The Journal of Laryngology & Otology

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Bilateral Ménière's disease according to its form of debut: synchronous and metachronous disease

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Main Article

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

Presented at 71st congress of the Spanish ENT Society, 14 July 2020, Madrid, Spain

Cite this article: Pérez-Carbonell T, Orts-Alborch M, Pla-Gil I, Pérez-Guilén V, Tenías-Burrillo JM, Marco-Algarra J, Pérez-Garrigues H. Bilateral Ménière's disease according to its form of debut: synchronous and metachronous disease. *J Laryngol Otol* 2023; **137**:782–788. https://doi.org/10.1017/S0022215122002262

Accepted: 26 September 2022
First published online: 6 October 2022

Key words:
Meniere Disease; Vestibular System; Vertigo; Endolymphatic Hydrops; Longitudinal Studies; Vestibular Diseases

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Abstract

Objective. Bilateral Ménière's disease is classified according to the time of appearance of symptoms in each ear into synchronous and metachronous types. A descriptive longitudinal study, involving 59 bilateral Ménière's disease patients, was carried out to assess the two forms of bilateral Ménière's disease.

Method. Data on symptomatic chronology in each ear, auditory evolution and evolution of vertiginous crisis, among other aspects, were obtained, analysed and compared. Possible risk factors for Ménière's disease becoming bilateral were analysed after conducting nested case–control studies in a cohort.

Results. The metachronous form was seen in 76.3 per cent of cases, and the time it took for the disease to become bilateral took a median time of seven years. The symptomatic triad was the most frequent symptomatic debut for the first ear in both forms. Synchronous debut presented a greater average hearing loss. Suffering from migraine and a symptomatic onset with a greater number of symptoms appear to be possible predictors of conversion to bilateral Ménière's disease.

Conclusion. Bilateral Ménière's disease temporal models presented differences. The study of them helps to better understand, prevent and predict the behaviour of these patients.

Introduction

Compared with unilateral Ménière's disease,[1] bilateral Ménière's disease is more complicated in terms of its management and treatment. Bilateral Ménière's disease usually presents a more aggressive behaviour, involving less well-tolerated episodes of vertigo, and its evolution involves bilateral hearing loss that in most cases requires some kind of rehabilitation. These facts largely condition treatment, requiring a more cautious and conservative attitude with regard to the use of techniques that may cause hearing and/or vestibular impairment.

The diagnosis of bilateral Ménière's disease requires a clinical diagnosis of Ménière's disease in each of the ears,[1] although once the disease has developed in one ear, it is very difficult to determine which ear is causing the episodes of vertigo: the ear previously affected or the contralateral ear, which may be in the early stages of the disease. Furthermore, if severe vestibular dysfunction, areflexia or hyporeflexia already exist in the ear initially affected, patients may not suffer from vertigo episodes but only experience instability. Thus, most authors agree that the diagnosis of Ménière's disease in the second ear can only be established when the hearing loss characteristic of the disease occurs in that ear together with a sensation of otic fullness and tinnitus.[2] In many cases when bilateral Ménière's disease is diagnosed by the presence of *de novo* auditory affectation in the second ear, tests should be performed at the onset of this disease to rule out a possible differential diagnosis associated with hearing loss and tinnitus as symptoms.[3]

As no specific time interval has been established for bilaterality to occur, any patient diagnosed with unilateral Ménière's disease is susceptible to developing the disease in the contralateral ear. Two different types of bilateral Ménière's disease may be considered: a synchronous type, in which bilateral Ménière's disease occurs in both ears simultaneously or within a short (as yet ill-defined) time interval, which may differ,[4,5] and the more frequent metachronous type, including patients with unilateral Ménière's disease in whom the disease in the contralateral ear evolves over months or years. Indeed, it is generally considered that metachronous bilateral Ménière's disease develops in the first five to seven years of the disease.[4,5] Both these types of bilateral Ménière's disease evolve distinctly in terms of their onset and the evolution of vertigo episodes and hearing impairment. Moreover, the proportion of patients with these two types of bilateral Ménière's disease varies between 17 and 41 per cent for the synchronous type, and between 58 and 83 per cent for the metachronous type.[4–6]

There is considerable heterogeneity in the literature regarding the number of patients who develop bilateral Ménière's disease, ranging from 2 to 78 per cent of patients with Ménière's disease.[7,8] This variation may be related to the follow-up time in the different studies, with more patients with bilateral Ménière's disease directly related to a longer follow-up time[4] as well as to stricter compliance with clinical criteria.[8] Indeed, in most cases, the incidences of bilateral Ménière's disease reported are between 20 and 30 per cent of patients with Ménière's disease.[4]

Although it is often thought that vertigo episodes do not differ in duration, frequency and intensity between bilateral Ménière's disease and unilateral Ménière's disease patients,[9] patients with bilateral Ménière's disease refer to a higher level of perceived disability and worse quality of life, in addition to reporting more disabling dizziness compared with patients with unilateral Ménière's disease.[10] The existence of bilateral Ménière's disease suggests it may be a systemic disease that affects both ears. Indeed, there is evidence that it could be mediated by the immune system, and it has previously been associated with several autoimmune diseases as well as being attributed to a possible genetic origin.[6]

This study aimed to define different clinical variables in patients with bilateral Ménière's disease, the evolution of their vertigo episodes and hearing affectation, as well as to assess whether these variables differed following the development of synchronous or metachronous bilateral Ménière's disease. In addition, we attempted to elucidate prognostic factors for the conversion from unilateral Ménière's disease to bilateral Ménière's disease by comparing our series of bilateral Ménière's disease patients with those with unilateral Ménière's disease.

Materials and methods

The study was carried out on patients with bilateral Ménière's disease managed at two referral centres, collecting data in a database from 1977 to 2019 using MEN medical management software.[11] All the patients included in the cohort met the updated bilateral Ménière's disease diagnostic criteria.[12,13]

The time elapsed between the first and the last visit to the otolaryngologist (ENT specialist) was considered the patient's follow-up time. For those who underwent surgical or ablative treatment, the date of the intervention was defined as the end of the follow-up period for our study because the following procedures alter the natural course of the disease: chemical labyrinthectomy (including intratympanic injection of gentamicin from the first dose), surgical labyrinthectomy, decompression of the endolymphatic sac, vestibular neurectomy and/or cochlear implant. Accordingly, for patients who underwent more than one intervention, any revisions after the first of these were not considered.

The date of occurrence of the disease in each ear was defined by the date of symptom onset in each ear. The disease was considered to be established in the first ear affected by the occurrence of the symptomatic triad, whereas disease occurrence in the second ear was confirmed by hearing loss and tinnitus. Bilateral Ménière's disease onset in patients was classified as metachronous when the interval between the onset of the disease in one ear and that in the contralateral ear was greater than one year, whereas it was classified as synchronous when this interval was less than one year.

After their first visit, the patients visited the ENT specialist every six months for a check-up, even if they were not symptomatic or their symptoms were controlled with the treatments previously prescribed. Different clinical (timing and duration of vertigo episodes, date of onset of each symptom, associated diseases, presence of Tumarkin's crisis), therapeutic (surgical or ablative treatments and the date when the treatment began or the surgical intervention was performed) and audiometric (low-frequency (0.12, 0.25 and 0.5 kHz), high-frequency (1, 2 and 4 kHz) and pantonal hearing loss) variables were collected.

A dual statistical design was employed, with a descriptive longitudinal study on the one hand and an analytical and observational nested case–control study on the other.

Graphical representations of 'survival' curves were used to describe the temporal evolution of the disease, which allow the median time to reach certain events to be defined, in our case the bilaterality of the disease, and to gain a global idea of the temporal disease evolution.

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

The temporal evolution of vertigo episodes was modelled over time based on the mean episodes suffered in each year of the follow up, reflecting this evolution in a similar way to routine clinical practice. These mean episodes were plotted against the years of disease evolution.

In order to assess the risk of conversion from unilateral Ménière's disease to bilateral Ménière's disease (metachronous), a nested case–control study of the cohort was carried out. The case group included patients with metachronous bilateral Ménière's disease, studying them throughout their evolution from unilateral Ménière's disease until the onset of the symptoms in the second ear, and using a control group of unilateral Ménière's disease patients with the same time of disease evolution as these corresponding cases but with no conversion to bilateral Ménière's disease. The risk factors that could influence the time that elapses between unilateral and bilateral involvement were analysed using conditional logistic regression models, and the odds ratio with a 95 per cent confidence interval (CI) was used as a measure of any association. A *p*-value less than 0.05 was used as a level of statistical significance for all the comparisons between the two groups.

Results

General descriptive data

Data were collected from 59 patients with bilateral Ménière's disease, including 39 men (66.1 per cent) and 20 women (33.9 per cent) with a mean age at diagnosis of 50.1 years (standard deviation (SD) = 15.6; range: 15–87 years). Most cases were metachronous bilateral Ménière's disease ($n = 45$, 76.3 per cent) with fewer synchronous bilateral Ménière's disease cases ($n = 14$, 23.7 per cent).

The median time elapsed between the onset in one ear and the involvement of the other ear in the patients with metachronous bilateral Ménière's disease was 7 years (95 per cent CI = 5.8–8.4 years) (Figure 1).

Symptoms timeline

Of all the total patients with bilateral Ménière's disease, those presenting with the classic triad of symptoms at the onset of

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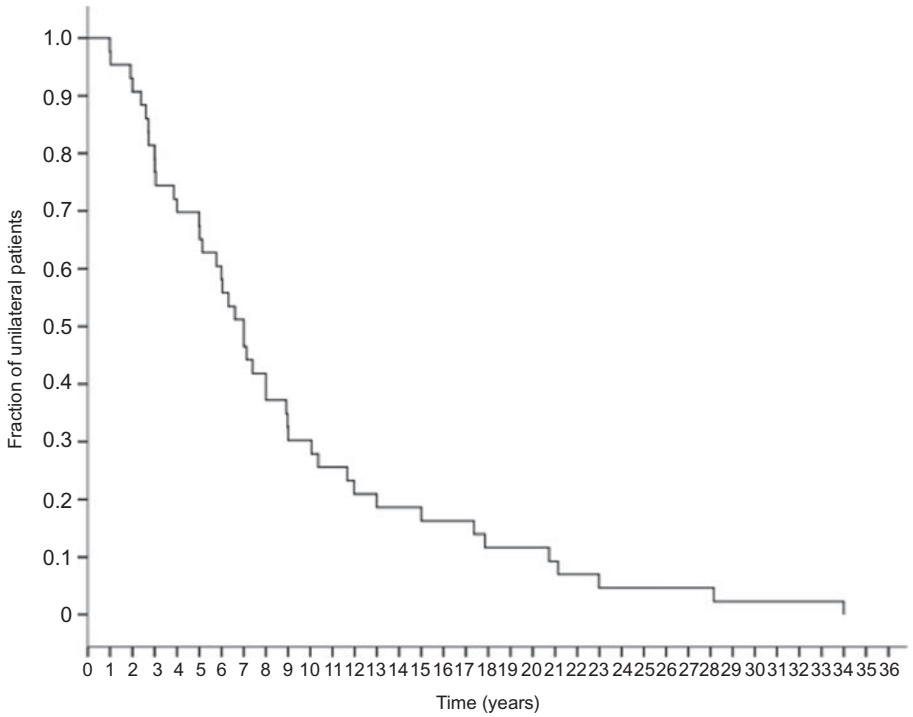

Figure 1. Kaplan–Meier plot of the median time elapsed from the onset of the disease in one ear to bilateral involvement.

the disease in the first ear were the most common (50 per cent), whereas the hearing loss and tinnitus dyad was the most common at the onset of second ear involvement (37 per cent). When analysing data using clinical models of disease onset in patients with metachronous bilateral Ménière's disease, the most frequent initial symptom in the first affected ear was the triad of symptoms (45.5 per cent), whereas it was the hearing loss and tinnitus dyad in the second ear (81.8 per cent). Regarding the synchronous onset, most patients presented with the triad of symptoms in both ears, with 64.3 per cent in the first ear and 50 per cent in the second ear (Table 1).

Table 1 shows the symptoms with which Ménière's disease debuted in each patient, differentiating these debut symptoms to the onset of the disease in each ear. These results are shown as a percentage and number of patients, on the total number of patients and in each of the forms of bilateral Ménière's disease.

Evolution of vertigo episodes

The mean number of annual vertigo episodes in the bilateral Ménière's disease patients decreased progressively over the first 10 years of the disease, punctuated with periods of exacerbation (Figure 2).

The mean number of annual vertigo episodes during the first years of the disease was higher in patients with synchronous onset than in those with metachronous onset, while the latter showed a slower extinction of these and a higher mean number of annual episodes in the subsequent years (Figure 3).

Evolution of hearing

The patients with bilateral Ménière's disease exhibited a moderate degree of mean hearing loss at the beginning of the disease follow up, whereas this was severe at the end of the follow up. Hearing loss was greater in synchronous bilateral Ménière's disease cases, especially at lower frequencies (Table 2).

Risk factors for bilateral Ménière's disease

Risk factors for the development of bilateral Ménière's disease were studied in a specific cohort using a nested case–control design, defining those factors that could contribute to bilaterality (Figure 4). Although we cannot rule out the role of chance, more symptoms at onset and, especially, the presence of migraine were two candidate factors to be considered as predictors of conversion from unilateral Ménière's disease to bilateral Ménière's disease.

Discussion

In this study the prevalence of different clinical variables was assessed in patients with bilateral Ménière's disease, comparing them between metachronous and synchronous bilateral Ménière's disease. Bilateral involvement in bilateral Ménière's disease is assessed distinctly in different published studies, from evaluating small hearing changes in the contralateral ear in older studies to evaluating compliance with diagnostic criteria in more recent studies. In an earlier study of 126 patients with unilateral Ménière's disease, only 5 per cent of the patients developed bilateral Ménière's disease when diagnosed by hearing fluctuations and the presence of tinnitus in the contralateral ear, as well as by simultaneous vertigo episodes, even when appearing within a short period.[8] However, if only hearing changes were considered, the percentage of patients considered to evolve to bilateral Ménière's disease ranged from 16 per cent to 29 per cent. Elsewhere, involvement of the contralateral ear was detected in 11 per cent of Ménière's disease cases at baseline and in 14 per cent of cases during the follow-up period.[4] However, when only those cases that presented hearing changes or cochlear hydrops were considered as bilateral Ménière's disease, they represented 6.5 per cent of the cases at baseline and 26 per cent during the follow up.

Here, bilateral Ménière's disease was diagnosed when hearing loss and/or fluctuation, tinnitus and episodes of vertigo were evident. However, when verifying these onset symptoms

https://doi.org/10.1017/S0022215122002262 Published online by Cambridge University Press

Table 1. Number and percentage of patients according to the symptoms at bilateral Ménière's disease onset in each ear and based on the synchronous and metachronous clinical models of disease onset

Parameter	Total bilateral Ménière's disease patients				Onset type							
					Metachronous				Synchronous			
	Symptoms at onset in the first ear		Symptoms at onset in the second ear		Symptoms at onset in the first ear		Symptoms at onset in the second ear		Symptoms at onset in the first ear		Symptoms at onset in the second ear	
	Value (*n*)	Value (%)	Value (*n*)	Value (%)	Value (*n*)	Value (%)	Value (*n*)	Value (%)	Value (*n*)	Value (%)	Value (*n*)	Value (%)
T	0	0.0	2	3.5	0	0	1	2.3	0	0	1	7.1
H	1	1.7	6	10.3	1	2.3	6	13.6	0	0	0	0
H+T	11	19	37	63.8	10	22.7	36	81.8	1	7.1	1	7.1
V	11	19	3	5.2	9	20.5	1	2.3	2	14.3	2	14.3
V+T	5	8.6	1	1.7	4	9.1	0	0	1	7.1	1	7.1
V+T+H	29	50	7	12	20	45.5	0	0	9	64.3	7	50
V+H	1	1.7	2	3.5	0	0	0	0	1	7.1	2	14.3

V = vertigo; T = tinnitus; H = hearing loss

in the second ear in patients with metachronous bilateral Ménière's disease, episodes of vertigo were not taken into account as an onset symptom because it may not be clear which ear is causing vertigo. Accordingly, the disease evolution and the tests performed confirmed our suspected diagnosis. Hence, of the 81.8 per cent of patients in our study with metachronous bilateral Ménière's disease who developed the hearing loss and tinnitus dyad at disease onset in the second ear, a high percentage might have presented with the classic Ménière's disease triad at the onset of second ear involvement. The presence of migraine in our sample may have been underestimated,[14] perhaps because of a less rigorous assessment of the presence of migraine in the first years of data collection when the migraine–Ménière's disease relationship did not have the relevance that it currently has. This may explain some differences between our findings and those presented elsewhere, in which the prevalence of migraine-type headaches reached 41–49 per cent in bilateral Ménière's disease.[10,15]

It has been proposed that the proportion of patients with bilateral Ménière's disease among patients with Ménière's disease increases with disease duration.[16,17] The median time here to convert to bilateral involvement in patients with metachronous bilateral Ménière's disease was seven years, similar to that indicated previously in a series of patients,[5] some of whom were included in this study. Although it is true that the time our patients took to display bilateral Ménière's disease ranged from 1 to 34 years, if we had analysed this at different times, the proportion of patients developing bilaterality would fall progressively over the years. It should be noted that, despite the progressive increase in bilaterality, this mostly takes place in the first seven years of the disease. Hence, we believe that, if possible, an interval of about seven years should be allowed before considering ablative treatment to reduce the possibility of Ménière's disease becoming bilateral, given both the decline in bilateral auditory function and the significant instability associated with bilaterality.

As all surgical techniques can modify the course of the disease, we classified patients as 'operated' and 'not operated' without analysing the results according to each technique used because this was not the purpose of our study. In our series, 28.8 per cent of the patients with bilateral Ménière's disease required intervention in one of the two ears at some point in their disease evolution. We did not find any existing data on the proportion of patients with bilateral Ménière's disease who required surgical treatment. A few studies have analysed the differences between the clinical types of bilateral Ménière's disease and, consistently with previous findings,[6] we did not find significant differences between the synchronous and metachronous bilateral Ménière's disease subgroups in terms of the presence of migraines, Tumarkin's crisis, diabetes, dyslipidaemia or arterial hypertension. However, patients with synchronous bilateral Ménière's disease were previously thought to present a significantly more advanced stage of hearing loss than those patients with metachronous bilateral Ménière's disease. By contrast, in this study the hearing loss in patients with synchronous bilateral Ménière's disease was greater than that in patients with metachronous bilateral Ménière's disease, with significantly worse hearing loss at low frequencies.

The nested case–control study of a cohort of patients allowed us to compare a patient with metachronous bilateral Ménière's disease with a patient with unilateral Ménière's disease who was at the same stage of their disease evolution just

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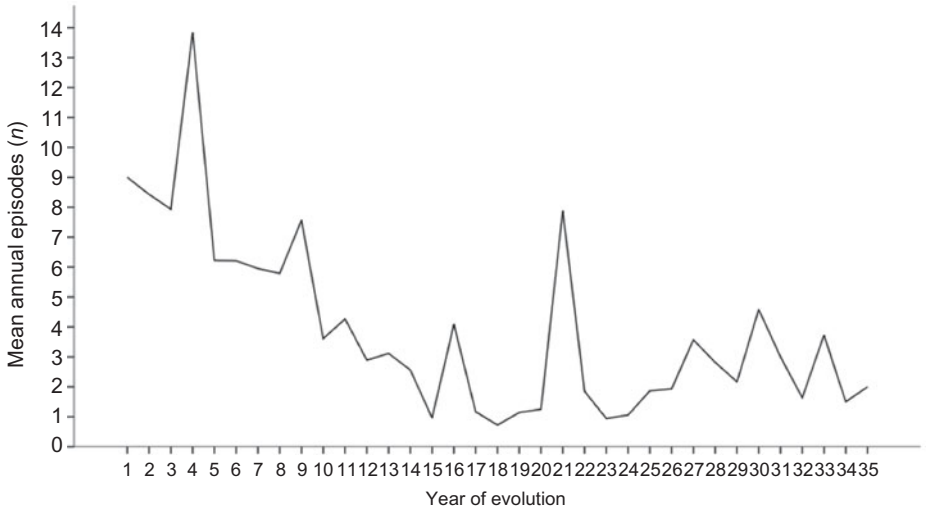

Figure 2. Mean number of annual episodes in patients with bilateral Ménière's disease.

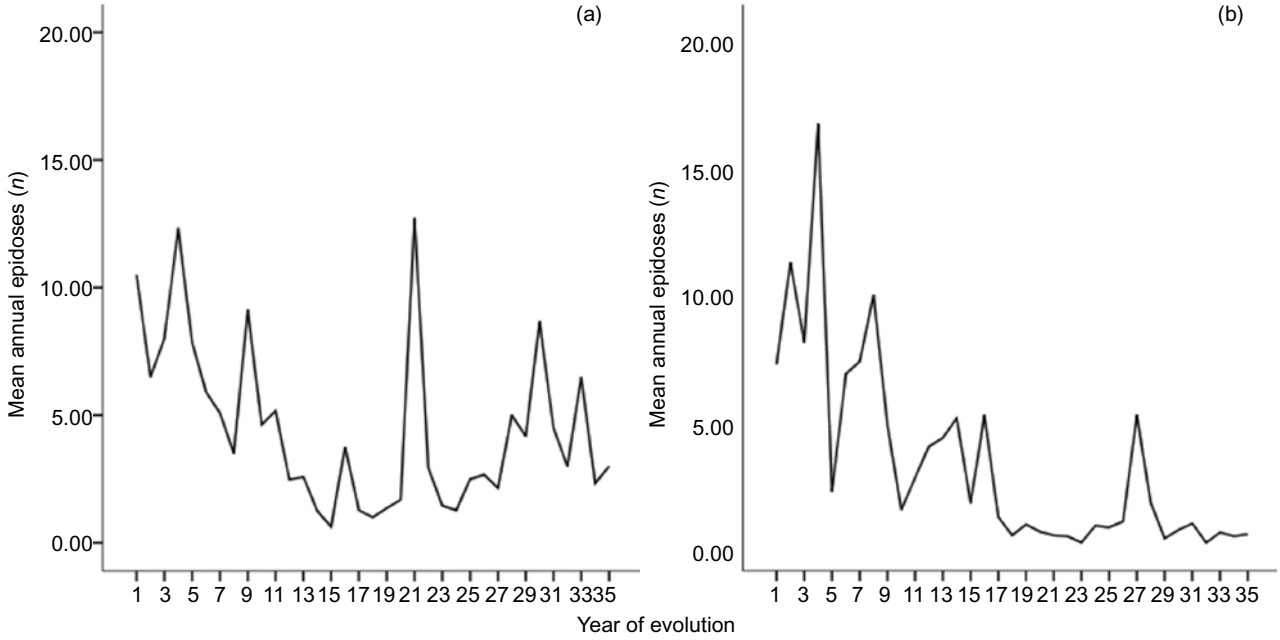

Figure 3. Mean number of annual episodes in patients with (a) metachronous and (b) synchronous bilateral Ménière's disease.

Table 2. Hearing loss in bilateral Ménière's disease patients according to clinical models and grouped by frequency

Hearing loss	Type	Patients (*n*)	Mean (dB)	SD (dB)	*P*-value
Pantonal	Metachronous	84	29.14	19.95	0.18
	Synchronous	34	34.75	21.88	
Low frequency	Metachronous	84	28.35	20.00	0.049
	Synchronous	34	36.71	22.42	
High frequency	Metachronous	84	29.94	21.56	0.53
	Synchronous	34	32.79	23.68	

SD = standard deviation

before the onset of the disease in the second ear. This comparative analysis enabled the factors associated with the development of metachronous bilateral Ménière's disease to be determined in those patients who presented with unilateral Ménière's disease. Although none of the results reached statistical significance, the presence of migraine and the number of symptoms at onset appear to be factors related to the development of bilateral Ménière's disease, without being able to rule this out as a chance finding. Currently, another factor that might predispose an individual to the development of bilateral Ménière's disease is thought to be hypoplasia of the endolymphatic sac.[18,19]

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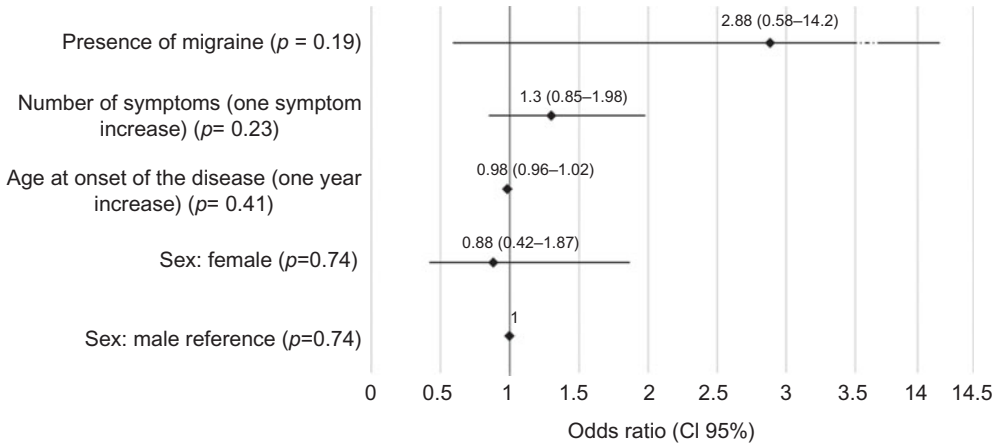

Figure 4. Results of the nested case–control study within a cohort. CI = confidence interval

We can consider several limitations of our study. As it is an observational study of variables collected in real-life clinical practice, there may be a potential information bias related to the data provided by the patient or requested by the researcher. Although this bias is inherent in the observational study design, the careful collection of data and the homogeneity in the follow up of the patients by the same observers, as well as the revision and correction of each patient's data in the database, lead us to think that the effect of any such bias is minimal and that it does not invalidate the conclusions of the study. There have also been different changes in the diagnostic criteria for Ménière's disease over the years, and although the diagnosis of each patient in our study has been double-checked, there may be isolated cases where the diagnosis may be inaccurate. In addition, we assumed that non-surgical treatments have no impact on the natural evolution of the disease, as there is currently no evidence to the contrary.

- Compared with the unilateral form, bilateral Ménière's disease is more complicated in terms of management and treatment
- Bilateral Ménière's disease has a worse prognosis because it involves progressive hearing and vestibular loss that does not imply greater functional disability
- Most studies generically assess bilateral Ménière's disease patients without assessing the possible differences or characteristics based on subgroups
- One way to classify bilateral Ménière's disease is based on the symptomatic onset of the disease in each ear as synchronous and metachronous
- Most patients with bilateral Ménière's disease have metachronous presentation; the synchronous form, although infrequent, presents greater auditory repercussions
- Attempts have been made to identify factors that predict conversion from unilateral to bilateral disease: the number of onset symptoms and migraine could be some predictive factors

The weakest point of our study is perhaps the fact that we have not taken into account variables such as the association with autoimmune diseases or family history. There are currently studies in the literature that suggest these variables may define possible subtypes of Ménière's disease. By contrast, our work takes advantage of a database that contains data from a very large number of patients collected over a very long follow-up time, allowing us to better understand the behaviour of the disease in our setting. Thanks to having data available from the whole course of the patient's disease, we have been able to perform a statistical analysis that is uncommon in this type of setting: a nested case–control study within a cohort of patients that allowed us to assess factors related to the development of bilateral Ménière's disease.

Conclusion

In our setting, 50 per cent of patients with bilateral Ménière's disease presented with the classic triad of symptoms at disease onset in the first ear, whereas the presentation of the dyad of hearing loss and tinnitus was most common at the onset of involvement of the second ear (37 per cent). Regarding the onset of vertigo, a higher mean number of annual episodes are observed in the first years of disease evolution for synchronous bilateral Ménière's disease, and the metachronous type of bilateral Ménière's disease showed a slower disease evolution with more annual episodes in the subsequent years.

With regard to hearing impairment, those patients with synchronous bilateral Ménière's disease suffer worse hearing loss at low frequencies than those cases of metachronous bilateral Ménière's disease. The presence of migraine seems to be a factor that may predict the conversion from unilateral Ménière's disease to bilateral Ménière's disease; thus, it would be of great interest to study this further. Our work defines the symptomatic evolution of bilateral Ménière's disease in detail based on different variables, which we believe will help improve the symptomatic control of Ménière's disease patients and provide a better understanding of the disease evolution, perhaps enabling its possible evolution to be prevented in some cases.

Acknowledgements. The authors acknowledge all the Ménière's disease patients who participated in this study with special reference to our friend and professor, Doctor Herminio Pérez-Garrigues who worked all his life with Ménière's disease patients trying to give them a better quality of life.

Competing interests. None declared

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