supervision: Klockars and Kentala.

Financial Disclosure: None reported.

Funding/Support: This study received financial support from the Wilhelm och Else Stockmanns Stiftelse.

Acknowledgment: We thank Teppo Varilo, MD, PhD, for discussions concerning the genealogical search for common ancestors.

REFERENCES