A longitudinal study of unilateral Ménière's disease and clinical evolutionary models Ménière's based on the vertigo episodes.

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April 16, 2024

Abstract

INTRODUCTION: The variability in symptomatic evolution of vertiginous crisis in Ménière's disease (MD) is just one more fact that indicates the great heterogeneity attributed to MD. Recently, these variations and differences between patients are being defined by different subtypes of MD. OBJECTIVES: We have defined subtypes of MD based on the evolution of vertigo crisis in the first 10 years of the disease, in addition to defining the natural history of Unilateral MD (UMD) in our environment. DESIGN: A longitudinal descriptive study of patients with UMD was carried out. In a subgroup of patients followed from the onset of the disease, three subtypes or models of UMD were defined according to the individual review and our experience according to the vertiginous crisis suffered the first 10 years of the disease. In these models a differential behavior has been studied attending to different variables analyzed. RESULTS: Data were collected from 327 patients with UMD, of which 87 were followed from the onset of the disease. In this subgroup, patients were grouped in 3 models. Model No. 3 was associated with a worse auditory prognosis, a greater number of Tumarkin crisis, the need for surgery, and a more frequent mononymptomatic debut. Model No. 1 presented a lower hearing loss compared to the rest of the models. CONCLUSION: Several studies tried to define subtypes of MD. In our study we have defined 3 models of behavior in UMD based on the number of crisis suffered, which present a differential behavior according to different aspects.

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worse auditory prognosis, a greater number of Tumarkin crisis, the need for surgery, and a more frequent mononymptomatic debut.

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CONCLUSION: Several studies tried to define subtypes of MD. In our study we have defined 3 models of behavior in UMD based on the number of crisis suffered, which present a differential behavior according to different aspects.

Keywords: “Meniere Disease”, “vestibular diseases”, “longitudinal studies”, “vestibular disorders”, “inner ear”, “clinical models”, “Subgroups”, “neurotology”.

Five succinct points:

1. In most of uMD patients after the first four years of follow-up, there is a reduction and stabilization of the average annual number of vertigo crises
2. An exhaustive medical follow-up from the onset of the disease may reduce the need for a future surgical intervention.
3. Unilateral MD patients can be classified according the number of vertigo crises suffered the first ten years of the disease, on three clinical evolutionary models.
4. Significant differences has been observed when the extent of hearing loss has been considered in association with the different clinical models.
5. Patients included in model three had a worse disease prognosis in terms of the number of vertigo episodes, Tumarkin crises and need for surgical intervention.

2.Body of text

1.INTRODUCTION

After the first episode, episodes of vertigo are recurrent in MD. However, how the behaviour of the disease evolves as a function of the number of vertigo episodes it still not absolutely clear. From the first year of the disease, there is a gradual decrease in the number of vertigo episodes over the first eight years of the disease, which is followed by a subsequent stabilization, and then by a mild and progressive decrease in the following 10 years (1). However, there are reports of an increase in the number of seizures/year in those patients who have experienced episodes for more than 10-15 years (2,3). In contrast, MD is also associated with periods of remission in which the individual does not experience any episode of vertigo, with a variable duration between the episodes of vertigo (4,5) 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% of patients who do not have episodes of vertigo for one year will not experience any episode during the following year (1).

Although the course of the vertigo episodes in MD is well-defined for the general population of MD patients, *it* does not accommodate the wide clinical variability presented by each individual patient. In addition, there is considerable heterogeneity regarding the evaluation of these episodes of vertigo, their duration and intensity. The heterogeneity among patients with MD, 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 MD. In recent years, new studies have emerged that attempt to explain this variation or the heterogeneous behaviour of the disease, attempting to identify clinical subgroups to help explain the different forms of the disease (6–8).

2. OBJECTIVES

After analyzing the course of the disease in a very large series of patients who have been followed since the onset of the disease, we found that the evolution of the symptoms in patients 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 MD based on the frequency of vertigo episodes in the initial years of the disease, and help to define the natural evolution of unilateral MD (uMD).

3. MATERIALS AND METHODS

A longitudinal descriptive study was carried out on patients from two referral centres with UMD. The patients' data was collected and stored from 1977 to 2018, after which the data collected was processed and analysed. All the patients data were revised to confirm that they met updated criteria for complete MD.

At their first visit to each of the centers, the patients were advised to consult the Otorhinolaryngology (ENT) specialist every six months. At the first and subsequent visits, different variables were registered: clinical - onset of each symptom, date of the first visit, follow-up time, number of vertigo episodes in the last 6 months, type and date of the different surgical interventions undertaken, associated diseases, presence of Tumarkin crisis; audiometric - hearing parameters according to liminal pure tone audiometry at frequencies of 250, 500, 1,000, 2,000 and 4,000 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, or in the case of those who underwent a surgical intervention, the date of this intervention was taken as the end of the follow-up for our study. We consider the following as surgical procedures that can modify the natural evolution of the disease: chemical labyrinthectomy, surgical labyrinthectomy, endolymphatic sac decompression, vestibular neurectomy, or 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 were attended at the care centers. 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 [?]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 accordingly, 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.

Analytic strategy

- Univariate analysis: Descriptive statistics appropriate to the nature of each variable were estimated, including the measures of central tendency, dispersion, 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 (ANOVA) or their non-parametric equivalents (Mann-Whitney U test and Kruskall-Wallis H test).
- The evolution of the episodes over time was modelled out 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/time elapsed since the last visit).

The statistical package SPSS(r) *v.22* was used for the statistical analysis.

4.RESULTS

During the course of the longitudinal study, data were collected from 327 patients with unilateral UMD, of which 87 (26.6%) were followed up from the onset of the disease.

Evolution of vertigo episodes and clinical models

In the UMD group of patients, the mean incidence of annual episodes reached a maximum value of 7.56 in the first year (SD +-13.68), 4.36 (+-7.44) in the second year, and 2.94 (+- 5.47) in the third and fourth

years of follow-up. Subsequently, the number of episodes stabilized to a value of less than 2 episodes per year until the tenth year, and they reduced until there was a cessation in the episodes in subsequent years (figures 1 and 2).

In the subgroup of patients followed from the onset of the disease, 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/year experienced during the first 10 years of the disease (Figure 3).

Model 1: 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%).

Model 2: Sudden onset followed by a period of relapse. Episodes of vertigo are experienced in the first four 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%).

Model 3: Multiple relapses throughout the course of the disease or with a 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 one or two years with no episodes (N=18, 20.7%).

General descriptive data

Table 1 shows the results for the different variables analysed in each group.

Timeline of the 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 a bi-symptomatic onset or that involving a triad of symptoms. This was not the case 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.(Table 1).

Hearing outcomes

All groups of patients with UMD 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 follow-up.

Significant differences were observed when the extent of hearing loss was considered in association with the different clinical models (Table 2).

4.DISCUSSION

Evolution of vertigo episodes and clinical models

Understanding the general evolution of vertigo episodes 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. We decided to define a series of criteria according to which the whole cohort of patients could be assigned to different subgroups.

We defined a series of subgroups based on the evolution and behaviour of vertigo episodes, although there are many ways of grouping the clinical variations typical of MD (6–8).

In our view, the most relevant work in this regard is that in which five subgroups of patients were defined (7): classic MD, delayed MD, familial MD, MD associated with migraine and MD associated with autoimmune disorders. In our models, familial association and a history of autoimmune diseases are not taken into account, although some hypothetical associations and comparisons could be made with these groups. Our model number 2 was that in which patients most frequently also suffered from migraine and that in which there was an earlier disease onset, as previously reported for the subgroup of patients with MD associated with migraine. Model number 3 had the highest proportion of patients that suffered a Tumarkin crisis and

no patient with migraines, and it was the model in which the patients experienced the largest number of vertigo episodes, as reported previously(7), as the subgroup of patients with MD associated with autoimmune diseases.

Accordingly, in different studies in this field groups of patients have been classified based on specific criteria(6,7). However, as they share common features, it would appear that there are different forms of MD that can be distinguished on the basis of the criteria used in these studies.

Migraine and Tumarkin Crisis

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 UMD. Thus, early care and a close follow-up of the disease may be associated with a better management of this type of headaches. Taking into account that approximately 12% of the general population suffers from migraine (9), and 10 to 51% of patients with MD (10–12), 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, as the migraine-MD relationship 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.

In our series 12,2% patients reported the presence of Tumarkin crises, that is consistent with the published, 5-15% of patients (13–16). Patients within model number 3 are those that experienced the highest proportion of Tumarkin crises between episodes (17.7%), which augmented the perceived severity of MD in these patients.

Surgical treatments

Around 10-20% of patients with MD require surgical treatments (17), those have been reduced to those patients 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.

In our series the proportion of patients operated for their UMD is 16%, increasing to 27% in model number 3.

The 16% of the MD patients followed from the onset of the disease that required a surgical intervention was lower than the whole group of patients with UMD. 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 MD.

Timeline of the symptoms

In our series, 34.1% of patients with UMD presented with the triad of symptoms at disease onset, which is consistent with many studies (18–20). We observed a different behaviour of patients included in model number 3 in this sense, half of patients has a monosymptomatic onset.

The evolution of hearing

During the first years of the disease, the greatest degree of hearing loss coincides with a higher prevalence of vertigo episodes (1), even though these subsequently diminish or disappear while hearing loss persists (21,22). In this regard, our results show that patients within model number one, who suffer from vertigo episodes for a shorter time, experience less hearing loss. This could be explained by the fact that, experiencing episodes of vertigo for a shorter period of time is associated with better preservation of hearing. However, model number two presented greater mean hearing loss than those in model number three, which is that in which there was a worse severity in the temporal evolution of vertigo episodes.

Limitations and strengths

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 as variables defining possible subtypes of MD.

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 MD 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 hence, we believe that our study may offer a new perspective to define the existence of different subtypes of uMD.

5.CONCLUSIONS

In most of the uMD patients, after the first four years of disease follow-up, there is a reduction and a stabilization 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. The patients included in model three had a worse disease prognosis in terms of the number of vertigo episodes, number of Tumarkin crises, a greater need for surgical intervention and a mono-symptomatic onset.

The data presented here offer criteria that may help to predict the evolution of MD in different subsets of patients, enabling their treatment to be better personalized, while encouraging a close follow up of the episodes of vertigo in UMD patients.

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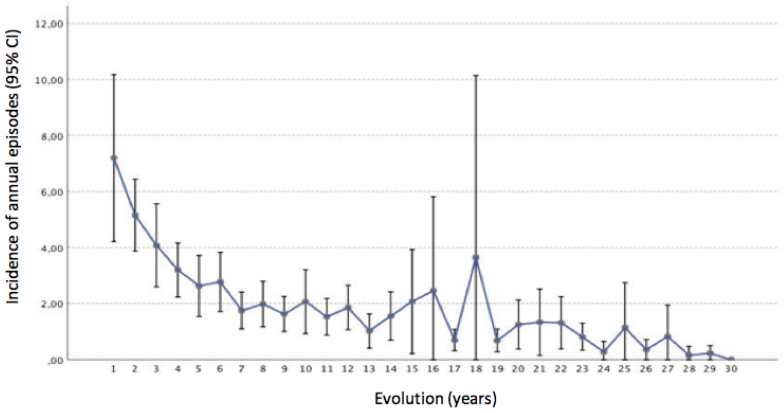
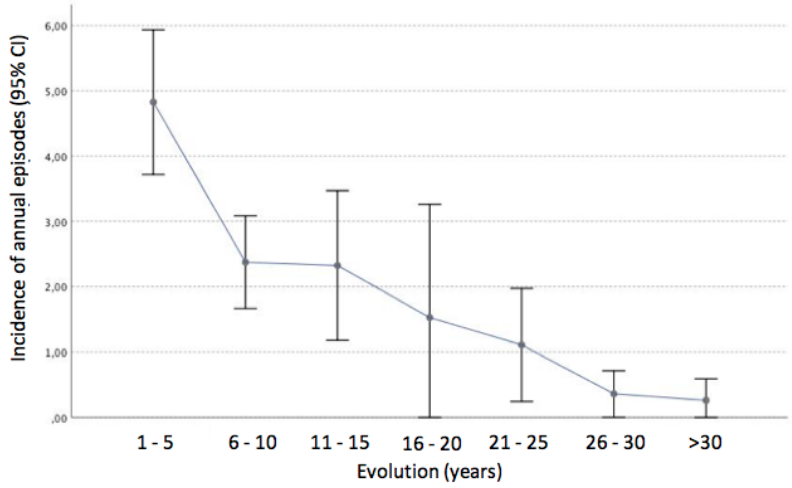
9. FIGURE CAPTIONS

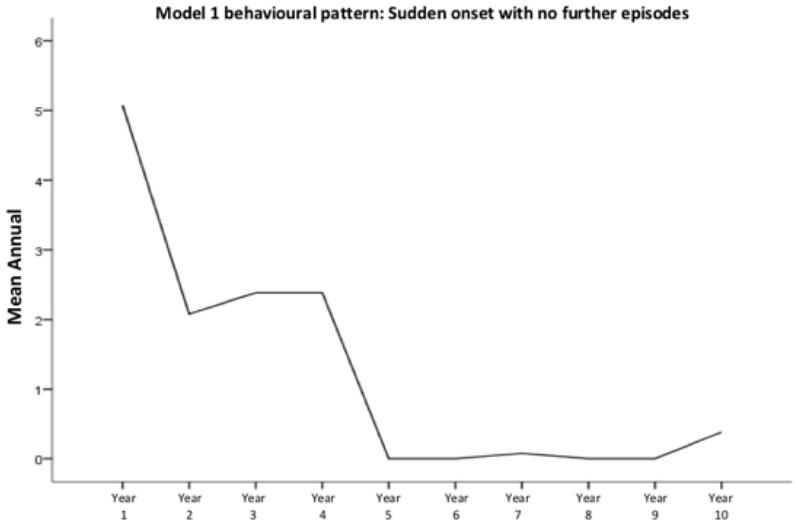
Fig 1. Average incidence according to year of follow-up of the disease in UMD patients.

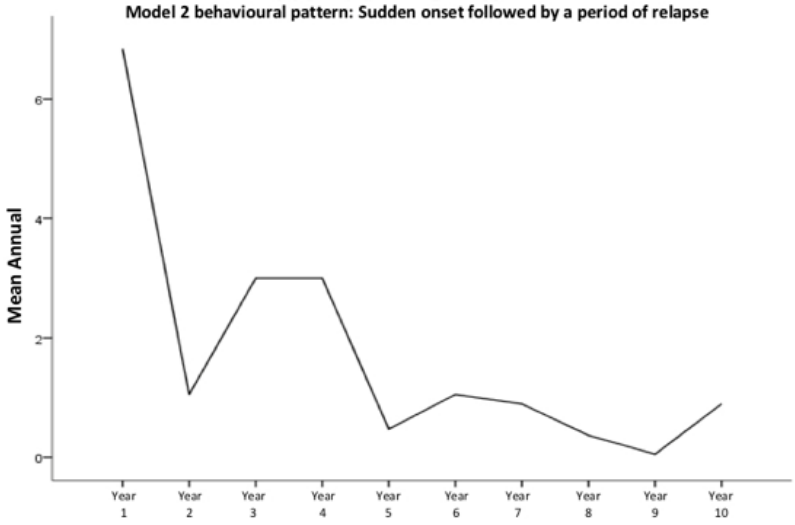
Fig 2. Average incidence according to five-year follow-up of the disease in UMD patients.

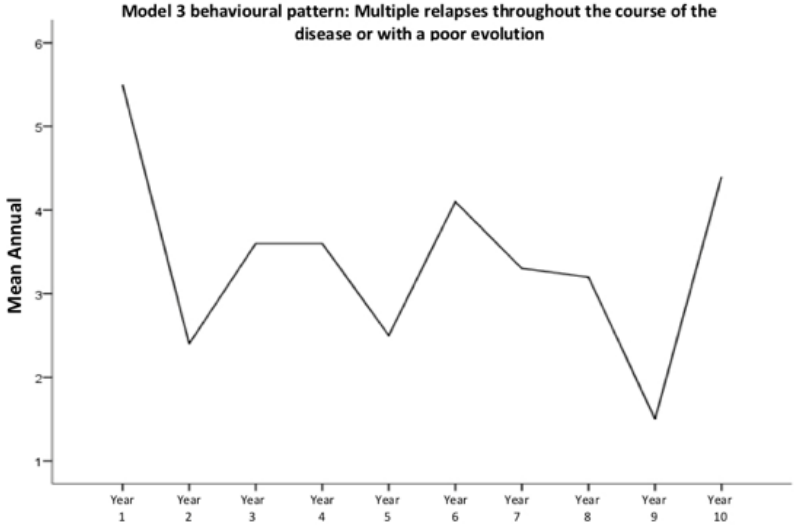
Fig 3. Course of disease for each subtype expressed in the mean annual number of vertigo episodes suffered in the first ten years.











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