The Journal of Laryngology & Otology (2009), ***123***, *29–37.*

doi:10.1017/S0022215108002788

Main Article

Familial Ménière's disease: clinical and genetic aspects

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Abstract

Background and purpose: Ménière's disease is not uncommon, with an incidence in Caucasians of about one in 2000. The incidence peaks in the fifth decade. Cases are usually isolated or sporadic, but in perhaps five per cent other family members are affected. We report here the clinical and genetic characteristics of a comprehensive set of familial Ménière's disease cases from the UK.

Methods: Forty-six affected families were studied. All cases were diagnosed using the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium 1995, or more stringent, criteria.

Outcomes and results: Autosomal dominant inheritance with reduced penetrance was the most likely mode of inheritance overall. Apparent genetic anticipation was observed, but may also be a result of ascertainment bias given the collection strategy. There was also a slight tendency for cases to result from maternal transmission within the families in this set. The family pedigrees are presented, and the authors have also set up a website at which all the pedigrees may be viewed in greater detail.

Key words: Ménière's Disease; Familial; Epidemiology; Genetics; Dominant; Anticipation

Introduction

Ménière's disease is a defined clinical entity in which the sufferer experiences sudden and recurring episodes of vertigo, often with nausea and vomiting, together with hearing loss and tinnitus, usually occurring in just one ear at onset. A feeling of fullness or pressure in the affected ear is common.

Typically, around the time of a Ménière's vertigo attack the fullness, tinnitus and hearing loss will worsen, then recover fully or partially after the episode. The disease runs in quiescent and then in more active periods; in the latter there are more frequent or more severe vertigo attacks, often remaining troublesome for a few months at a time. Between attacks, balance frequently returns to normal, but in active periods some continuous disequilibrium and vague dizziness may persist. Initially, the hearing loss tends to be fluctuating and spontaneously reversible. Over years, however, it becomes more permanent and progressive. Eventually, the condition 'burns out'; the vertigo attacks cease more or less completely, but by this time hearing loss can be severe. Over time, there is an increasing likelihood of involvement of the second ear, leading to the disease becoming bilateral.

The American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium 1995 guidelines for the diagnosis of Ménière's disease are widely accepted.[1] Diagnosis requires the combined presence of three different clinical features: (1) at least two attacks of vertigo lasting 20 minutes or longer, (2) the presence of either aural fullness or tinnitus, or both, and (3) a sensorineural hearing loss on the affected side which is at least 25 dB worse than that on the non-affected side (taken as the average threshold for 0.5, 1.0, 2.0 and 3.0 kHz).

Incidence

Ménière's disease usually arises de novo in midlife (i.e. after the usual age of reproduction), less commonly in younger adults or in the elderly, and rarely in children. Supplementary Figure 1 shows the distribution of age of onset for 406 sequential patients presenting to the authors with sporadic Ménière's disease. These new data are an extension of a previously published series.[2] This figure also shows, for comparison, the younger age of onset found in familial Ménière's disease cases, based on the 46 families reported in this paper.

Globally, the great majority of Ménière's cases are sporadic, there being no other close family members similarly affected. The reported cumulative lifetime incidence for Ménière's disease varies greatly, ranging from as low as 0.8 per 1000 in Italy[3] to

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Accepted for publication: 7 February 2008. First published online 11 July 2008.

as high as 1.57 per 1000 in the UK.[4] Harrison and Naftalin[5] proposed a UK figure of one per 1000, which seems a fair estimate. In 1983, Watanabe reviewed the published reports;[6] Frieberg and Stahle did so more recently.[7] In Finland, an extrapolated prevalence estimate of 0.43 per 1000 was reported.[8] The Swedish figure of 0.46 per 1000 (approximately one in 2000), coming from a well documented, homogeneous population, seems the most acceptable.[9]

Ethnic distribution

Ménière's disease is predominantly a disease of Caucasians and Eurasians. In 1963, a report from the USA described it as a disease of whites, seldom seen in those of African origin.[10] In 1964, Fick reported its rarity in the Bantu people.[11] A similar finding was reported for West Indians in 1967.[12] In 1979, Gibson commented on its rarity in those of Afro-Caribbean origin.[13] In the same year, Wiet noted the near absence of Ménière's disease in American Indians.[14] In Japan, the incidence is lower than in Europe, at approximately 0.035–0.160 per 1000, depending upon which survey is accepted.[6] All these findings support the conclusion that the incidence of Ménière's disease varies between populations of different continents.

Familial Ménière's disease

Familial Ménière's disease is now a well recognised entity. However, this was not so in 1941, when Brown described two brothers with Ménière's disease whose symptoms had started at the ages of 49 and 50 years.[15] In 1949, she followed this with a second report of two families.[16] The first consisted of three definite Ménière's disease patients from a sibship of five, the normal parents being first cousins. The mother had two brothers, both of whom had an affected son. The second family consisted of identical twin boys, both deaf, but only one with dizzy spells for about two years; the hearing losses were conductive on clinical and audiometric testing, and the diagnosis was probably otosclerosis.

After a gap of nearly 20 years, in 1965, Bernstein published on familial deafness and vertigo.[17] In 1967, Hinchliffe's clinical record on psychosomatic aspects of Ménière's disease contained mention of familial cases, but it was difficult to assess their frequency.[18] We can surmise that there were perhaps two affected sib pairs from 42 cases, giving a frequency of approximately 5 per cent.

There was another significant hiatus until 1981, when Morrison reported that five of 190 patients with Ménière's disease had a positive family history, a frequency of 2.6 per cent.[19] At about the same time, an epidemiological study from Japan found that 5.8 per cent of Ménière's disease patients had an affected close relative.[20] In 1992, Martini reported two Italian families.[21]

Two further publications merit comment. In 1984, Birgerson *et al.*[22] reported the frequency of familial Ménière's disease in Sweden to be as high as 12 per cent (11 familial cases from 91 Ménière's disease patients). The latter figure was based largely on a questionnaire and thus may have been misleading; however, many of these findings were restated in a 1987 publication by the same authors.[23] A 2007 paper from Finland gives a comparable figure of approximately 15 per cent.[24] In our second paper, published in 1987, we reported 35 first degree relatives from a series of 671 confirmed Ménière's disease patients (a frequency of 5.4 per cent); the overall frequency of familial cases rose to 7.7 per cent if second and third degree relatives were included.[25] However, these figures were extracted from the family history in the patients' clinical records, without actual diagnostic confirmation in many of the relatives. The statistic of 5.4 per cent frequency in first degree relatives is probably reasonably accurate. Two further recent reports have described medium-to-large, multiply affected families.[26,27]

If familial Ménière's disease was encountered in clinical practice with a frequency as high as 7.7 or 12 per cent, this finding would be very apparent. However, the paucity of such reports over the years and the difficulty in collecting a sizeable series argue against such figures. One is left with the impression that a familial Ménière's disease frequency statistic of 5 per cent at most, possibly less, would be more realistic.

In summary, there seems to be a case for believing that predisposition to Ménière's disease, at least in a proportion of cases, has a significant genetic component. Two of the commonly accepted criteria are observed: differences in disease incidence between populations, and familial clustering. The third recognised criterion, evidence or report of greater concordance in monozygotic twins, compared with dizygotic twins, has not been reported, presumably because of the relative rarity of affected twins.

Materials and methods

Identification of families ascertainment

Our search for UK Caucasian families with more than one living member considered to have Ménière's disease began in 1992. The majority of cases were identified over the next few years.[28,29] Most cases were identified from private practice, a few from the UK National Health Service (NHS), some from a circular letter sent to UK ENT surgeons, and a small number from the Ménière's Society, a patient support group. In 1993, the senior author (AWM) appeared on a national television news programme and appealed to such families to come forward; hundreds of letters were forwarded, but only six possible families were ascertained.

A circular letter was given or sent to all interested enquirers, requesting a copy of their family tree (based on an example supplied). Probable Ménière's disease family members were contacted and appropriate, unaffected family members were requested to attend the clinic (all expenses were reimbursed). The response and cooperation were 100 per cent.

The family pedigrees and clinical data were collected and assimilated using Cyrillic 2 software (Cherwell Scientific Publishing, Oxford, England).

https://doi.org/10.1017/S0022215108002788 Published online by Cambridge University Press

Ethical approval for this ongoing research, and for our subsequent genome search for genes predisposing to Ménière's disease, was obtained from the Cambridge local research ethics committee (reference 02/375).

Exclusion criteria

After examination, several families were excluded as only one member had classical Ménière's disease, the other(s) having any of a variety of other vestibular problems. For example, one patient had multiple sclerosis, one a moderately large acoustic neuroma, one otosclerosis plus benign paroxysmal positional vertigo (BPPV) and another the Chiari malformation. There were three children with congenital anomaly of one ear who, earlier in childhood, had developed the classical features of Ménière's disease. One had undergone computed tomography scanning, which had shown an osseous dilatation of the superior semicircular canal.

The family set

By 1994, from 12 possible families, only eight had been identified as suitable for inclusion in a study also concerned with environmental factors.[28] However, by 1995, after further exclusions, 41 families with 89 Ménière's disease affected cases were included in the series,[29] and by 2002 the series consisted of 46 families with 118 affected individuals.[2] Since then, some of these patients have been excluded after revision of their diagnoses. Many of the families have been followed up at regular intervals by one of the authors over the past 14 years. A few new families have been added.

At the time of writing, the total series comprised 61 families which had been investigated for a possible history of familial Ménière's disease. Sixty families contained more than one Ménière's disease sufferer, or one Ménière's disease case and one or more individuals with partial vestibular syndromes but not certain Ménière's disease. Of these families, 46 had at the time of writing been confirmed as having two or more family members with classical Ménière's disease.

Sampling methods

Venous blood samples were taken from affected and unaffected family members, from which genomic deoxyribonucleic acid (DNA) was extracted at St Mary's Hospital Medical School, London, or at the Regional Genetics Laboratory, Addenbrooke's Hospital, Cambridge. Repeat samples were also stored at Addenbrooke's Hospital. As Ménière's disease is a condition of late onset, unaffected children below the age of 16 years were not subjected to venepuncture.

Clinical characterisation and diagnosis

Personal interview and full clinical examination by the authors confirmed the diagnosis in almost all cases. In a few cases, other British otologists established the diagnosis. A detailed history was taken for each family member. Diagnosis in suspected cases was backed up by laboratory investigation.[30] The American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium has issued guidelines on Ménière's disease diagnosis and treatment assessment three times, in 1972, 1985 and 1995.[1,31,32] Of these, the 1995 version is widely accepted. As mentioned above, a diagnosis of full or definite Ménière's disease requires the satisfaction of at least three clinical and audiometric criteria: (1) either tinnitus or aural fullness; (2) at least two attacks of vertigo lasting 20 minutes or longer; and (3) sensorineural hearing loss on the affected side of 25 dB or worse. There is a severity staging system based only on average hearing thresholds, as follows: stage one = ≤25 dB; stage two = 26–40 dB; stage three = 41–70 dB; and stage four = >70 dB. There is also a functional scale based on patient selection of the best fit of six questions describing increasing incapacity in relation to vertigo-related symptoms see Table II.

We began to collect familial Ménière's disease cases in 1992, three years before the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium guidelines appeared. We initially employed our own severity classification (on a scale of one to three), which depended to some extent upon when the patient was first examined in relation to the natural history. In the very early stages of Ménière's disease, there can be a diversity of vertiginous symptoms (such as transient dizziness with fluctuant hearing loss). Later, classical episodes can last up to 24 hours. With the passage of time, amelioration of disease intensity can be observed, with shorter and less violent attacks. In the later stages, when there is more marked hearing loss, attacks can be replaced by vague dizziness and instability.

In our classification system, bilateral disease and 'drop attacks' were designated as class three, likewise symptoms so severe as to be incapacitating, equating to the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium scales four, five or six. For hearing loss severity, our classification, although not based on deafness levels, was similar to that of the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium, that is: our stage one patients mostly had moderate hearing losses of up to 35 dB; our stage two patients had losses of 35–50 dB; and our stage three patients had losses of >50 dB, sometimes sub-total. During the 14 years' follow up, some scaling changes were made in many families, usually for the worse, based mainly on deafness severity or the need for destructive surgery. A few deaths occurred, of both affected and unaffected individuals.

Stahle *et al.* reviewed the natural history of Ménière's disease and confirmed that, over time, the frequency of second ear involvement increases, approaching 50 per cent after 20 years.[33] They found that the main cochlear and vestibular symptoms and damage occurred in the first five to 10 years, and that thereafter hearing thresholds stabilised at 50–60 dB.

https://doi.org/10.1017/S0022215108002788 Published online by Cambridge University Press

Morrison, in an assessment of 330 patients with sporadic Ménière's disease, was in general agreement, save that after 15 years continued hearing deterioration was noted.[34] This also applies to familial Ménière's disease cases, some of which eventually suffer sub-total hearing loss. An examination of the cochlear implant literature confirms this finding.

Reclassification of partial syndromes

Prior papers on our families have included a few cases labelled vestibular or cochlear Ménière's disease.[2,28,29] The 1972 American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium guidelines included both of these sub-varieties.[31] It was assumed, as with any such study, that phenocopies had been excluded. The 1995 criteria excluded such variants, instead defining probable and possible Ménière's disease, and accepting that over time the full symptom complex could develop.[1]

Probable Ménière's disease was defined as one definite episode of vertigo and audiologically documented hearing loss on at least one occasion, and tinnitus or aural fullness in the affected ear.

Possible Ménière's disease had two definitions: (1) episodic vertigo of the Ménière type without documented hearing loss; and (2) sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definite episodes of vertigo.

We have re-examined all cases previously designated as partial syndromes and altered their diagnoses according to the most recent American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium guidelines. The reclassified status of these individuals is not always an accurate reflection of their clinical phenotype. An example is provided by individual IV:4 in family MX (see Figure 1). This woman had episodic, classical attacks lasting two to four hours, remitting and relapsing over a period of several years. Prior to each attack, she experienced tinnitus and an uncomfortable, blocked sensation, with possible hearing loss, always in her right ear, but no hearing loss had ever been documented. This case has been redesignated with the lesser description of possible Ménière's disease. When considering partial syndromes, it is advisable to remember that although half of Ménière's disease patients develop the full symptom complex within six months, one-third experience deafness and tinnitus only, and one-fifth experience episodic vertigo alone for periods in excess of six months, sometimes even for years.[34] During the first five years of illness, hearing thresholds can revert to normal limits in a substantial majority.[34] Thus, in a near certain Ménière's disease case, objective hearing loss may be missed (i.e. may fail to have been observed owing to fluctuations up to normal hearing at the time of medical examinations). As will be seen, our efforts have concentrated on families most likely to be of use in genetic analysis; in these, the length of follow up excludes misdiagnoses.

Episodes of positional vertigo frequently occur in Ménière's disease. Sometimes, a true attack starts in bed when the patient turns on the affected side. At some stage in the natural history, usually when the disease is well developed, many patients experience transient positional episodes indistinguishable from classical BPPV. We have recorded such episodes in our family pedigrees, along with the finding of unaffected relations with BPPV.

There are several causes of positional vertigo, as analysed by Morrison and Morrison.[35] The commonest cause is idiopathic (44 per cent), while the next commonest, resulting in one or more attacks of vestibular failure, is usually presumed to be viral (22 per cent). Both these aetiologies have features in common, including a three-to-two female/male ratio, an age of onset showing a normal distribution around the fifth decade, and active and quiescent spells, akin to Ménière's disease. Hearing is unaffected. The Hallpike manoeuvre confirms a peripheral nature, short latent period, rotary nystagmus to the undermost ear, adaptation and fatigue, all implicating the posterior canal ampulla, presumably due to cupulothiasis or canalithiasis. Many of these family members have repeated episodes of BPPV over years, whether idiopathic in origin or following acute vestibular failure. However, the clinical diagnosis of isolated BPPV is very distinct from that of Ménière's disease with associated peripheral type positional vertigo, since in BPPV there is no fullness, tinnitus or hearing loss. The pathophysiology of BPPV is considered to result from otolith crystals and debris becoming freed and then misplaced within the labyrinth, and it is likely that any cause of vestibular end-organ damage can lead to this phenomenon. Therefore, BPPV can occur with classical symptomatology and be secondary to Ménière's disease.

Results

The pedigrees

From the originally investigated entire set of 61 families, 137 patients with Ménière's disease and 41 other patients with partial vestibular syndromes were identified.

Of these 61 families, 15 were eventually excluded from further consideration, leaving 46 families confirmed as having two or more family members with classical Ménière's disease (i.e. definite Ménière's disease under the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium 1995 criteria), yielding 120 affected individuals in total. Twenty-two other patients were classified with a partial syndrome, either probable or possible Ménière's disease, or occasionally with isolated idiopathic BPPV. In several of the 46 families, there were individuals with non Ménière's disease related causes of hearing loss (e.g. post-infection or congenital).

Of the excluded 15 families, at the end-point of this study 14 had been confirmed to have only one member with classical Ménière's disease, with other dizzy patients in those families being categorised with partial syndromes. One further family had one member with Ménière's disease and one member with a congenital ear anomaly only.

https://doi.org/10.1017/S0022215108002788 Published online by Cambridge University Press

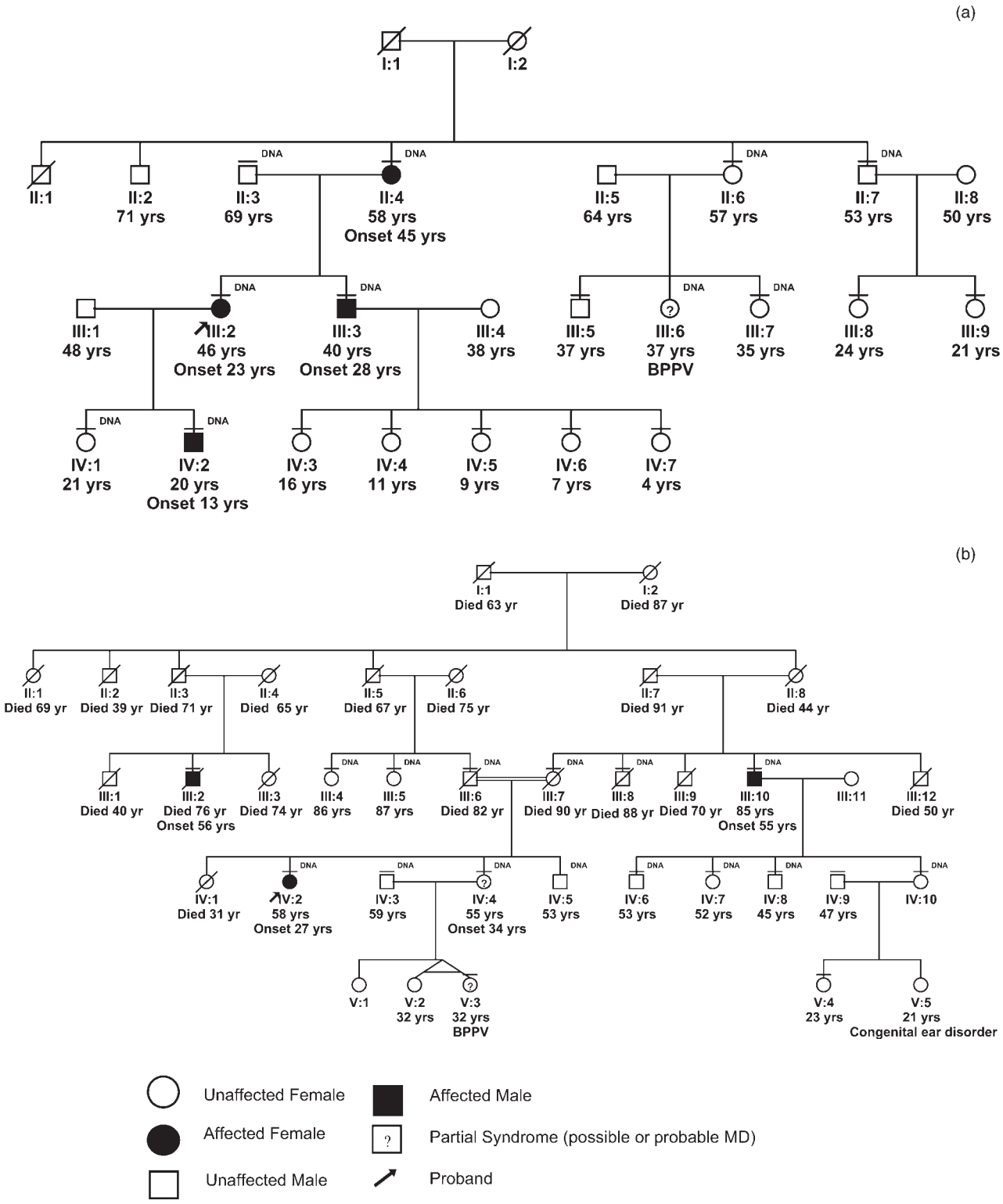

FIG. 1

Familial Ménière's disease pedigrees of families (a) GW and (b) MX. A horizontal line above an individual indicates that they were personally examined for diagnosis (or exclusion of diagnosis) by the authors. MD = Ménière's disease in probable and possible MD cases and in unaffected relatives; DNA = deoxyribonucleic acid was collected; '*n* yr' = age of individual in 2003 or age at death; 'Onset *n* yr' = age (years) of affected individual at first clear symptom of MD; BPPV = benign paroxysmal positional vertigo in probable and possible MD cases and in unaffected relatives

From the series of 46 confirmed multiply-affected families, the 18 pedigrees considered most appropriate for our genetic analysis (implemented in a subsequent genome scan; manuscript in preparation) are shown in Supplementary Figure 2, plus a recently added 19th family (family AA). A further nine families were included as part of a larger screening panel of affectands, and some of these were used in

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screening for candidate genes (manuscript in preparation). This entire series of 46 pedigrees, in ongoing draft research format can be viewed in full at http://www.GavinMorrison.com.

Inheritance patterns and parameters

Of the 46 confirmed families, 27 had two affectands, 12 had three affectands, six had four affectands and one had five members with Ménière's disease. Of the 14 families with affected sibling pairs, 10 also had one affected parent and four had parents without Ménière's disease.

Sex ratios. In the entire set of 61 families with cases of definite Ménière's disease, there were a total of 75 affected females and 62 affected males, giving a female-to-male ratio of 1.2:1. This is a weaker female predominance than previously noted.[29] However, interestingly, if the sex ratio includes those patients with partial syndromes (31 females and five males), the female preponderance becomes much stronger (female-to-male ratio of 106:67, approximately 1.6:1). Amongst the 46 families with multiple Ménière's disease affected members, 63 definite Ménière's disease cases were in females and 57 were in males, again only a marginal female predominance.

Age of onset and genetic anticipation. The distribution of age of onset for the familial cases in our series is shown in Supplementary Figure 1. The age of onset in familial cases differs from that in sporadic Ménière's disease cases, the peak onset being in the fourth rather than the fifth decade, respectively. Genetic anticipation describes the phenomenon of progressively younger onset and more severe affectation of a genetic disease in succeeding generations. Thus far, every confirmed example of genetic anticipation has been shown to involve a causal pathway characterised by mutation of specific tracts of DNA sequence consisting of three-base tandem repeats (i.e. trinucleotide repeats), with increased severity and decreased age of onset being associated with an increase (i.e. expansion) in the number of repeats present in each successive generation (hence, trinucleotide repeat expansions). Our pedigrees, with few exceptions, demonstrate apparent genetic anticipation, certainly regarding age of onset, and to a lesser extent regarding disease severity; this has also been reported previously.[28,29] Thus, the age at onset in the child is earlier than that in the parent in all but one of the parent–offspring pairs in our family set. Supplementary Figure 3 demonstrates this apparent genetic anticipation graphically, with all points appearing on or below the diagonal line (this line indicates equity of age of onset between generations). In the 35 patients with an age of onset under 30 years, 10 had bilateral disease, suggesting that severity had increased in families with early-onset cases, perhaps reflecting a stronger genetic influence on predisposition. In comparison, the incidence of bilateral disease in sporadic Ménière's disease patients younger than 30 years has never been reported; however, we estimate it to be no greater than 10–15 per cent. However, some caution should be exercised over this conclusion of genetic anticipation, since from our series the proband (or propositus) was the immediate offspring or close relative of another affected individual in 22 families, while the proband originated from the highest generation in only eight families. (The proband was in the same generation as other affected members in a further 12 families.) This preponderance of younger probands may therefore represent some ascertainment bias in the analysis of genetic anticipation.

In the 19 family pedigrees shown in Supplementary Figure 2, 55 patients had Ménière's disease, 12 bilaterally. Of these 55, 23 were classified as stage three (i.e. severe) disease, 23 were classified as stage two and only seven were classified as stage one (i.e. mild) disease. Of these 19 families, 15 showed a progression in the staged severity of disease through a descending generation; only three showed no progression, and only one exhibited a less severe grade in descendants. These individual data are shown in the pedigree charts for the entire series, available at http://www.GavinMorrison.com.

Mode of inheritance. Of the 46 families, 32 exhibited direct transmission from parent to offspring. In 20 cases, there was a parent transmission to one offspring, in 11 cases there was a parent transmission to two offspring, and in one case there was a direct transmission to three offspring. Three families also showed a linear transmission directly through two generations from grandparent to parent to child. Male to male transmission was observed, and there was no evidence for genomic imprinting, which would be characterised by transmission of the disease to offspring of either sex from parents of one sex only. The predominant pattern visible in the family pedigrees was most consistent with autosomal dominant inheritance. Under this hypothesis, we estimate penetrance in all 46 families to be about 60 per cent, some pedigrees appearing to have segregation ratios consistent with full penetrance. Family GW (Figure 1) is a typical example of one of the pedigrees showing apparent autosomal dominant inheritance. Some of the families are also consistent with autosomal recessive inheritance, particularly family MX (Figure 1), in view of the consanguinity in this family. However, two of four offspring of the unaffected cousin marriage in family MX were affected (we consider individual IV:4 likely to have been affected, although we did not treat her as definite Ménière's disease in our analyses; see above discussion in Methods section on diagnosis and partial syndromes), and the third affected was in the parental generation, making recessive transmission less likely unless a common allele existed in the population (three mutation-carrying founders are required if the true mode of inheritance is recessive, versus one if it is dominant). Overall, there is no compelling evidence in favour of recessive inheritance in this set of families.

https://doi.org/10.1017/S0022215108002788 Published online by Cambridge University Press

TABLE I

TRANSMISSION PATTERNS BY GENDER IN THE 46 FAMILIES

Sex of offspring	Transmitting parent		Total
	Mother	Father	
Daughter	41	11	52
Son	15	24	39
Total	56	35	91

Data shown represent number of patients.

Sex-ratio transmission bias. Transmission ratios were biased ($p < 0.001$; Fisher's exact test for overall comparison), as illustrated in Table I . Females tended to transmit to female offspring and males to male offspring ($p < 0.001$ and $p < 0.05$, respectively; chi-square tests with continuity correction, one degree of freedom). There was also an overall bias favouring transmission from mothers over transmission from fathers ($p < 0.04$; chi-square with continuity correction = 4.4). However, these data have been interpreted bearing in mind the fact that, in our series, for all female affectands who showed direct Ménière's disease transmission to their offspring, there were a total of 40 female offspring and only 27 male offspring (affected and unaffected children). Affected transmitting fathers also showed a female-biased offspring sex ratio, with 24 daughters and 16 sons. These biases may therefore reflect either a genuinely biased transmission mechanism, or an ascertainment bias favouring recognition of families in which affected females predominate, and especially those in which affected mothers have passed the condition onto affected daughters. Overall, there was no significant bias in the proportion of transmissions to sons versus those to daughters ($p > 0.2$; chi-square with continuity correction).

Discussion

Transmission characteristics and segregation ratios

Previous reports have differed as to whether the sex ratio was equal amongst Ménière's disease patients. Some reports have concluded an equal sex ratio for sporadic Ménière's disease,[34] while others have reported a modest female preponderance.[33] However, the senior author's earlier series of familial Ménière's disease demonstrated a preponderance of affected females ($n = 70$), compared with 49 affected males.[29] Examination of the pedigrees in this current, updated and expanded series now suggests only a very weak female predominance. However, when patients with partial syndromes were included in the sex ratio analysis, the female predominance became much stronger. Why more females appeared to have partial syndromes remains unclear.

Mode of inheritance

Martini[21] reported two families suggesting autosomal dominant inheritance of Ménière's disease. The first consisted of three affected individuals, a mother and two daughters, all with an early age of onset. The second included three generations of affected males and showed apparent anticipation, although this was not mentioned in the paper.

Birgerson *et al.* reported 11 pedigrees.[36] They concluded that eight of the families were compatible with either autosomal or X-linked dominant inheritance, and that three could be recessive. In one family, an affected mother and daughter both had a structural abnormality of chromosome 7 in some of their cells. Birgerson and colleagues' report was also concerned with autoimmune disease. No age of onset data were provided.

A 1992 Brazilian report by Oliveira and Braga suggested autosomal dominant inheritance, based on one family; the affected father had two of eight children with Ménière's disease, and when widowed his second family of six produced one child with Ménière's disease.[37] Although not commented upon, this family showed possible genetic anticipation.

From Essen in Germany, Arweiler *et al.* described five families with apparent autosomal dominant inheritance.[38] Genetic anticipation was recorded, especially in their four-generation family E, the age of onset in generation F1 being of the order of 50 years, falling to 20 years in F4.

- **Ménière's Disease has an incidence of 1 in 2000**
- **The peak age of onset is the 5th decade**
- **5% of Ménière's disease in the UK is familial**
- **This article reports the largest published series of Familial Ménière's Disease**
- **61 Families had multiple members with vertigo, 120 patients had Ménière's Disease within 46 families**
- **Autosomal dominant inheritance with reduced penetrance was demonstrated**
- **Apparent genetic anticipation was noted although ascertainment bias could be operating**
- **There was a tendency for cases to result from maternal transmission**

A Canadian publication, reported in 2002 by Fung *et al.*[39] involved six affected individuals across two families, with both families showing autosomal dominant inheritance and genetic anticipation.

In 2002, a research letter by Lynch *et al.* described eight families with autosomal dominant Ménière's disease, six showing definite genetic anticipation, as commented upon by the authors.[40] One family involved siblings only, and the eighth family included an unspecified youngster.

A recent Finnish paper[8] suggested autosomal dominant inheritance as the most likely mode in most of the reported families.

These studies seem to converge on autosomal dominant inheritance as the most likely mode, over

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TABLE II

MÉNIÈRE'S DISEASE DIAGNOSTIC SCHEMA AND SEVERITY SCALES

Diagnostic status	AAO-HNS CHE criteria	AAO severity scale	Morrison severity scale
Definite	Vertigo: ≥2 attacks >20 mins Hearing loss: 25 dB on affected side Tinnitus present or aural fullness present	Stage 1: ≤25 dB Stage 2: 26–40 dB Stage 3: 41–70 dB Stage 4: >70 dB Functional scale (0–6) for degree of vertigo-related incapacitation	Class 1 (mild): ≤35 dB Class 2 (moderate): 35–50 dB Class 3 (severe): >50 dB to sub-total; bilateral; 'drop attacks'; patients with AAO incapacity scale scores of 4–6
Probable	Vertigo: ≥1 attack Hearing loss: present & measured on ≥1 occasion Tinnitus present or aural fullness present		
Possible	Vertigo: present (Ménière type, but without hearing loss) or Hearing loss: present, fixed or fluctuant, with disequilibrium but no definite episodes		

AAO-HNS CHE = American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and equilibrium; mins = minutes

a wide range of sources. Apparent age-of-onset genetic anticipation is widely prevalent. Several kinds of objection have been raised to the possibility of genetic anticipation. The primary objection is that apparent anticipation is due to ascertainment bias, that is, for every pair characterised by late onset in the parental generation and early onset in the offspring generation, there should be a corresponding pair with early onset parent and a late onset offspring. The latter are argued to be less often ascertained, because the offspring have not yet developed their disease and/or the parents have died or been less fertile because of their severe disease. The ascertainment scheme employed in the collection of the authors' family series was susceptible to the former bias, but there is no evidence that Ménière's disease patients die early or have significantly reduced fertility, ruling out one potential source of bias. The best that can be said is that the jury is still out, and that rigorous analyses of a larger series with correction for all known forms of ascertainment bias is required before the question can be settled.

Conclusion

Ménière's disease is usually sporadic, but in about 5 per cent of cases there is a positive family association. Between 1992 and 2005, 61 families with possible familial disease were identified in the UK. Full pedigrees were checked. After stringent reassessment of these families, based on the American Academy of Otolaryngology–Head and Neck Surgery committee on hearing and disequilibrium 1995 diagnostic criteria, 15 families were excluded. The remaining 46 families with familial Ménière's disease represented a unique series and have been studied further. Within these families, 120 individuals suffered classical Ménière's disease. Autosomal dominant inheritance with reduced penetrance (approximately 60 per cent) was the most likely mode of inheritance overall. Apparent genetic anticipation was observed, but caution should be exercised as this finding may also have been a result of ascertainment bias given the collection strategy. There was perhaps a mild female predominance for familial Ménière's disease in the series, and a strong tendency for females to be diagnosed with partial Ménière's syndromes. There was also a slight tendency for cases to result from maternal transmission within the families in this set, and for affected offspring to be of the same sex as their affected parent. All of these observations may also be influenced by the recruitment strategy, which may have resulted in an ascertainment bias towards families with more female cases. The family pedigrees are presented, and a website has been set up by the authors to allow clinicians to view the families in greater detail. Genetic mapping studies have been carried out and will be reported elsewhere.

Acknowledgements

Grateful thanks go to Yvonne Lowe and Carlos Celis Morales for their assistance with the family pedigrees and graphical preparations for this manuscript.

Supplementary material

Supplementary Figures are available online at http://www.jlo.co.uk.

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Mr G A J Morrison takes responsibility for the integrity of the content of the paper.
Competing interests: None declared