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Anticipation in Menière's disease

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Abstract
The aetiology of Menière's disease (MD) remains obscure, but is likely to be multifactorial, one of the factors being a genetic predisposition. Forty-one families with more than one living member with MD were ascertained and affected and normal relations examined. Blood was collected and DNA extracted and stored. In these families the mode of inheritance is autosomal dominant, the penetrance of the mutation being about 60 per cent. Some of the family members exhibit a partial syndrome, vestibular symptoms predominating. Sporadic and familial cases exhibit the same clinical features. The striking finding is the phenomenon of anticipation, whereby with successive generations there is an earlier age of onset and a tendency to more severe manifestation. The inference, considering that the cells which regulate endolymph are of neuroectodermal origin, is that, like other neurodegenerative disorders which show anticipation, MD manifestation is likely to be related to trinucloetide expansion within a gene.

Key words: Menière's disease; Genetics, Autosomal dominant inheritance, Anticipation

Introduction

There have been several reports of familial Menière's disease (MD) dating from Brown in 1941. These were reviewed by Morrison *et al.* (1994), the reported incidence of familial as opposed to sporadic cases varying from 2.6 per cent to 12 per cent. Morrison & Xenellis (1987), from a series of 671 Menière's patients, reported 36 first degree relatives (5.4 per cent) similarly affected, 14 second degree and six third degree; the overall familial frequency being 52 from 671 propositi or 7.7 per cent. This was compared with a control population of 689 adults with other otological diseases from which number there were four first degree relatives with MD (0.6 per cent).

Menière's disease is commonly encountered in otological practice. Even in general practice, from a list of 4000, three new cases of MD were seen in a six month period, the diagnosis subsequently being confirmed (Griffiths, 1979). It is predominantly a disease of Caucasians. The incidence in Sweden in the 1970s was calculated at 46 per 100,000 (Stahle *et al.*, 1978). Watanabe (1983) reviewed the published reports and concluded that the prevalence in Great Britain was one per 1000, in Sweden circa one per 2000, while in Japan it was either 35 or 160 per million depending upon which survey was accepted. In Ugandan negroes and American Indians it was a rare disease. It is also reported as a rarity in West Indian negroes (Ashcroft *et al.*, 1967). The author, from experience of over 2000 patients with MD, encountered it once in a Jamaican of mixed blood.

Thus two of the three accepted criteria evidencing a genetic predisposition are seen to exist. There is a racial or ethnic distribution and there is familial clustering with a higher frequency in near relatives than in the population. No reports have been found regarding concordance in monozygotic compared with dizygotic twins.

Objectives of present study and methods

The long-term objective is to locate a mutation which predisposes to MD, even though it is likely that there is a multifactorial aetiology. Clinically there is no difference between sporadic and familial cases, both showing variable expressivity of severity and of bilaterality. Genetic heterogeniety seems unlikely. There are, however, two differences; in the familial cases there is a significantly higher number with a childhood or adolescent onset and there are more affected females than males, whereas in spasmodic disease the sex ratio is equal (*vide infra*).

United Kingdom (UK) Caucasian families with more than one living member with MD were ascertained from four sources. Private patients produced 19, a circular letter to otolaryngologists in the UK produced 15, the Menière's Society (a patient support group) produced nine and finally a short television appeal in the London area produced a further six, making 49 families in all. Eight families

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were excluded on diagnostic grounds. The diagnosis was confirmed in affected members by personal interview and examination in almost all, the remaining few having been diagnosed by experienced otologists. In addition, full medical histories were obtained from affected and non-affected relations. Being a disease with a peak onset in the fifth decade, though showing a normal distribution in both sexes (Morrison, 1975), unaffected children were not subjected to blood sampling. Blood was collected from available adults and affected children for DNA extraction and storage. In all 325 persons were assessed.

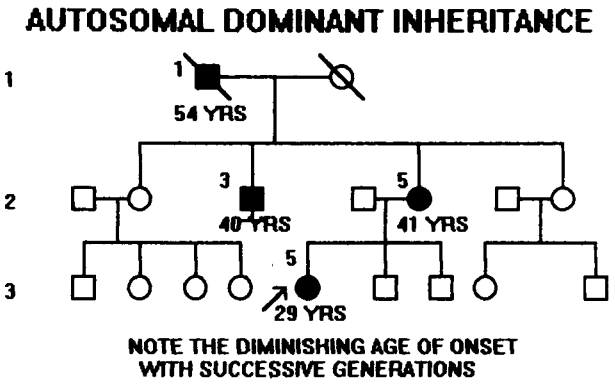

FIG. 1

Results

The mode of inheritance was manifestly autosomal dominant, as shown for example in Figure 1. Note the diminishing age of onset with successive generations. The mating types and their offspring (excluding young) are as follows:

31 Affected Mothers	<	27 Affected Offspring	(4 male: 23 female)
		42 Unaffected	(24 male: 18 female)
19 Affected Fathers	<	19 Affected Offspring	(12 male: 7 female)
		30 Unaffected	(16 male: 14 female)
36 Normal Parents	<	45 Affected Offspring	(18 male: 27 female)
		58 Unaffected	(27 male: 31 female)
1 Both Parents Affected	<	2 Affected Offspring	(1 male: 1 female)
		3 Unaffected	(1 male: 2 female)

In 50 sibships where one parent was affected there were 46 affected and 72 normal offspring. A better estimate of manifestation is shown in Table I, where the gene penetrance is about 60 per cent. In this calculation, to avoid bias, propositi were excluded. In all these families there was only one first cousin marriage. There is one family with a monozygotic twin, one with two dizygotic twins and a third with a dyzygotic twin but as yet none has reached the risk age.

It has previously been shown that sporadic Menière's disease affects the sexes equally (Morrison, 1975). In the present study there is a preponderance of affected females, 70, as compared with 49 affected males. Judging by the offspring numbers, it would appear that this may be because affected females are much more likely to produce affected girls than boys; likewise when both parents are "normal". In this latter situation examination of the family trees revealed a preponderance of a "carrier state" having passed via the mother (11 times) compared with the father (six times).

The next finding of interest was the occurrence within 14 of the 41 families of some members with a partial syndrome. This consisted mostly of vestibular Menière's disease, i.e., classical attacks and tinnitus but without objective hearing loss. Some of these patients also exhibited benign paroxysmal positional vertigo, something which is commonly found from time to time in classical MD. To date, during the two years of this study, some of the partial syndromes have become complete. By comparison cochlear hydrops, fluctuant hearing loss alone, was conspicuous by its absence. Normally one is reluctant to diagnose vestibular MD but it is difficult to ignore this concept when encountered within such families. An example is given in Figure 2 which includes the single cousin marriage. In these 41 families there were 89 patients with classical MD and 39 with the partial syndrome.

Anticipation

The phenomenon of anticipation is defined as the finding of a genetic condition at progressively earlier ages in successive generations.

The age of onset of symptoms was recorded in all affected persons.Within the sibships there were only

TABLE I
DEGREE OF MANIFESTATION IN MENIÈRE'S DISEASE

Relationship to propositi	Number affected	Number normal	Total	Expected ratio	Expected affected	Manifestation in %
1st degree relatives	63	146	209	1/2	104.5	60.3%
2nd degree relatives	26	124	150	1/4	37.5	69.3%
3rd degree relatives	5	62	67	1/8	8.4	59.7%

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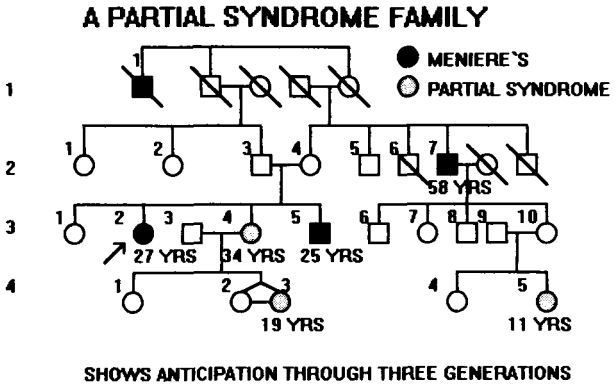

FIG. 2

small differences in the age of onset. From 31 sibpairs the age of onset difference showed an arithmetical mean of 6.16 years with a SD of 5.62.

In every family without exception the disease started at an earlier age with successive generations. From 42 parent/child age of onset differences the surprisingly high mean of 17.45 years emerged with a SD of 9.2.

Reference has been made to childhood onset cases. In sporadic cases the frequency of onset under the age of 20 years is 9/330 or 2.7 per cent (Morrison, 1975). In the present study there are 10 childhood or early adolescence onset cases from 128 affected or 7.8 per cent. Childhood cases, over time, tend to become bilateral and experience shows that they tend to be more severe.

The severity of MD is one of the problems which besets any attempt to assess therapy. The severity classification employed here depended to some extent upon when the patient was examined in relation to the natural history. In the early stages, for example, attacks tend to be more frequent and disabling. In late disease when there is marked hearing loss episodic vertigo assumes less significance and can be replaced by instability. Despite these problems the attempt to classify has been made. The condition has been designated 1, 2 or 3 depending mainly upon the frequency and severity of the vertiginous symptoms. The hearing thresholds tend to be worse with class 2 and 3 disease. The partial syndromes were mainly classed as 1. If they are excluded, there is evidence of increasing severity from one generation to the next. Of 31 parent/child MD cases the severity increased in 14, was in the same category in 14, and decreased in severity in only three.

There is thus ample evidence of significant anticipation in familial MD.

Discussion

In recent years a number of non-Mendelian mechanisms have been found such as imprinting, a one generation phenomenon whereby gene function depends upon its maternal or paternal origin, the example of interest to otolaryngologists being familial chemodectomas. The preponderance of females in this study might suggest such a mechanism.

Mitochondrial disorders form a group of non-nuclear DNA disorders, only females, who supply the cytoplasm for the zygote, transmitting the disease. Familial susceptibility to aminoglycoside ototoxicity is an example. This mechanism can be excluded in MD since there are plenty of examples of affected fathers transmitting the disease.

Anticipation can now be explained in molecular terms. This phenomenon is due to unstable DNA, whereby within the gene trinucleotide repeats are greatly increased in number. When the triplet expansion is sufficiently large the condition becomes manifest; the age of onset and severity of the disorder are related to the number of repeats assuming the threshold has been exceeded. A diminished expansion might also apply in some cases. Thus the skipping of generations, the appearance of apparently sporadic cases, and the incomplete penetrance can be explained. A recent review article has explained the background (Harper *et al.*, 1992).

The three common disorders due to trinucleotide repeat expansions are Huntington's disease, myotonic dystrophy and the fragile X syndromes. Others have been described more recently and there is now a growing list (Willems, 1994). These disorders are of a neurodegenerative nature, often of late onset, and mostly involve cytosine adenine guanine basis (CAG) amplifications, the CAG insert size correlating with the age of onset and severity, the expansion increasing with successive generations and the disease being manifest at a critical expansion.

The aetiology and pathogenesis of MD remains obscure despite much detailed knowledge of the histopathology and ultrastructural abnormalities. It is generally recognized that in the cochlear duct, the stria vascularis and in the vestibular labyrinth the dark cells are responsible for maintaining the electrolyte balances and the electrical potentials. The intermediate of the three cell layers of the stria contains melanocytes and similar pigmented cells are found in close relationship to the secretory dark cells of the vestibular apparatus. The extensive capillary networks are in intimate contact with these pigmented areas. Developmentally they should, therefore, have a neural origin. The embryological development of the inner ear has been eloquently described (Van de Water *et al.*, 1988). For its full development the otocyst, of cephalic ectodermal origin, requires the influence and contribution of the rhombencephalon and the mesoderm, though the neural crest seems to have a minor contribution.

The dense bone of the optic capsule contains a number of mesodermal cartilaginous rests. It is from these that foci of otosclerosis or otospongiosis develops. Otosclerosis is another heredity disease, autosomal dominant and showing incomplete penetrance but, unlike MD, some 70 per cent-80 per cent of cases are familial. The significance of mentioning this condition is that it also displays the phenomenon of anticipation (Morrison, 1967) though at the time

when this was described molecular genetics was in its infancy. From 45 parent/child otosclerotic patients the mean age of onset in the parents was 33.3 years and in their offspring 26.6 years.

Conclusions

Menière's disease is a common disorder with a frequency in Caucasians of between 0.5 and 1 per 1000. About 10 per cent of cases are familial, the remainder being sporadic. It is genetically determined, family studies showing an autosomal dominant inheritance with penetrance of the mutation in some 60 per cent. In the family studies some members exhibit a partial syndrome, vestibular symptoms predominating. The striking feature is the phenomenon of anticipation, whereby with successive generations there is an earlier age of onset and a tendency to more severe manifestations of the disorder; this is reflected in some 10 per cent of the cases having a childhood or adolescent onset. The inference, considering that the cells which regulate the endolymphatic composition and turnover are of neuroectodermal origin, is that, like other neurodegenerative disorders which show anticipation, MD manifestation is likely to be related to the size of a trinucleotide expansion within a gene. This phenomenon can explain the incomplete penetrance, the skipping of generations and even "sporadic" cases. From the stored DNA, the next stage will be a search for such a mutation.

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