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A longitudinal study of unilateral Ménière's disease and clinical evolutionary models

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Abstract

Objective. The heterogeneity of Ménière's disease is presently defined by a variety of subtypes. This study introduced three different subtypes of unilateral Ménière's disease based on the evolution of vertigo crises from their inception.

Method. A longitudinal descriptive study of 327 unilateral Ménière's disease patients was performed. In a subgroup of patients followed from the onset of the disease, 3 subtypes of unilateral Ménière's disease were defined according to the vertiginous crises suffered during the first 10 years of the disorder.

Results. Data was available for 87 patients with unilateral Ménière's disease from the start of their disease (26.6 per cent of the original sample). These patients were grouped into three models according to their symptomatic evolution. Model 3 was associated with a worse hearing prognosis, a greater number of Tumarkin's otolithic crises and the need for surgery. Model 1 presented less hearing loss.

Conclusion. Unilateral Ménière's disease models based on the evolution of vertiginous crises present differences according to aspects such as hearing loss, vertiginous crisis, Tumarkin's otolithic crisis and the need for surgery.

Introduction

The signs and symptoms that define the natural course of Ménière's disease are well known, given the extensive descriptions of the evolution of this disease in patients who have not undergone any surgical or ablative treatment for vestibular function.[1,2] Indeed, it is not always clear what possible effects standard medical treatments will have on the disease course as their effectiveness remains unclear.

After the very first episode, episodes of vertigo are recurrent in Ménière's disease, whether or not they are each associated with the other classic symptoms of the disease that constitute its characteristic triad of symptoms: tinnitus, vertigo and hearing loss. However, the way that the behaviour of the disease evolves as a function of the number of vertigo episodes is still not clear. From the first year of the disease, there is a gradual decrease in the number of vertigo episodes over the first 8 years of the disease, which is followed by a subsequent stabilisation and then by a mild and progressive decrease in the following 10 years.[3] However, there are reports of a gradual increase in the number of seizures per year in those patients who have experienced episodes for more than 10–15 years.[4,5] In contrast, Ménière's disease is also associated with periods of remission in which the individual does not experience an episode of vertigo, with a variable duration between the episodes of vertigo[2,6] that may ultimately lead to a complete cessation of the episodes of vertigo. We do not know how or when these periods of remission arise, yet it has been proposed that 70 per cent of patients who do not have episodes of vertigo for one year will not experience any episode during the following year.[3]

Although the course of the vertigo episodes in Ménière's disease is well-defined for the general population of Ménière's disease patients, it does not accommodate the wide clinical variability presented by each patient. In addition, there is considerable heterogeneity regarding the evaluation of these episodes of vertigo, their duration and intensity. The heterogeneity among patients with Ménière's disease, not only in the course of vertigo episodes but in several other aspects of the disease, makes us think that there are different subtypes of Ménière's disease. In recent years, new studies have emerged that attempt to explain this variation or the heterogeneous behaviour of the disease and attempt to identify clinical subgroups to help explain the different forms of the disease.[7–9]

Objectives

After analysing the course of the disease in a very large series of patients who were followed since onset of the disease, we found that the evolution of the symptoms in patients

Main Article

Dr T Pérez-Carbonell takes responsibility for the integrity of the content of the paper

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differed based on the annual number of vertigo episodes in the first 10 years of the disease. Therefore, we wanted to assess the possible existence of subtypes of Ménière's disease based on the frequency of vertigo episodes in the initial years of the disease, and help to define the natural evolution of unilateral Ménière's disease.

Materials and methods

A longitudinal descriptive study was carried out on patients with unilateral Ménière's disease from two referral centres. The patients' data were collected and stored from 1977 to 2018, after which the data collected was processed and analysed. During the period of patient inclusion in the study, different diagnostic criteria for Ménière's disease existed, such that all the patients' data were revised to confirm that they met updated criteria for Ménière's disease at the end of the inclusion period. In this way, we were able to exclude those patients with incomplete phenotypic forms of Ménière's disease, such as individuals with possible or probable Ménière's disease.[10]

On their first visit to each of the centres, the patients were advised to consult the otorhinolaryngology (ENT) specialist every six months even if they were asymptomatic or their symptoms were controlled with the treatments prescribed. At the first and subsequent visits, different variables were registered including: clinical (the onset of each symptom, date of the first visit, follow-up time, number of vertigo episodes in the last six months, type and date of the different surgical interventions undertaken, associated diseases and presence of Tumarkin's otolithic crisis) and audiometric (hearing parameters according to liminal pure tone audiometry at frequencies of 250, 500, 1000, 2000 and 4000 Hz).

After recording the different variables, we analysed the evolution of the vertigo episodes in each patient during the period in which they were followed. This period was defined as the time elapsed between the first and the last visit to one of the referral centres, or in the case of those who underwent surgical intervention, taking the date of this intervention as the end of the follow up for our study. We consider the following to be surgical procedures that can modify the natural evolution of the disease and thus the condition that represented the end of the follow up: chemical labyrinthectomy (intratympanic injection of gentamicin from the first dose administered), surgical labyrinthectomy, endolymphatic sac decompression, vestibular neurectomy and cochlear implantation.

Many of the patients came to seek care a few months or years after the onset of disease symptoms. Thus, we could not precisely define the exact evolution of their disease before they attended the care centres. For this reason, a subgroup of patients who had been followed from the onset of the disease was defined. This subgroup included those patients in whom the time elapsed from the onset of the first symptom and the first visit to the ENT service was equal to or less than 365 days.

In this group, for which we have reliable information on the evolution of the disease, the number of annual vertigo episodes was revised individually, and 3 clinical evolutionary models were defined according to the evolutionary behaviour of the episodes in the first 10 years of the disease.

All patients gave their written consent that they wanted to participate in this work. This study protocol was reviewed and approved by Comité Ético de Investigación Clínica Hospital Clinic, University of Valencia (reference number: 40/19).

Analytic strategy

Univariate analysis

As a longitudinal descriptive study was carried out, the statistical analysis focused on the description of the different variables collected. Descriptive statistics appropriate to the nature of each variable were estimated, including the measures of central tendency (mean or median, depending on the distribution of the variable), dispersion (standard deviation or interquartile range), and tables of the absolute and relative frequencies of each variable.

Bivariate analysis

A contrast analysis was used to test the relationship between the variables, employing chi-squared tests to examine relationships between categorical variables, correlation tests to examine relationships between quantitative variables and a comparison of means using Student's *t*-tests, analysis of variance or their non-parametric equivalents (Mann–Whitney U test and Kruskal–Wallis H test).

Temporal evolution of vertigo episodes

The evolution of episodes over time was modelled using the mean episodes suffered during each year of the follow up, reflecting this evolution in a similar way to routine clinical practice. On some occasions, the incidence rate was the parameter used in each follow-up period (number of episodes suffered per time elapsed since the last visit).

The statistical package SPSS® (version 22) was used for the statistical analysis, except for the conditional logistic regression that was carried out using the Stata (version 14.0) statistical analysis software.

Results

During the course of the longitudinal study, data were collected from 327 patients with unilateral Ménière's disease, of which 87 (26.6 per cent) were followed up from the onset of the disease, based on the aforementioned criteria.

Evolution of vertigo episodes and clinical models

In the unilateral Ménière's disease group of patients, the mean incidence of annual episodes reached a maximum value of 7.56 in the 1st year (standard deviation (SD), 13.68), 4.36 (SD, 7.44) in the 2nd year and 2.94 (SD, 5.47) in the 3rd and 4th years of follow up. Subsequently, the number of episodes stabilised to a value of fewer than 2 episodes per year until the 10th year, and they reduced until there was a cessation in the episodes in subsequent years (Figures 1 and 2).

When the subgroup of patients followed from the onset of the disease was considered, they presented different patterns or models of the evolution of vertigo episodes during the first 10 years. After analysing each case individually, specific criteria were defined by which all these patients can be grouped into 3 behavioural or evolutionary models based on the number of vertigo episodes per year experienced during the first 10 years of the disease.

Model 1 included sudden onset with no further episodes from the fourth year after disease onset. These patients experience episodes of vertigo in consecutive years during the first four years of the disease ($n = 39$, 44.8 per cent).

Model 2 included sudden onset followed by a period of relapse. Episodes of vertigo are experienced in the first four

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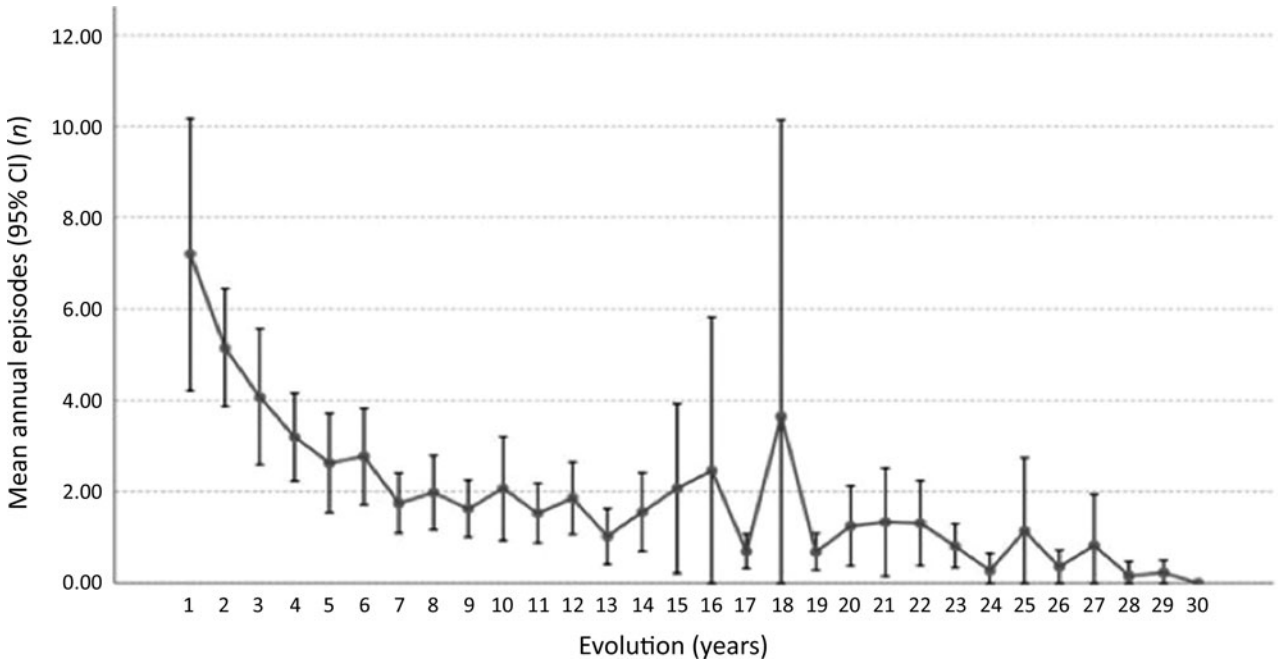

Fig. 1. Average incidence after a year of follow up of disease in unilateral Ménière's disease patients. CI = confidence interval

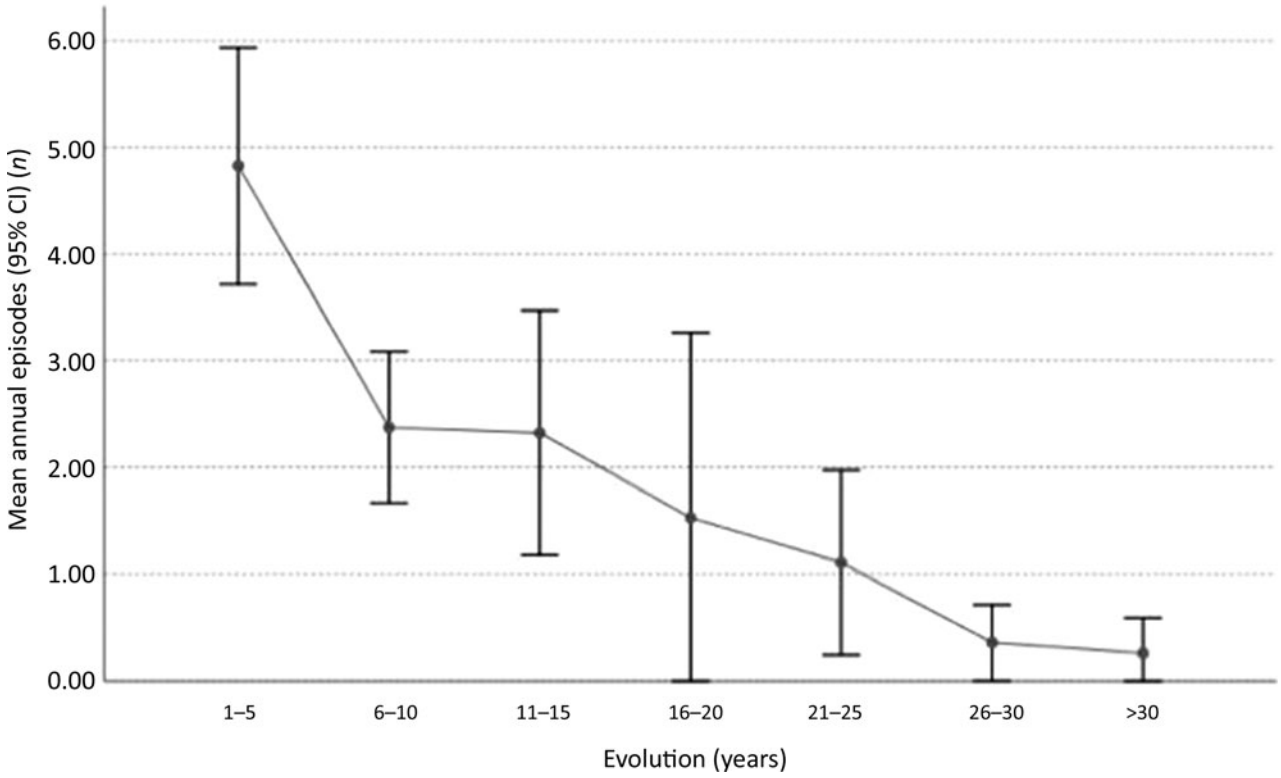

Fig. 2. Average incidence after five years of follow up of disease in unilateral Ménière's disease patients. CI = confidence interval.

years of the disease followed by a period with no episodes that lasted for at least one year, with a subsequent relapse or occurrence of episodes of vertigo in one or more consecutive years ($n = 30$, 34.5 per cent).

Model 3 included multiple relapses throughout the course of the disease or with the worst evolution. During the first 10 years of disease, episodes of vertigo are recorded in at least 7 years, whether consecutively or followed by intercritical periods of 1 or 2 years with no episodes ($n = 18$, 20.7 per cent).

The course of disease for each subtype expressed in the mean annual number of vertigo episodes suffered in the first 10 years is shown in Figure 3.

General descriptive data

Table 1 shows the results for the different variables analysed in each group. It should be stressed that none of the patients in model 3 reported suffering from migraine headaches during the first 10 years of the disease. However, a higher proportion

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of patients in this group reported suffering from Tumarkin's otolithic crisis and needed surgical treatment. In addition, a smaller proportion of the subgroup of patients followed and controlled from the onset of the disease required surgical or ablative treatment (16 per cent) compared with the whole group of patients with unilateral Ménière's disease (22 per cent).

Timeline of symptoms

In most of the subgroups analysed, there was a slight predominance in the occurrence of a single symptom at disease onset relative to individuals with bi-symptomatic onset or those with a triad of symptoms. This was followed by the presence of the triad of symptoms at disease onset. However, this was not the situation in the cases that were considered in model 3 of clinical evolution, where the difference between the occurrence of a single symptom and the occurrence of the triad of symptoms at disease onset was much greater. Indeed, in this model half of the patients presented with a single symptom, and only 11.1 per cent of patients developed the triad of symptoms at the onset of the disease (Table 1).

The time between the occurrence of the first symptom and the appearance of the triad of symptoms differed between clinical models with a mean of 1345 days (SD, 3030 days) for model 1, 835 days (SD, 1292 days) for model 2 and 1882 days (SD, 2849 days) for model 3.

Hearing outcomes

All groups of patients with unilateral Ménière's disease exhibited a mean tonal threshold corresponding to moderate hearing loss, with a greater degree of low-frequency hearing loss at the beginning of the disease. These thresholds evolved to a more severe degree of hearing loss by the end of the follow up, maintaining a greater extent of low-frequency hearing loss.

Significant differences were observed when the extent of hearing loss was considered in association with the different clinical models, with a lower mean hearing loss at all frequencies in the patients ascribed to model 1 relative to those in models 2 and 3 (Table 2).

Discussion

Evolution of vertigo episodes and clinical models

The evolution of the episodes of vertigo in patients with unilateral Ménière's disease studied here shows a similar behaviour to that published previously in this regard.[3] Understanding the general evolution of vertigo episodes in patients with unilateral Ménière's disease and their mean number, and taking into account our clinical experience and the individual revision of each case, we observed that the evolution of vertigo episodes differed considerably between cases during the first 10 years of the disease. Thus, we decided to define a series of criteria according to which the whole cohort of patients could be assigned to different subgroups.

Based on the evolution of the episodes of vertigo during the first 10 years of the disease, we defined different clinical models that fit the evolution of these events in all patients with unilateral Ménière's disease followed from the onset of their symptoms. We found that the patients grouped within these models showed distinct but not always significant behavioural patterns according to their sex, first symptom presented at the onset of the disease, the need for surgical or ablative treatments, the number of Tumarkin's otolithic crises suffered, and the evolution of hearing loss.

We defined a series of subgroups based on the evolution and behaviour of vertigo episodes, although there are many ways of explaining the differences between patients with Ménière's disease or grouping the clinical variations typical of Ménière's disease. Indeed, in other studies, they have been explained based on the familial association of Ménière's disease with other diseases, such as migraine or autoimmune diseases, or based on objective hearing and vestibular parameters.[7–9]

In our view, the most relevant work in this regard is that in which five subgroups of patients were defined:[8] classic Ménière's disease, delayed Ménière's disease, familial Ménière's disease, Ménière's disease associated with migraine and Ménière's disease associated with autoimmune disorders. In our models, familial association and a history of autoimmune diseases were not taken into account, although some comparisons could be made with these groups from which only hypothetical associations could be inferred. Our evolutionary model number 2 was that in which patients most frequently also suffered from migraine and had an earlier disease onset, as previously reported for the subgroup of patients with Ménière's disease associated with migraine. Model number 3 had the highest proportion of patients who suffered a Tumarkin's otolithic crisis and no patients with migraines; it was also the model in which the patients experienced the largest number of vertigo episodes (during the first 10 years of the disease), as reported previously[8] in a paper on the subgroup of patients with Ménière's disease associated with migraine.

Accordingly, in different studies in this field, groups of patients have been classified based on specific criteria.[7,8] However, as they share common features, it would appear that different forms of Ménière's disease can be distinguished based on the criteria used in these studies.

Migraine and Tumarkin's otolithic crisis

As it is difficult to define the date from which studies assessing the prevalence of migraines in patients with Ménière's disease are not biased by the existence of patients with vestibular migraine in the Ménière's disease cohorts, our discussion of this issue is based on the studies published since 2012 once the diagnostic criteria for vestibular migraine had been published.[11] However, the most recent studies show that the prevalence of migraine among patients with Ménière's disease ranges from 10 to 51 per cent.[12–14]

In our series, a smaller proportion of patients in the group of patients followed from the onset of the disease reported migraines relative to the total group of patients with unilateral Ménière's disease. Thus, early care and a close follow up of the disease may be associated with better management of this type of headache. Taking into account that approximately 12 per cent of the general population suffers from migraine,[15] this may be underestimated in our sample. The reason for this may be that we were not sufficiently cautious in assessing the presence of migraine in the initial years of data collection because the relationship between migraine and Ménière's disease was not as relevant at that time as it is at present. However, these would be non-differential biases equally distributed throughout the sample and that would not lead to an incorrect estimate of the associations but rather to a reduction in the existing estimates.

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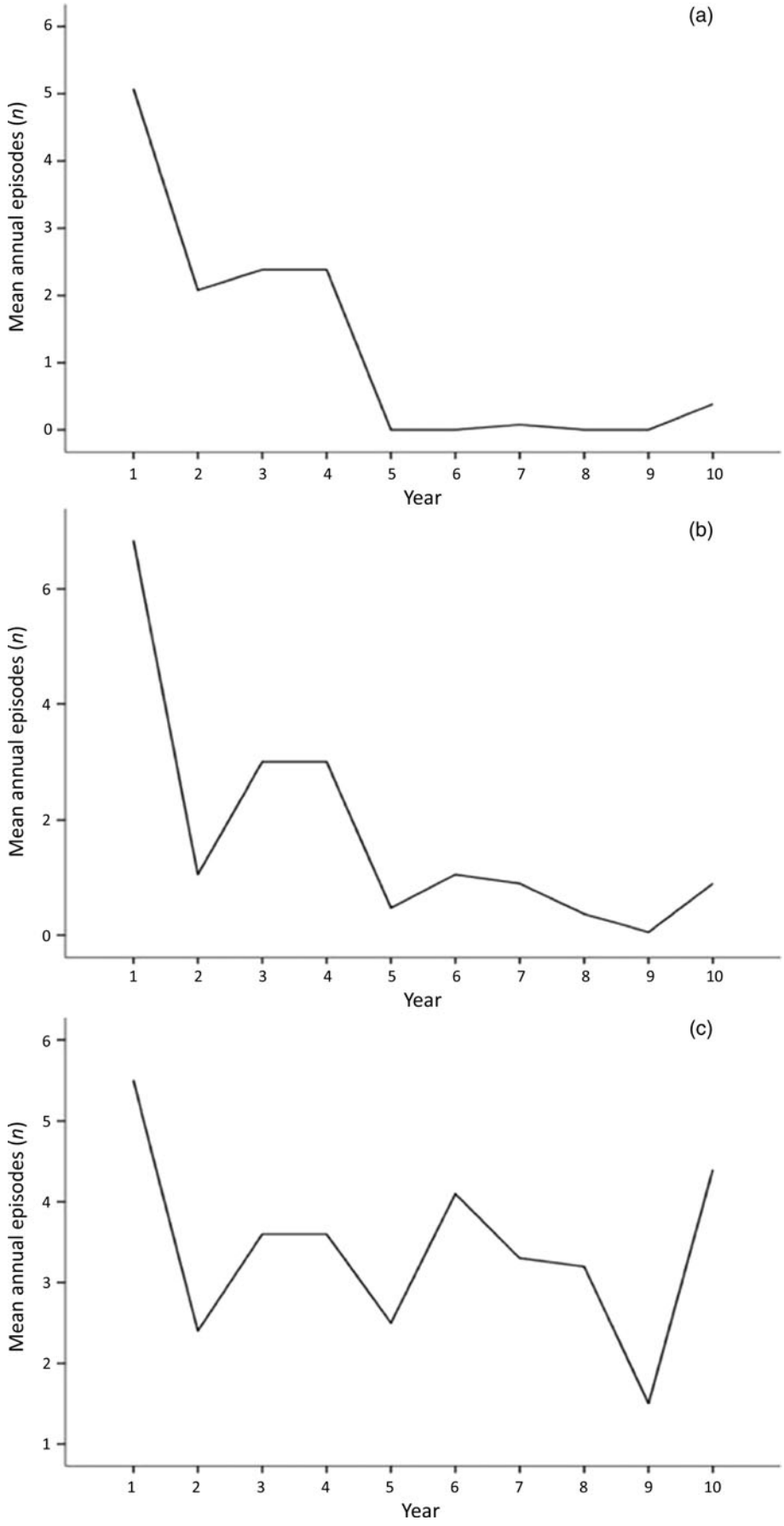

Fig. 3. Mean number of annual episodes in the first 10 years of Ménière's disease for (a) model 1 (sudden onset with no further episodes), (b) model 2 (sudden onset followed by a period of relapse and (c) model 3 (multiple relapses throughout the course of the disease or with a poor evolution).

Most studies have reported the presence of Tumarkin's otolithic crisis in 5–15 per cent of patients suffering from Ménière's disease,[16–19] which is consistent with the results from our series (12.2 per cent of patients). Patients within model number 3 are not only those with the highest number of episodes of vertigo in the first 10 years of the disease but also those who experienced the highest proportion of Tumarkin's otolithic crises between episodes (17.7 per cent),

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Table 1. Distribution of the different variables studied in each group

Parameter	Unilateral MD patients*	MD patients followed from onset of the disease†	MD patients within the clinical evolutionary models followed from onset of the disease		
			Model 1‡	Model 2**	Model 3§
Age at first vertigo episode (mean; years)	46.7	–	48.16	46.08	50.24
Age at first visit to specialist (mean; years)	49.8	48.2	–	–	–
Sex (% males)	53.5	56.3	67	53	39
High blood pressure (% patients)	19.6	24.1	25.5	23.3	22.2
Dyslipidaemia (% patients)	15.9	17.2	17.9	16.7	16.7
Diabetes mellitus (% patients)	7.3	10.3	7.7	13.3	11.1
Migraine (% patients)	5.2	2.3	2.6	3.3	0
Tumarkin's otolithic crisis (% patients)	12.2	12.6	10	13	17
Patients operated on in each group (% patients)	22	16	10.3	16.7	27.8
Patients with triad of symptoms at onset (% patients)	34.1	27.9	34.2	30	11.1
Patients with bi-symptomatic onset (% patients)	29.1	30.2	23.7	33.3	38.9
Patients with mono-symptomatic onset (% patients)	36.8	41.9	42.1	36.7	50

*$n = 327$; †$n = 87$; ‡$n = 39$; **$n = 30$; $n = 18$. MD = Ménière's disease

Table 2. Average hearing loss according to grouped frequencies in each group

Parameter	Unilateral MD patients*	MD patients followed from the onset of the disease†	MD patients within the clinical evolutionary models followed from the onset of the disease			*P*-value
			Model 1‡	Model 2**	Model 3§	
Pantonal hearing loss						
– Mean	21.13	26.6	15.55	37.78	31.71	0.001
– Standard deviation	21.83	23.2	13.09	29.51	17.94	
Hearing loss at 250, 500 & 1000 Hz						
– Mean	21.96	27.5	16.15	39.61	32.04	0.001
– Standard deviation	23.01	24.8	14.19	31.49	19.74	
Hearing loss at 2000, 3000 & 4000 Hz						
– Mean	20.30	25.6	14.96	35.94	31.39	0.001
– Standard deviation	22.77	24.0	15.57	29.53	20.30	

*$n = 327$; †$n = 87$; ‡$n = 39$; **$n = 30$; $n = 18$. MD = Ménière's disease

which augmented the perceived severity of Ménière's disease in these patients.

Surgical treatments

Currently, the surgical treatment for Ménière's disease has been reduced to a limited number of cases: those with a worse evolution and less symptomatic control. As all surgical procedures can modify the disease course, we classified the patients as 'operated' or 'not operated', and we performed the analysis irrespective of the surgical procedure undertaken, as we did not set out to assess the effectiveness of these in our study.

Although it is not feasible to plan a single- or double-blind study to accurately assess the effects of surgical interventions to treat Ménière's disease, many studies have assessed the efficacy of the different surgical options.[20–24] It has been reported that around 10–20 per cent of patients with Ménière's disease require surgical treatment.[25] These data are consistent with those we obtained, where the proportion of patients who underwent operation for their unilateral Ménière's disease was 16 per cent, increasing to 27 per cent in the patients included in evolutionary model number 3. No clear criteria currently exist for the indication of surgical treatment, which in most cases is closely linked to the knowledge and experience of the surgeon.

The 16 per cent of Ménière's disease patients followed from the onset of the disease who required a surgical intervention was lower than the 22 per cent of the whole group of patients with unilateral Ménière's disease analysed here. As such, carrying out an exhaustive medical follow up from the onset of the disease may reduce the need for a future surgical intervention aimed at controlling the symptoms of Ménière's disease.

Timeline of symptoms

In our series, 34.1 per cent of patients with unilateral Ménière's disease presented with the triad of symptoms at disease onset,

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which is consistent with data reported by several studies in the literature.[26–28] Elsewhere, other studies have reported that about half of the unilateral Ménière's disease patients presented with the triad of symptoms,[29,30] although here we observed a different behaviour of patients included in clinical model number 3 in this sense.

The evolution of hearing

In some studies, it was found that during the first years of the disease, the greatest degree of hearing loss coincided with a higher prevalence of vertigo episodes,[3] even though these subsequently diminish or disappear while hearing loss persists.[31,32] In this regard, our results show that patients within model number 1, who suffer from vertigo episodes for a shorter time, experience less hearing loss compared with those in the other two models. This could be explained by the fact that experiencing episodes of vertigo for a shorter period is associated with better preservation of hearing. However, this is not consistent with the degree of hearing loss we observed in the patients included in the other two models because those in model number 2 showed greater mean hearing loss than those in model number 3, the model in which there was a worse severity in the temporal evolution of vertigo episodes.

Limitations and strengths

As our work is an observational study of variables collected in a clinical practice setting, it has certain limitations. Likewise, the present study suffers from biases typical of an observational study, although these would be non-differential biases whereby all patients would be equally affected, regardless of the subgroup they belong to. As such, the estimated associations would tend towards a null value (no association). Furthermore, we have not taken into account variables such as the association with autoimmune diseases or any family history of the disease, which are now considered variables defining possible subtypes of Ménière's disease.

Conversely, we provide data from a longitudinal study carried out on a large number of patients with a long follow up. Moreover, we have performed an analysis of variables related to Ménière's disease and their outcomes in different subgroups. To date, no study has yet attempted to explain the existence of different evolutionary models of the disease in this sense, and therefore we believe that our study may offer a new perspective to define the existence of different subtypes of unilateral Ménière's disease.

Conclusion

In most unilateral Ménière's disease patients, after the first four years of disease follow up there is a reduction and a stabilisation in the mean number of annual episodes of vertigo. An in-depth analysis of the number of episodes of vertigo over the first 10 years of disease evolution has enabled us to define 3 clinical models based on the evolution of the episodes of vertigo suffered in the first 10 years of the disease. Patients included in model number one showed significantly less hearing loss at the end of follow up compared with patients within models 2 and 3. The patients included in model 3 of clinical evolution had a worse disease prognosis in terms of the number of vertigo episodes during the course of the disease, they more often suffered from Tumarkin's otolithic crisis, they had a greater need for surgical intervention, they more often had a mono-symptomatic onset and they required more time to display the full triad of symptoms relative to the unilateral Ménière's disease patients assigned to the other models. Furthermore, none of the cases assigned to model number 3 had a history of migraine.

- New studies have attempted to explain the heterogeneous behaviour of unilateral Ménière's disease by trying to identify clinical subgroups
- To date, there have been no study attempts to explain the variability of Ménière's disease in terms of the annual number of vertigo episodes
- This study described 3 behavioural or evolutionary models based on the number of vertigo episodes per year experienced during the first 10 years of the disease
- Patients included in model 1 showed significantly less hearing loss at the end of follow up compared with patients in models 2 and 3
- Patients included in model 3 had a worse disease prognosis regarding the number of vertigo episodes, Tumarkin's otolithic crisis and need for surgical intervention
- In future, it may be possible to define more consistently different subtypes of Ménière's disease

The data presented here offer criteria that may help to predict the evolution of Ménière's disease in different subsets of patients, enabling their treatment to be better personalised while encouraging a close follow up of the episodes of vertigo in unilateral Ménière's disease patients.

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Competing interests. None declared

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