ORIGINAL ARTICLE

Time Course of Episodes of Definitive Vertigo in Ménière's Disease

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Objective: To evaluate the frequency and duration of episodes of definitive vertigo in Ménière's disease.

Design: Prospective longitudinal study.

Setting: Multiple tertiary referral centers.

Patients: Five hundred ten individuals from 8 hospitals that met the American Academy of Otolaryngology–Head and Neck Surgery diagnostic criteria for definitive Ménière's disease.

Intervention: Conservative treatment.

Main Outcome Measure: Frequency and duration of episodes of definitive vertigo during follow-up.

Results: Ménière's disease affects both sexes and both ears equally, with onset generally in the fourth decade of life. The number of episodes of vertigo is greater in the first few years of the disease. Although episodes of vertigo that last longer than 6 hours are less frequent than shorter episodes, they occur with similar frequency throughout the natural course of the disease. The percentage of patients without episodes of vertigo increases as the disease progresses, and 70% of patients who did not have an episode of vertigo for 1 year will continue to be free of episodes during the following year. Thus, there is a relationship between the frequency of episodes in consecutive years, although this association decreases rapidly as the number of years increases.

Conclusion: The frequency of definitive episodes of vertigo in Ménière's disease decreased during follow-up, and many individuals reached a steady-state phase free of vertigo.

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Understanding the natural history of a disease requires analysis of a substantial number of patients and a long-term follow-up. These goals are difficult to achieve in less common conditions such as Ménière's disease[1,2] and are possible only in large collaborative multicenter studies. In such studies, it is important that the participating centers use standardized criteria for making the diagnosis and for patient evaluation during follow-up. For Ménière's disease, the most commonly accepted criteria are those of the diagnostic scale of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS).[3]

Ménière's disease is an idiopathic syndrome associated with endolymphatic hydrops[4] and characterized by episodes of vertigo, hearing loss, tinnitus, and aural fullness. Although hearing loss[5-7] and tinnitus[8] have been studied extensively, the information available about the progression of episodes of vertigo is limited. Hearing loss increases during follow-up until it reaches a moderate or severe level, and, similarly, tinnitus becomes constant, causing a decrease in the health-related quality of life in many individuals.[9] However, the time course of episodes of vertigo is less clear, even though the primary goal of treatment is to decrease the frequency and duration of these episodes. Some studies have described stabilization of the disease during follow-up, with a decreased number or absence of episodes of vertigo.[10,11] In contrast, other studies have failed to detect differences in the frequency, intensity, or duration of episodes of vertigo during the course of the disease.[12]

The objective of this study was to evaluate the frequency and duration of definitive episodes of vertigo in patients with a diagnosis of Ménière's disease who were treated conservatively. It was not our intention to examine or assess any specific treatment method or procedure.

METHODS

PATIENTS

A group of 588 patients who met the AAO-HNS criteria for the diagnosis of Ménière's disease were included in a prospective longitudinal study carried out between January 1, 1999, and December 31, 2006, in a multicenter tertiary referral setting involving 8 hospitals. Of these, 78 patients considered to have possible or probable Ménière's disease were excluded, which resulted in a final group of 510 patients with definitive Ménière's disease. The diagnosis of definitive Ménière's disease requires individuals to have had at least 2 episodes of vertigo associated with tinnitus or aural fullness and that lasted at least 20 minutes, as well as documented hearing loss on at least 1 occasion. In all cases, other causes that might produce this clinical status were excluded.[3] According to the AAO-HNS guidelines, for a case to be considered bilateral, the diagnosis of Ménière's disease must be established independently for each ear. All patients underwent clinical examination and an otoneurologic examination that included electronystagmography and auditory tests. Radiologic studies and serologic tests were performed when considered necessary.

Conservative treatment included a salt-restricted diet or administration of betahistidine dihydrochloride, trimetazidine,[13] carbamide peroxide, or diuretic agents. Many patients had used various combinations of these treatments since developing the disease. If during the study a patient underwent surgery, the time course of definitive episodes of vertigo was evaluated only until the time of surgery. During the 7-year course of this study, 103 patients (20.2%) underwent surgery: transtympanic gentamicin injection in 33.3%, endolymphatic sac surgery in 27.2%, vestibular nerve section in 21.9%, labyrinthectomy in 15.8%, and aural pressure therapy in 1.8%.[14] At their first visit, patients were made aware of the possibility that surgical treatment could be used to alleviate the episodes of vertigo and of the risks associated with the various interventions. If during the development of the disease they considered, along with a consultant, that a surgical intervention was the most appropriate treatment, this was the therapy adopted. No preestablished conditions were applied because the decision to undergo surgery differs among patients and may be influenced by factors such as age, profession, tolerance of the crises, and fear of surgery.

DATA COLLECTION AND EVALUATION OF VERTIGO

The information was obtained in the outpatient clinics of the various centers by means of a standardized, structured, clinical protocol designed for follow-up in patients with Ménière's disease. When patients agreed to participate in the study, they were informed that at each hospital visit they must provide information about the number and duration of episodes of vertigo they had experienced since the previous visit. All data from the various centers were then included in a single database.[15]

Demographic data for each patient included sex, date of birth, and age at onset of disease. The difference between age at onset of disease and current age represented the years of evolution of the disease.

According to the AAO-HNS guidelines, an episode of vertigo in definitive Ménière's disease or Ménière-like episodic vertigo involves spontaneous rotational vertigo lasting at least 20 minutes, often leaving the patient prostrate and lacking balance, which can last for days.[3] It is usually accompanied by nausea and vomiting or retching; however, consciousness is not lost. Evolution was considered from the time that the AAO-HNS diagnostic criteria were met, and the first 2 episodes of vertigo were not included. Episodes of vertigo lasting less than 20 minutes or the sensation of instability usually observed in chronic disease were not considered in this study.

Episodes of vertigo were characterized by their frequency (number of episodes per year) and duration. The frequency of episodes of vertigo is commonly used to assess the severity of vertigo; however, that a few episodes of severe vertigo may be considered to be worse than frequent longer episodes is not taken into consideration. To resolve this problem, we used a 3-point scale to estimate the duration of the episodes: grade 1, 20 minutes to 2 hours; grade 2, 2 to 6 hours; and grade 3, longer than 6 hours.

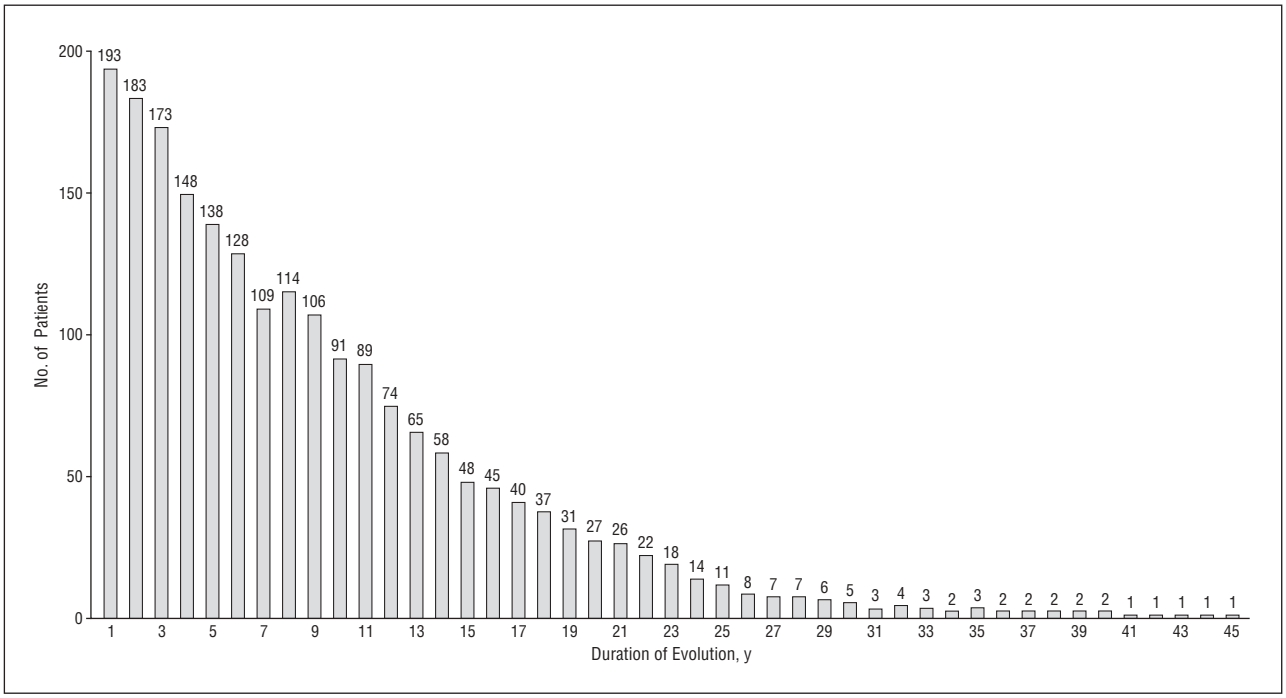

Figure 1. Number of patients studied per year of Ménière's disease evolution.

In most of the patients in this study, the disease was in the early phase, and, thus, we have more information about the time course of episodes of vertigo in the first years of the disease (**Figure 1**). Each patient provided information from the year in which he or she was entered into the study to 2006, the year in which the study ended; thus, information over 4 years was available for a patient entered in 2003. Accordingly, if the onset of disease was in 1995, information about its course would be available for years 8 (2003) through 11 (2006). If a patient underwent surgery in 2005, only information from years 8 through 10 would be available.

STATISTICAL ANALYSIS

A descriptive analysis was performed for all variables using commercially available software (SPSS version 14; SPSS Inc, Chicago, Illinois), and categorical variables were compared using the χ^2 test. The mean values of quantitative variables were compared between groups using the *t* test or the nonparametric Mann-Whitney test if the data did not fit a normal distribution. Variances were compared with the Levene test, and paired data were compared using the Wilcoxon signed rank test. The correlations between variables were estimated using the Spearman rank correlation coefficient. $P<.05$ was considered statistically significant.

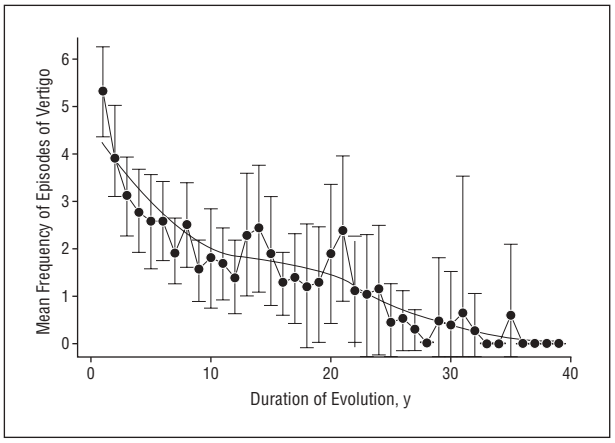

Figure 2. Mean frequency of episodes of vertigo per year of Ménière's disease evolution. Bars indicate 95% confidence intervals. Soft curve represents smoothing of the means achieved by local regression.

RESULTS

DISTRIBUTION BY SEX, EAR, AND AGE AT ONSET OF DISEASE

In the population studied, no significant difference was noted in sex distribution; there were 257 men (50.4%) and 253 women (49.6%; $P=.90$). In 2006, there was no difference in the percentage of patients in whom the right or left ear alone was affected (223 patients; 43.7%); both ears were affected in 64 patients (12.5%). Moreover, sex did not influence the distribution of the affected ears (χ^2 test, 4.37; $P=.11$). The mean (SD) patient age at the onset of disease was 44.9 years (12.8 years) (age range, 8-81 years). However, a significant difference was noted in the age of onset of disease between men and women; on average, onset occurred 2.23 years earlier in men than in women ($P=.03$).

EVOLUTION OF EPISODES OF VERTIGO

Frequency

The frequency of episodes of vertigo each year showed a rapid decline over the first 8 years (**Figure 2**), subsequently stabilizing over the following 10 years before declining gradually. However, with longer periods of disease evolution when the sample sizes were smaller, there was a significant increase in the confidence intervals. To complement this initial study, the evolution of episodes of vertigo was grouped into 4 categories and disease progression over only the first 15 years was analyzed, including at least 45 patients in each year (**Table 1**). Accordingly, it was evident that the percentage of patients who did not experience episodes of vertigo increased as the disease progressed.

Table 1. Number of Individuals Grouped According to Number and Mean Frequency of Episodes of Vertigo per Year of Disease Evolution

	Episodes of Vertigo, No. (%)				
Year	0	1-2	3-5	>5	Mean
1	35 (18.1)	49 (25.4)	51 (26.4)	58 (30.1)	5.31
2	69 (37.7)	39 (21.3)	31 (16.9)	44 (24.0)	4.06
3	79 (45.7)	37 (21.4)	22 (12.7)	35 (20.2)	3.12
4	73 (49.3)	26 (17.6)	27 (18.2)	22 (14.9)	2.80
5	75 (54.3)	28 (20.3)	17 (12.3)	18 (13.0)	2.57
6	71 (55.5)	17 (13.3)	18 (14.1)	22 (17.2)	2.58
7	61 (56.0)	18 (16.5)	20 (18.3)	10 (9.2)	1.95
8	65 (57.0)	19 (16.7)	13 (11.4)	17 (14.9)	2.50
9	71 (67.0)	15 (14.2)	9 (8.5)	11 (10.4)	1.55
10	59 (64.8)	16 (17.6)	10 (11.0)	6 (6.6)	1.79
11	57 (64.0)	16 (18.0)	5 (5.6)	11 (12.4)	1.69
12	46 (62.2)	15 (20.3)	10 (13.5)	3 (4.1)	1.41
13	38 (58.5)	13 (20.0)	5 (7.7)	9 (13.8)	2.29
14	30 (51.7)	16 (27.6)	4 (6.9)	8 (13.8)	2.43
15	32 (66.7)	6 (12.5)	2 (4.2)	8 (16.7)	1.96

A paired-comparison data analysis per case of the total frequency of the episodes of vertigo in each year with the frequency in each of the following years (**Table 2**) showed a significant difference between the first year and the remaining years. The second year also showed significantly more episodes compared with the third year; however, not until the 10th year were there differences from the data obtained from the third year onward. Likewise, from the 10th year onward, not until the 18th year of disease evolution were there significant differences, and thereafter there were insufficient data to detect significant differences.

The Spearman correlation coefficient was used to evaluate whether there was a correlation between the frequency of episodes of vertigo in 1 year with the frequency of episodes in subsequent years in the same patient. We typically obtained significant correlations between one year and the next, and this ratio decreased rapidly as the difference in the number of years between the 2 points increased. The sample sizes for the first years of disease evolution were reasonable for the purposes of this study; however, the samples available for the longer periods of evolution were small (**Table 3**). To study the correlation between the number of episodes of vertigo in consecutive years, we analyzed the possibility of a patient without episodes continuing to be free of episodes in the following year. The patients were classified each year as having or not having an episode of vertigo, and we assessed whether they also had a crisis in the following year. When consecutive years were compared over the first 9 years of disease evolution, 70% of patients without episodes of vertigo did not have an episode in the following year (**Table 4**). In contrast, the likelihood that patients who had episodes of vertigo continued to have them was slightly greater than 50%.

Table 2. Significant Differences in Frequency of Episodes of Vertigo Between Years of Disease Evolution[a]

Comparison Years	No. of Episodes	*z* Value	*P* Value
1-2	142	–3.11	.002
2-3	133	–3.02	.002
3-10	47	–3.02	.002
10-18	19	–2.31	.03

[a] Values *z* and *P* (exact significance) of the Wilcoxon rank test.

Duration

The severity of the episodes of vertigo in terms of duration was classified into 3 groups. The frequency of grade 1 episodes (20 minutes to 2 hours) and grade 2 episodes (2-6 hours) was similar over time (**Figure 3**A), and the duration of these episodes decreased constantly over the 30 years of disease evolution. Smoothing the series of means demonstrates more clearly how the duration of the episodes develops. The frequency of grade 3 episodes (>6 hours; Figure 3B) was less than that of grade 1 and grade 2 episodes, and they remained more constant over the first 20 years of evolution.

Comparison of Frequency of Episodes of Vertigo Between Patients Who Did and Did Not Undergo Surgery

Comparison of the number of episodes of vertigo in patients who underwent surgery (before the operation) and in those who were not operated on demonstrates significant differences only during the first 5 years of the disease. However, from the sixth year of disease evolution onward, the differences are not significant (**Table 5**).

Table 4. Patients With and Without Episodes of Vertigo Conditioned to the Previous Year's Results (With or Without Episodes)

Year of Evolution/ Previous Year	Patients With Episodes of Vertigo, No. 1/No. 2 (%)	Patients Without Episodes of Vertigo, No. 1/No. 2 (%)	*P* Value[a]
2/1	67/117 (57.3)	15/25 (60.0)	.12
3/2	45/79 (57.0)	40/54 (74.1)	<.001
4/3	41/68 (60.3)	38/54 (70.4)	.001
5/4	33/58 (56.9)	43/54 (79.6)	<.001
6/5	25/49 (51.0)	41/57 (71.9)	.02
7/6	24/43 (55.8)	38/50 (76.0)	.002
8/7	20/38 (52.6)	39/53 (73.6)	.01
9/8	20/40 (50.0)	46/57 (80.7)	.001

Abbreviations: No. 1, number of patients corresponding to the year of evolution; No. 2, number of patients corresponding to the previous year.
[a] χ^2 Independence test.

Table 3. Correlation of the Frequency of Episodes of Vertigo Between Years of Disease Evolution[a]

Year	Year + 1	Year + 2	Year + 3	Year + 4
1	0.33 (142)[b]	0.19 (104)	0.14 (73)	–0.006 (61)
2	0.42 (133)[b]	0.23 (94)[d]	0.16 (79)	0.04 (63)
3	0.40 (122)[b]	0.16 (92)	0.18 (71)	0.23 (57)
4	0.41 (112)[b]	0.06 (87)	–0.09 (67)	0.10 (60)
5	0.27 (106)[c]	0.02 (76)	0.11 (70)	–0.002 (65)
6	0.24 (93)[d]	0.22 (84)[d]	0.16 (77)	0.09 (59)

[a] Spearman ρ nonparametric correlation values; sample size in parentheses.
[b] $P<.001$.
[c] $P<.01$.
[d] $P<.05$.

COMMENT

To our knowledge, this is the first multicenter study of the time course of episodes of vertigo in Ménière's disease conducted in southern Europe; the most relevant studies of this disease to date have been conducted in the United States and Scandinavian countries. The characteristics of our population did not differ substantially from those in these earlier studies, and we found a similar percentage of men and women as observed previously,[5,12,16] a similar distribution of unilateral Ménière's disease in each ear, and bilateral Ménière's disease in only 12.5% of patients. The mean age at onset of disease (44.9 years) is also similar to that in other studies,[6,10] although we found a slightly earlier onset in men than in women (2.23-year difference). While uncommon, we also found that the disease may affect both children and the elderly.[17]

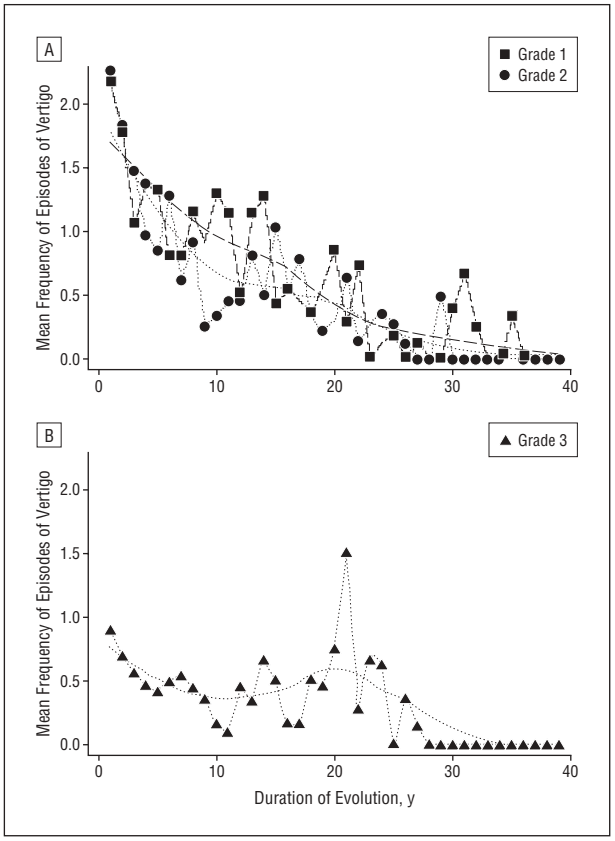

Figure 3. Mean frequency of grade 1 (20 minutes to 2 hours) and grade 2 (2-6 hours) episodes of vertigo (A) and grade 3 (>6 hours) episodes (B) per year of disease evolution. Soft curve represents smoothing of the means achieved by local regression.

At times it is difficult to directly compare the evolution of episodes of vertigo between studies, especially when it is not specified how the episodes were evaluated or whether the characteristics of the episodes differed from those considered herein. However, the global conclusions can be compared with the information in the literature. Accordingly, Stahle et al[10] observed that the global frequency of episodes of vertigo diminished at advanced stages of the disease, and similarly, Green et al[11] suggested that the disease reaches a plateau at which the frequency of episodes of vertigo is lower, lying somewhere between the onset of disease and 9-year follow-up. Our results indicate that 2 phases may exist in the natural evolution of definitive episodes of vertigo (Figure 1). The first phase includes approximately the first 8 years of the disease, and the second phase extends from years 9 to 20. During the first phase, there are more crises in the initial years and their frequency diminishes until the second phase is reached, when the frequency of the episodes is stable. However, Havia and Kentala[12] did not find any difference in frequency, intensity, or duration of episodes of vertigo on the basis of disease duration, although they included episodes that lasted only seconds and patients with continuous vertigo in their analysis.

We found that episodes of vertigo lasting from 20 minutes to 2 hours are more common in the first few years of evolution and that they decline progressively up to the second decade, when the frequency of such events stabilizes. Episodes lasting longer than 6 hours are less common, and the frequency with which they occurred did not change substantially, at least during the first 20 years. Furthermore,

Table 5. Comparison of Frequency of Episodes of Vertigo

	Frequency of Episodes of Vertigo				
	Patients Who Underwent Surgery[a]		Patients Who Did Not Undergo Surgery[b]		
Year	Mean (SE)	No. of Patients	Mean (SE)	No. of Patients	*P* Value[c]
1	7.86 (1.30)	35	4.74 (0.50)	158	.001
2	7.91 (1.26)	34	3.18 (0.50)	149	<.001
3	4.94 (0.87)	33	2.69 (0.47)	140	<.001
4	6.35 (1.98)	23	2.14 (0.37)	125	.01
5	6.00 (2.39)	21	1.96 (0.39)	117	.006
6	3.75 (1.27)	16	2.41 (0.45)	112	.14
7	2.73 (1.05)	11	1.87 (0.38)	98	.17
8	3.08 (1.41)	12	2.43 (0.47)	102	.80
9	1.90 (0.96)	10	1.51 (0.35)	96	.14
10	3.58 (1.27)	12	1.52 (0.57)	79	.01
11	3.42 (1.39)	12	1.42 (0.38)	77	.04
12	2.89 (1.63)	9	1.20 (0.38)	65	.31

[a] Number of crises per year of disease evolution up to the time of surgery.
[b] Number of crises per year of disease evolution.
[c] *P* value comparing 2 subgroups, using Mann-Whitney test.

as the disease evolves, the percentage of patients who experience episode-free years increases. In the first year after the disease is diagnosed, 18% of patients experience no episodes of vertigo, whereas from year 10 onward, this percentage increases to greater than 60%. However, this does not mean that episodes will not occur in the future.

We evaluated the progression of episodes of vertigo in the same patient from year to year. There is a significant relationship between one year and the next, which decreases rapidly as the duration between the years studied increases. It is interesting to note what happens when a patient who is free of episodes continues to be episode-free during the following year. If the first and second years of disease evolution are disregarded, the general trend is that 70% of patients remain episode-free in the following year. This may mean that the activity of the etiologic factor causing the episodes persists for a few months and then ceases to be active. However, the problem remains latent until this or another factor again alters inner-ear function. Logically, the evolution of Ménière's disease depends on certain unknown variables such as etiology and personal characteristics. After analyzing our results, we believe it would be interesting to study whether patients can be classified into groups with the same evolutionary process and to investigate the variable or variables that might define such groups.

The patients who underwent surgery were excluded from the study after the operation. Strictly speaking, to describe the progression of vertigo in patients who are untreated or who receive pharmacologic therapy, none should undergo surgery. However, for ethical reasons, patients in whom the disease responds poorly to medical treatment must be offered the possibility of surgery. Nevertheless, were these patients to have remained in the study and continued to receive the same noninvasive treatment, substantially more episodes of vertigo would probably have been studied.

The final results may be influenced by 2 factors that are difficult to avoid: the point at which a patient enters the study and the point at which a patient leaves the study to undergo surgery. That patients with more severe symptoms may have sought care more frequently and sooner than patients with fewer episodes of vertigo might be a source of selection bias. In this case, we would lose information about the years of disease evolution with the fewest crises. We consider that this factor would not have a strong influence in Spain because it is common for patients with Ménière's disease to come to a hospital otoneurology department for examination as soon as there is suspicion of the disease, after which point they can be followed up.

CONCLUSIONS

The frequency of definitive episodes of vertigo in Ménière's disease decreases during follow-up, especially in terms of episodes that last less than 6 hours. Episodes lasting longer than 6 hours are less common; however, their frequency remains similar throughout the course of the disease. The possibility of experiencing an episode-free year increases as the disease evolves. In any one patient, there is a relationship between the number of episodes from one year to the next.

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