FAMILIAL MÉNIÈRE'S DISEASE: CLINICO-GENETIC ASPECTS

A W MORRISON, MB ChB FRCS DLO,· M E S BAILEY, B.Sc. Ph.D.,$ G A J MORRISON, MA MB.BS FRCS# **

·Late Hon Consultant Otologist, The Royal London Hospital

#Consultant, Department of Otolaryngology, Guys and St Thomas' NHS Trust

$Division of Molecular Genetics, Institute of Biomedical and Life Sciences, University of Glasgow.

**Corresponding author:

Mr Gavin A. J. Morrison,

Dept. Otolaryngology

St Thomas' Hospital,

London SE1 7EH.

E-mail: GAJM@GavinMorrison.com

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 MD cases from the U.K.

Methods: Forty-six affected families have been studied. All cases were diagnosed using AAO-HNS CHE 1995, or more stringent, criteria.

Outcome/Results: Autosomal dominant inheritance with reduced penetrance was the most likely mode of inheritance overall. Apparent genetic anticipation is 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 a website has been set up to allow professionals to view the family set in greater detail. (148 words)

Key Words: Ménière's disease. Familial. Epidemiology. Genetics. Dominant. Anticipation

INTRODUCTION

Ménière's disease comprises 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 and tinnitus will exacerbate and the hearing loss will become worse, then recovering fully or partially after the episode. The disease runs in quiescent and then in more active periods in which 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 more or less cease completely, but by this time the 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 (AAO-HNS CHE) 1995 guidelines for the diagnosis of MD are widely accepted [1] and diagnosis requires the combined presence of 3 different clinical features: (i) at least two attacks of vertigo lasting 20 minutes or longer, (ii) the presence of either aural fullness or tinnitus (or both) and (iii) a sensorineural hearing loss on the affected side of at least 25dB worse than that on the non-affected side, (taken as the average threshold for 0.05, 1.0, 2.0 and 3.0 kHz).

Incidence. Ménière's disease (MD) 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.

3

The data in grey bars in Figure 1 show the age of onset distribution of 406 sequential patients presenting to the authors with sporadic MD. These new data are an extension of the previously published series [2]. Figure 1 also shows, for comparison, the younger age of onset distribution found in familial MD cases (black bars), based on the 46 families being reported in this paper.

Globally the great majority of Ménière's cases are sporadic, there being no other close family members similarly affected. Reported cumulative lifetime incidence for MD varies greatly, ranging from as low as 0.8 per 1,000 in Italy [3] to as high as 1.57 per 1,000 in the UK [4]. Harrison and Naftalin [5] proposed a UK figure of 1 per 1000, which seems a fair estimate. In 1983 Watanabe [6] reviewed the published reports. Frieberg and Stahle did so more recently [7]. In Finland, an extrapolated prevalence estimate of 0.43 per 1,000 was reported [8]. The Swedish figure [9] of 0.46 per 1,000 (*circa* 1 in 2000), coming from a well-documented homogeneous population, seems the most acceptable.

Ethnic Distribution. Ménière's Disease is predominantly a disease of Caucasians or 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 [11] reported its rarity in the Bantu. A similar picture came from the West Indies in 1967 [12]. Gibson commented on its rarity in those of Afro-Caribbean origin [13]. Also in 1979, Wiet noted the near absence of MD in American Indians [14]. In Japan the incidence is lower than in Europe, at about 0.035 - 0.160 per 1,000 depending upon which survey is accepted [6]. All these findings support the conclusion that incidence of MD varies between populations of different continents .

Familial Ménière's disease is now a well-recognised entity, but was not in 1941 when Brown [15] described two brothers with MD whose symptoms had started at ages 49 and 50, respectively. She followed this with a second report in 1949 of two families [16]. The first consisted of three definite MD 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; the diagnosis was probably otosclerosis.

After a gap of nearly twenty years, in 1965, Bernstein [17] published on familial deafness and vertigo. In 1967 Hinchliffe's [18] clinical record on psychosomatic aspects of MD contains mention of familial cases but it is difficult to assess their frequency; we can surmise that there were perhaps two affected sib pairs from 42 cases, giving a frequency of approximately 5%.

There was another significant hiatus until 1981, when Morrison [19] reported that five of 190 patients with MD had a positive family history, a frequency of 2.6 per cent. About the same time an epidemiological study from Japan [20] found that 5.8 per cent of MD patients had an affected close relative. In 1992 there was also a report of two Italian families by Martini [21]. Two further publications merit comment. In 1984, from Sweden, Birgerson et al [22] reported the frequency of familial MD to be as high as 12 per cent (11 familial from 91 MD patients); the latter figure is based largely on a questionnaire, which can be misleading: this paper was largely reproduced in 1987 [23]. A recent paper from Finland gives a comparable figure of approx. 15 per cent [24]. In our second paper, also in 1987 [25], we reported 35 first degree relatives from a series of 671 confirmed MD patients (5.4 per cent) rising to an overall frequency of familial cases of 7.7 per cent if second and third degree relatives were included:

these figures however were extracted from the family history in clinical records without actual diagnostic confirmation in many of the relatives. The 5.4% in first-degree relatives is probably reasonably accurate. Two further recent reports [26, 27] describe medium-to-large multiply-affected families.

If familial MD was encountered in clinical practice with a frequency as high as 7.7 % or 12 %, this finding would be very apparent. The paucity of such reports over the years and the difficulty in collecting a sizeable series argues against such figures. One is left with the impression that a figure for the frequency of familial MD 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 MD, 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 than dizygotic twins, has not been reported, presumably because of the relative rarity of affected twins.

MATERIALS AND METHODS

THE FAMILIAL SERIES.

Ascertainment - Our search for UK Caucasian families with more than one living member considered to have MD started in 1992. The majority were ascertained in the first few years [28, 29]. Most came from private practice, a few from the UK National Health Service (NHS), some from a circular letter to UK ENT surgeons, and a small number from the Ménière's Society, a patient support group. In 1993, after the 6pm Carlton TV news, the senior author (AWM)

was given a few minutes to appeal for such families; hundreds of letters were forwarded, but only six possible families were ascertained.

A circular letter was given, or sent, to all propositi requesting a copy of their family tree based on a provided example. Likely MD families were contacted and requested to attend with appropriate unaffected family members, all expenses being offered. The response and cooperation was one hundred per cent. The family pedigrees and clinical data were collected and assimilated using Cyrillic 2 software (Cherwell Scientific Publishing Ltd.). Ethical approval for this ongoing work and our subsequent genome search for genes predisposing to MD was obtained from Cambridge Local Research Ethics Committee, REC ref 02/375.

Exclusion criteria - After examination, several families were excluded, only one member having classical MD, the other(s) having any of a variety of other vestibular problems. One, for example, had MS, one a moderately large acoustic neuroma, one otosclerosis plus BPPV and another, the Chiari malformation. There were three children with a congenital anomaly of one ear who, in childhood, developed the classical features of MD, one having, on CT scanning, an osseous dilatation of the superior semicircular canal.

The family set - By 1994, from twelve possible families, only eight were suitable for inclusion in a paper also concerned with environmental factors [28]. By 1995 [29] after further exclusions, forty-one families with eighty-nine MD-affected cases were included in the series and by 2002 [2] the series consisted of 46 families with 118 affected individuals. Since then, some of these have been excluded after revision of their diagnosis. Many of the families have been followed up at regular intervals by one or other of the authors over the past fourteen years. A few new families have been added.

The total series now comprises 61 families who were investigated with a possible history of familial Ménière's disease. 60 contain >1 sufferer of MD or one MD case and one or more with partial vestibular syndromes but not certain MD. Of these, 46 families have currently been confirmed as having two or more family members with classical Ménière's disease.

Sampling - Affected and unaffected family members gave venous blood samples from which genomic DNA was extracted at St Mary's Hospital Medical School, London or at the Regional Genetics Laboratory at Addenbrooke's Hospital in Cambridge. Repeat samples were also stored at Addenbrooke's. Being a disease of late onset, unaffected youngsters below the age of 16 were not subjected to venepuncture.

Clinical characterisation. Diagnostic schema - Personal interview and full clinical examination by the authors confirmed the diagnosis in almost all cases. In a few, 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 (AAO-HNS) Committee on Hearing and Disequilibrium (CHE) has issued guidelines three times on the diagnosis and treatment assessment, in 1972, 1985 and 1995 [31,32,1]. The 1995 AAO-HNS CHE guidelines are widely accepted. As mentioned above, a diagnosis of full/definite MD requires satisfaction of at least three clinical and audiometric criteria, either tinnitus or aural fullness, at least two attacks of vertigo lasting 20 minutes or longer, and sensorineural hearing loss on the affected side of 25 dB or worse. There is a severity staging system based only on the average hearing thresholds, Stage 1 being<=25dB: Stage 2 being 26-40dB: Stage 3 measuring 41-70dB: and Stage 4 >70dB. 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.

Our collection of the familial MD series started in 1992, three years before the AAO-HNS CHE guidelines appeared. We initially employed our own severity classification (on a scale of 1-3), which depended, to some extent, upon when the patient was first examined in relation to the natural history. In the very early stages there can be a diversity of vertiginous symptoms such as transient dizziness with fluctuant hearing loss, later classical episodes lasting up to 24 hours, and with the passage of time, amelioration 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 bilateral disease and drop attacks were designated class 3, likewise those whose symptoms were so severe as to be incapacitating, equating to the AAO-HNS CHE scales 4, 5 or 6. For hearing loss severity, our classification, though not based on deafness levels, turned out to be similar to AAO-HNS CHE; stage 1 patients mostly had moderate losses of up to 35dB; our stage 2, losses of 35dB-50dB; and stage 3, losses over 50dB, sometimes subtotal. During follow-up in many families over the fourteen years some scaling changes were made, usually for the worse, based mainly on the deafness severity or the need for destructive surgery. A few deaths have occurred among both affected and unaffected.

Stahle et al [33] have reviewed the natural history confirming that, with the passage of time, second ear involvement increases, approaching 50 per cent after 20 years. They found that the main cochlear and vestibular symptoms and damage were in the first five to ten years and that thereafter hearing thresholds stabilised at 50dB-60dB. Morrison [34] in an assessment of 330 patients with sporadic MD was in general agreement save that after fifteen years

continued hearing deterioration was noted. This also applies to familial MD cases, some finishing with sub-total hearing loss. An examination of the cochlear implant literature will confirm this.

Reclassifications - Partial Syndromes.

Prior papers on our families [2, 28, 29] have included a few individuals labelled vestibular or cochlear MD. The 1972 AAO-NHS CHE guidelines [31] included both of these sub varieties. It was assumed, as with any such study, that phenocopies had been excluded. The 1995 criteria [1] exclude such variants, instead defining Probable and Possible MD accepting that over time the full symptom complex could develop.

Probable MD is 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 MD has two definitions:-

1. Episodic vertigo of the Ménière type without documented hearing loss.
2. Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definite episodes.

We have re-examined all the previously designated cases with partial syndromes and altered them to the most recent AAO-HNS CHE guidelines. The reclassified status of these individuals is not always an accurate reflection of their clinical phenotype. Take, for example, the individual IV:4 in Family MX (see Figure 3). This lady has episodic classical attacks lasting two to four hours, on and off for years. Prior to each attack, she experiences tinnitus and an uncomfortable blocked sensation (? hearing loss), always in her right ear, but

no hearing loss has ever been documented. This now has the lesser description of Possible

MD. When considering partial syndromes, it is well to remember that though half of MD

patients develop the full symptom complex within six months, one third experience deafness

and tinnitus only and one fifth episodic vertigo alone for periods in excess of six months,

sometimes even for years [34]. During the first five years, in a substantial majority, hearing

thresholds can revert to normal limits [34]. Thus in a near certain MD case, objective hearing

loss may be missed. 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 MD. Sometimes a true attack starts in bed

when turning on the affected side. At some stage in the natural history, usually when well

developed, many patients experience transient positional episodes indistinguishable from

classical benign paroxysmal positional vertigo (BPPV). These are recorded in the pedigree, as

are the finding of unaffected relations also with BPPV. There are several causes of positional

vertigo that have been analysed by Morrison and Morrison [35]. The two commonest are,

firstly, idiopathic (44 per cent) and, secondly, following one or more attacks of vestibular

failure (22 per cent) usually presumed to be viral. These both have features in common

including a 3:2 female/male ratio, an onset age showing a normal distribution around the fifth

decade, and active and quiescent spells, akin to MD. Hearing is unaffected. The Hallpike

manoeuvre confirms the peripheral nature, a 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. The

clinical diagnosis of isolated benign paroxysmal positional vertigo (BPPV) however is very

distinct from that of MD 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. BPPV can therefore 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 families were eventually excluded from further consideration, leaving 46 families confirmed as having two or more family members with classical Ménière's disease (definite MD under the AAO-NHS CHE 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 benign paroxysmal positional vertigo (BPPV). In several of the 46 families there were individuals with non-MD-related causes of hearing loss (e.g. post-infection or congenital).

Of the excluded 15 families, at the end point of this study, 14 have 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 has one member with Ménière's disease and one member with a congenital ear anomaly only.

From the series of 46 confirmed multiply-affected families, the 18 pedigrees that were considered most appropriate for our genetic analysis (implemented in a subsequent Genome Scan, manuscript *in preparation*.) are published here in full electronically, in the Journal of Laryngology & Otology (electronic reference to be inserted) and a recently added 19th family (family A-A) is included. A further 9 families were included as part of a larger screening panel of affectands and some of these were used in screening for candidate genes (manuscript

in preparation). This entire series of 46 pedigrees, in ongoing draft research format can be seen in full at www.GavinMorrison.com.

Inheritance patterns and parameters –

Of the 46 families, 27 have 2 affectands, 12 have 3 affectands, 6 have 4 affectands and one family has had 5 members with Ménière's Disease. Of those families (n = 14) with affected sibling pairs, 10 also have one affected parent and 4 have parents without disease.

Sex ratios In the entire set of 61 families with cases of definite MD there are a total of 75 affected females and 62 males, giving a female : male ratio of 1.21. This is a weaker female predominance than previously noted [29]. Interestingly however, if the sex ratio of the patients with partial syndromes is included (31 females and 5 males) the female preponderance becomes much stronger (F:M = 106:67, approximately 1.6 : 1). Amongst the 46 families with multiple MD affected members, 63 definite MD cases were female and 57 were male, again only a marginal predominance of females.

Age of onset & Anticipation **–** The distribution of age of onset for the familial cases in our series is shown in Fig. 1. The age of onset in familial cases differs from sporadic MD, the peak onset being in the fourth rather than the fifth decade. 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 anticipation has been shown to involve a causal pathway characterised by mutation of specific tracts of DNA sequence consisting of 3-base tandem repeats (trinucleotide repeats), where increased severity and decreased age of onset are associated with increases (expansions) in the number of repeats

present in each successive generation, (hence, trinucleotide repeat expansions). Our pedigrees, with few exceptions, demonstrate apparent anticipation, certainly regarding age of onset, and to a lesser extent regarding disease severity; this was also 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. Figure 2 demonstrates this apparent anticipation graphically with all points appearing on or below the line. In the 35 patients with an age of onset under 30 years, ten have bilateral disease suggesting that severity is increased in families with early-onset cases, perhaps reflecting a stronger genetic influence on predisposition. The incidence of bilateral disease in sporadic MD in those under 30 years old, in comparison has never been reported but the authors estimate it to be no greater than 10% - 15 %. Some caution should be exercised over this conclusion of anticipation however, 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 8 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 anticipation.

Examining the 19 family pedigree published electronically here in full (electronic JLO journal reference), 55 patients had MD, of whom 12 were bilaterally involved. Of these 55, 23 were classified as stage 3 (severe) disease, 23 were classified as stage 2 and only 7 were found to be stage 1 (mild) disease. Of these 19 families, 15 showed a progression in the staged severity of disease through a descending generation, while only 3 showed no progression and only one exhibited a less severe grade in descendants. These individual data are available on the pedigree charts for the entire series at www.GavinMorrison.com.

Mode of inheritance

Of the 46 families, 32 exhibit 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 a direct transmission to 3 offspring was noted. Three families also show a linear transmission directly through two generations from grandparent to parent to child. Male to male transmission is observed and there is 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 is most consistent with autosomal dominant inheritance. Under this hypothesis, we estimate penetrance in all 46 families to be about 60%, some pedigrees appearing to have segregation ratios consistent with full penetrance. Family GW, (figure 3) 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 MX (figure 3) in view of the consanguinity in this family. Two of four offspring of the unaffected cousin marriage in MX are affected, however (we consider individual IV:4 likely to be affected although we have not treated her as definite MD in our analyses; see foregoing discussion in Methods section on diagnosis and partial syndromes), and the third affected is in the parental generation, making recessive transmission less likely unless a common allele exists 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.

Sex-ratio transmission bias

Transmission ratios are biased (P < 0.001 Fisher's Exact Test for overall comparison), as illustrated in Table 1. Females tended to transmit to female offspring and males to male offspring (P<0.001 and P<0.05, respectively; Chi-squared tests with continuity correction, 1 d.f.). There is also an overall bias favouring transmission from mothers over transmission from fathers (P<0.04; Chi-squared with continuity correction = 4.4). The interpretation of these data, however, has to be made bearing in mind that from our series, for all female affectands who showed direct MD 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 on to affected daughters. Overall, there is no significant bias in the proportion of transmissions to sons vs daughters (P>0.2, Chi-squared with continuity correction).

DISCUSSION

Transmission characteristics and segregation ratios – Previous reports have differed as to whether the sex ratio is equal amongst MD patients. Some reports have concluded an equal ratio for sporadic Ménière's disease [34], while others report a modest female preponderance [33]. The senior author's earlier series of Familial MD however, reported a preponderance of affected females, 70, compared with 49 affected males [29]. Examination of the pedigrees in this current updated larger series now suggests only a very weak female predominance. However, when the patients with partial syndromes were included in the sex ratio analysis, the female predominance becomes much stronger. Why more females appear to have partial syndromes remains unclear.

Mode of inheritance

Martini [21] reported two families suggesting autosomal dominant inheritance. The first consisted of three affected individuals, a mother and two daughters all with an early age of onset. The second covered three generations of affected males and showed apparent anticipation, though this was not mentioned in the paper. Birgerson et al. [36] provided eleven pedigrees. They concluded that eight of the families were compatible with either autosomal or an 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. This paper is concerned also with autoimmune disease. No age of onset data are provided. In 1992 a Brazilian report by Oliveira and Braga [37] suggested autosomal dominant inheritance based on one family: the affected father had two of eight children with MD and when widowed his second family of six produced one with MD. Though not commented

upon, this family shows possible anticipation.

From Essen in Germany, Arweiler et al [38] describe five families with apparent autosomal dominant inheritance. Anticipation is recorded, especially in their four-generation family E, the age of onset in the generation F1 being of the order of 50 years, falling to 20 years in F4. A Canadian publication, reported in 1992 by Fung et al [39], involved six affected across two families, both families showing autosomal dominant inheritance and anticipation. In 2002 a research letter by Lynch and Cameron [40] described eight families with autosomal dominant MD, six showing definite anticipation on which they comment. One family involved siblings only and the eighth included an unspecified youngster. The recent Finnish paper [8] suggests autosomal dominant as the most likely mode in most of the reported families.

These studies seem to converge on autosomal dominant as the most likely mode of inheritance over a wide range of sources. Apparent age-of-onset anticipation is widely prevalent. There have been several kinds of objection raised to the possibility of genetic anticipation. The primary objection is that apparent anticipation is due to ascertainment bias – 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 late onset offspring. The latter are argued to be less often ascertained because the offspring have not yet got 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 this family series was susceptible to the former bias, but there is no evidence that MD 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 are required before the question can be settled.

In conclusion, Ménière's Disease is usually sporadic but in about 5% there is a positive family association. Between 1992 and 2005, sixty-one families with possible Familial Disease were identified in the UK. Full pedigrees were checked and after stringent reassessment of these families based on AAO-HNS CHE 1995 diagnostic criteria 15 families were excluded. The remaining Forty-six families with Familial Ménière's Disease represent a unique series and have been studied further. 120 individuals from within these families have suffered classical Ménière's Disease. Autosomal dominant inheritance with reduced penetrance (approximately 60 %) was the most likely mode of inheritance overall. Apparent genetic anticipation may be observed, but as a caution, this may also be a result of ascertainment bias given the collection strategy. There is 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 to allow professionals to view the families in greater detail. Genetic mapping studies have been carried out and will be reported elsewhere.

REFERENCES

1. Committee on Hearing and Equilibrium guidelines for diagnosis and evaluation of therapy in Ménière's disease. Otolaryngol Head and Neck Surg. 1995; **113**: 181-185

2. Morrison AW, Johnson KJ. Genetics (molecular biology) and Ménière's disease. In Otolaryngol Clin N Am 2002; **35**: 497-516

3. Celestino D, Ralli G. Incidence of Ménière's disease in Italy. Am J Otol 1991; **12**: 135-138

4. Cawthorne T, Hewlett AB. Ménière's disease. Proc Roy Soc Med 1954; **47**: 663-70

5. Harrison MS, Naftalin L. Ménière's Disease: Mechanism and Management. Thomas CC Springfield IL, 1968

6. Watanabe I. Incidence of Ménière's disease, including some other epidemiological data. In: Oostervld WJ, ed. Ménière's disease. A comprehensive appraisal. J Wiley & Sons, Chichester, 1983: 9-23

7. Frieberg V, Stahle J. The epidemiology of Ménière's disease. In: Ménière's disease, Ed Harris JP. Kugler Publications, The Hague, 1999: 17-28

8. Kotimäki J, Sorri M, Aantaa E, Nuutinen J. Prevalence of Meniere disease in Finland. Laryngoscope 1999; **109**; 748-753

9. Stahle J, Stahle C, Arenberg IK. Incidence of Ménière's disease. Arch Otolaryng 1978; **104**: 99-102

10. Caparosa RJ. Medical treatment of Ménière's disease. Laryngoscope 1963; **73**: 666-672

11. Fick IA van N. Decompression of the labyrinth. Arch Otolaryg 1964; **79**: 447-458

12. Ashcroft MT, Cruickshank EK, Hinchcliffe R et al. A neurological,

ophthalmological and audiological survey of a suburban Jamaican community. West Ind Med J 1967; **16:** 233-245

13. Gibson WPR. The physical and functional examination of the ear. In Scott-Browne: Diseases of the ear nose and throat, 4th ed. vol 2. London, Butterworths; 1979: 1-48

14. Wiet RJ. Patterns of ear disease in south-western American Indians. Arch Otolaryng (Chicago) 1979; **105**: 381-385

15. Brown MR. Ménière's syndrome. Arch Neuro Psy 1941; **46**: 561-565

16. Brown MR. The factor of heredity in labyrinthine deafness and paroxysmal nystagmus (Ménière's syndrome) Ann Otol Rhinol Laryngol 1949; **56**: 665-670

17. Bernstein J M. Occurrence of episodic vertigo and hearing loss in families. Ann Otol Rhinol Laryngol 1965; **74**: 1011-1021

18. Hinchcliffe R. Personal and family medical history in Ménière's disease. J Laryngol Otol 1967; **81**: 661-668

19. Morrison AW. Ménière's disease. J R Soc Med 1981; **74**: 183-189

20. Mizukoshi K, Ino H, Ishikawa K et al. Epidemiological survey of definite cases of Ménière's disease collected by the seventeen members of the Ménière's disease research committee of Japan in 1975-1976. Adv Otorhinolaryngol 1979; **25**: 106-111

21. Martini A. Hereditary Ménière's disease; report of two families. Am J Otolaryngol 1982; **3**: 163-167

22. Birgerson L, Gustavson K-H, Stahle J. Familial Ménière's disease. A genetic investigation. Acta Otolaryngol (suppl) (Stockh) 1984; **412**: 71-73

23. Birgerson L, Gustavson K-H, Stahle J. Familial Ménière's disease: A genetic investigation. Am J Otol 1987; **8**: 323-326

24. Klockars T, Kentala E. Inheritance of Ménière's disease in the Finnish population. Arch. Otolaryngol. Head Neck Surg. 2007; **133**; 73-77

25. Morrison AW, Xenellis J. immunological aspects of Ménière's disease. In Veldman JE, ed. Immunology, histopathology and tumour immunology. Amsterdam: Kugler 1987: 9-14

26. Frykholm C, Larsen HC, Dahl N, Klar J, Rask-Andersen H, Friberg U. Familial Ménière's disease in five generations. Otol Neurotol. 2006 **27**:681-6

27. Oliveira CA, Messias CI, Ferrari I. Occurrence of familial Ménière's syndrome and migraine in Brasilia. All Otol Rhinol Laryngol 2002; **111**:229-236

28. Morrison AW, Mowbray JF, Williamson R, Sheeeka S, Sodha N, Koskinen N. On genetic and environmental factors in Ménière's disease. Am J Otol 1994; **15**: 35-39

29. Morrison AW. Anticipation in Ménière's disease. J Laryngol Otol 1995; **109**: 499-502

30. Morrison AW. Diagnostic and laboratory evaluation of Ménière's Disease. in: Ménière's disease, Ed Harris JP. Kugler Publications, The Hague, 1999:291-304

31. Committee on Hearing and Equilibrium. Ménière's disease: criteria for diagnosis and evaluation of therapy for reporting. Trans Amer Acad Ophth Otolaryngol 1972; **76**: 1462-1464

32. Committee on Hearing and Equilibrium. Ménière's disease: criteria for diagnosis and evaluation of therapy for reporting. AAO-HNS Bulletin 1985; **5** (July): 6-7

33. Stahle J, Friberg U, Svedberg A. Long-term progressive of Ménière's disease. Acta Otolaryngol (Stockh); Suppl 1991; **485**: 78-83

34. Morrison AW. Endolymphatic hydrops. In: Management of Sensorineural Deafness. Ed. Morrison AW London and Boston, 1975: 145-174

35. Morrison GAJ, Morrison AW. On Benign paroxysmal positional vertigo. Natural history and causation. In: Long-term Results and Indications in Otology and Otoneurosurgery. Ed: Charachon R, Garcia-Ibenez E. Kugler & Ghedini Publications. Amsterdam/Milan/New York. 1991: 269-272

36. Birgerson L, Gustavson K-H, Stahle J. Familial Ménière's disease. Acta Otolaryngol (Stockh) Suppl. 1984; **412**: 71-73

37. Oliveira CA, Braga AM. Ménière's Syndrome Inherited as an Autosomal Dominant Trait. Ann Oto Rhinol Laryngol 1992; **101**: 590-594

38. Arweiler DJ, Jahnke K, Grosse-Wilde H. Morbus Ménière ALS autosomal dominant vererbte Erkrankung. Laryngo-Rhino-Otol 1995; **74**: 512-515

39. Fung K, Xie Y, Hall SF, Lillicrap DP, Taylor SA. Genetic basis of familial Ménière's disease. J Otolaryngol 2002; **31:**1-4

40. Lynch M, Cameron TL, Knight M, Kwok TY, Thomas P, Forrest SM, Giersch AB, Briggs RJ, Pyman BC. Structural and Mutation Analysis of Antiquitin as a Candidate gene for Ménière's Disease. Am J Med Genet 2002; **110**; 397-399

LEGENDS TO FIGURES

Legend for Figure 1

Comparison in Age of Onset of Sporadic Ménière's Disease vs Familial Ménière's Disease.

(In bilateral cases the age of onset refers to the first affected ear. Sporadic MD n = 406,

Familial MD n = 116).

Legend for Figure 2

The graph shows age of onset (AOO) in parent-child pairs amongst the families reported here. One pair has been selected per family. Where more than one possible pair was present, the most conservative (smallest difference in AOO between the generations) was usually chosen. Where the most conservative pair included the proband, the alternative pair was chosen instead. This helps control for proband selection bias. Two series are plotted, those where the proband was in the parental generation (proband parent) and those where the proband was in the offspring generation (proband child). The diagonal line indicates equity of AOO between generations.

Legend to Figure 3

Familial Ménière's Disease Pedigrees of 19 families

Key to figure 3

◯ = Unaffected Female

● = Affected Female

☐ = Unaffected Male

■ = Affected Male

[?] = Partial Syndrome (possible or probable MD)

↗ = Proband

Horizontal line above individual = has been personally examined for diagnosis or exclusion of diagnosis by authors

'BPPV' = benign paroxysmal positional vertigo in probable and possible MD cases and in unaffected relatives

'nn yrs' = age of individual in 2003 or age at death

'Onset nn yrs' = age of affected individual at first clear symptom of MD

Legend to Table 1

Transmission patterns by gender in the 46 families

Table 1

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

Legend to Table 2

Diagnostic schema and severity scale

Table 2

Diagnostic Status	AAO-HNS CHE criteria	AAO Severity scale	Morrison Severity Scale
Definite	Vertigo – ≥2 attacks >20mins Hearing Loss – 25dB on affected side Tinnitus – Present or Aural Fullness - Present	Stage 1 - ≤25dB Stage 2 - 26-40dB Stage 3 – 41-70dB Stage 4 - >70dB Functional Scale – 0-6 for degree of vertigo-related incapacitation	Class 1 (Mild) – ≤35dB Class 2 (Moderate) – 35-50dB Class 3 (Severe) - >50dB to sub-total; bilateral; drop attacks; patients with AOO incapacity scale scores of 4-6
Probable	Vertigo – ≥1 attack Hearing Loss – Present and 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		

SUMMARY

- Ménière's disease (MD) is not uncommon, with an incidence in Caucasians of about one in 2000. It is of midlife onset, peaking in the fifth decade.

- It is known that cases are usually sporadic, but in a small proportion other family members are affected.

- We report here the clinical and genetic characteristics of the largest comprehensive set of familial MD cases yet identified, all from the U.K. Over 12 years, 61 families with multiple members suffering vestibular symptoms were identified. Of these 46 families had more then one member with true MD and these families contain 120 MD patients, who have been comprehensively studied.

- Familial cases of Ménière's Disease in the UK make up about 5% of the MD population.

- Autosomal dominant inheritance with reduced penetrance was the most likely mode of inheritance overall. Apparent genetic anticipation is 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 a website has been set up to allow professionals to view the family set in greater detail.

- Genetic mapping studies from these pedigrees have been carried out and will be reported shortly in independent publication.