



# Clinical Subgroups in Bilateral Meniere Disease

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Meniere disease (MD) is a heterogeneous clinical condition characterized by sensorineural hearing loss, episodic vestibular symptoms, and tinnitus associated with several comorbidities, such as migraine or autoimmune disorders (AD). The frequency of bilateral involvement may range from 5 to 50%, and it depends on the duration of the disease. We have performed a two-step cluster analysis in 398 patients with bilateral MD (BMD) to identify the best predictors to define clinical subgroups with a potential different etiology to improve the phenotyping of BMD and to develop new treatments. We have defined five clinical variants in BMD. Group 1 is the most frequently found, includes 46% of patients, and is defined by metachronic hearing loss without migraine and without AD. Group 2 is found in 17% of patients, and it is defined by synchronic hearing loss without migraine or AD. Group 3, with 13% of patients, is characterized by familial MD, while group 4, that includes 12% of patients, is associated by the presence of migraine in all cases. Group 5 is found in 11% of patients and is defined by AD. This approach can be helpful in selecting patients for genetic and clinical research. However, further studies will be required to improve the phenotyping in these clinical variants for a better understanding of the diverse etiological factors contributing to BMD.

**Keywords:** cluster analysis, vestibular disorders, hearing loss, tinnitus, Meniere's disease, migraine, autoimmune disorders, inner ear

## INTRODUCTION

Meniere's disease (MD) is a long-lasting disorder of the inner ear characterized by episodes of vertigo lasting from 20 min to hours, low-to-middle frequencies sensorineural hearing loss (SNHL, **Table 1**), tinnitus, and aural fullness (1). MD patients have phenotypic heterogeneity (2), and it is difficult to define the outcome of the disease in its early stages. Although the frequency of the spells of vertigo is typically greater during the earlier years (3–5), balance problems are observed during the course of the disease and might become severe if patients progress to a bilateral vestibular hypofunction (6, 7). Most of the patients start with SNHL in one ear, and it can appear in the other after several years (metachronic SNHL) (8), but a significant number of individuals show simultaneous SNHL (synchronic SNHL). Bilateral involvement is a major concern for patients because of the loss of vestibular function, and bilateral SNHL has a significant influence in the health-related quality of life in MD patients (9).

Several studies have reported contralateral ear involvement between 2 and 73% of cases, depending on the interval of follow-up and the diagnostic criteria used. However, if bilateral MD (BMD) was defined as the combination of clinical symptoms and audiometric tests, the frequency would be 2–47% (7). Some studies describe an interval of 5 years where the incidence was 10–35% (8, 10–13), while in other studies, with a follow-up of 10 years or more, the frequency of BMD ranges from 20 (14–16) to 46% (17). However, more than 20 years of follow-up have also been described, and the incidence rate of bilaterality rises up to 47% (18–22). Although there is a great disparity in the percentage of individuals with bilateral involvement, most of the studies highlighted that the number of patients with contralateral ear involvement increased with the duration of the disease (18, 21, 22).

Several comorbidities have been associated with MD, including autoimmune disorders and migraine. So, MD has been previously associated with several autoimmune diseases, such as systemic lupus erythematosus, psoriasis, or rheumatoid arthritis (6, 23), and autoimmunity has been suggested as a potential cause in MD (24) relying on the results of proteomic studies achieved in small series of patients (24–26). However, high levels of circulating immune complexes were not found in most of the patients with MD (27).

Furthermore, autoimmune mechanisms seem to be associated with the pathogenesis of some types of SNHL (28, 29), such as sudden SNHL (30), promptly progressive bilateral SNHL (31), and MD (32–34). Additionally, several genes of the immune system have been studied in case–control studies (35–38), but they have not been replicated. Moreover, some data suggest that allelic variants of *MICA* and *TLR10* genes, involved in the innate immune response, may influence the susceptibility and time course of hearing loss of MD in European population (39, 40).

Migraine has been consistently found to be more common in MD than in the general population in case–control studies (41), but it is not clear if this association has any role in the pathophysiology of MD. Vestibular migraine (VM), the condition of episodic vestibular symptoms linked to migraine spectrum (42), may occur in some patients concomitantly with MD (43).

Genetic factors are probably relevant in a subset of patients with MD. So, familial MD was first described in 1949 by Brown (44), and many studies have described familial cases of MD (45). The genetic contribution to MD has been recently reviewed (46, 47), and there are several evidences to support a genetic origin in MD. These evidences include (a) the prevalence is higher in European descent population than in Asian (48) or African populations (49) and (b) familial aggregation has been observed in 6% in South Korea and 8–9% in Spain (2), being

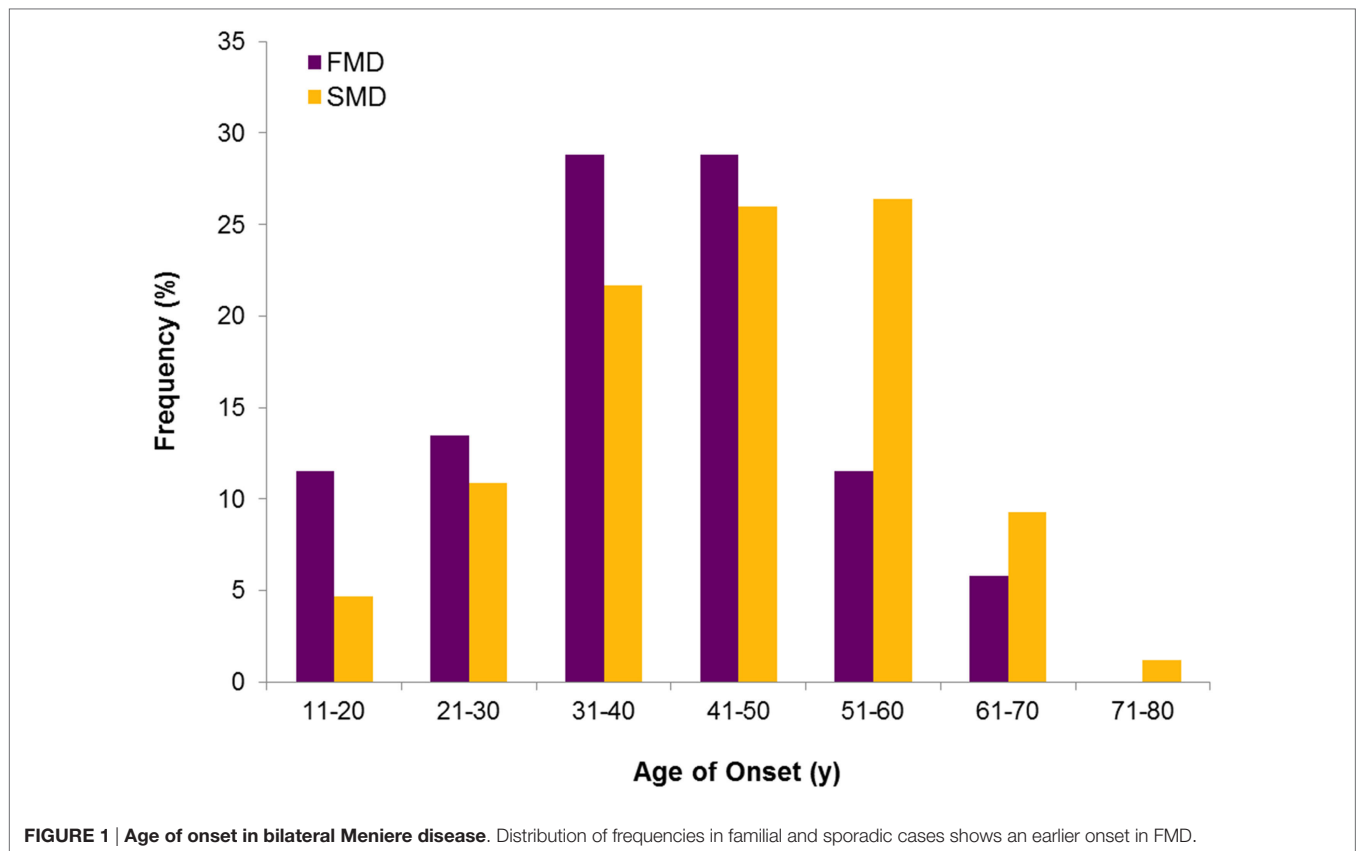
**TABLE 1 | List of abbreviations.**

AAO-HNS	American Academy Otolaryngology – Head Neck Surgery
AD	Autoimmune disorders/disease
AIED	Autoimmune inner ear disorder
BMD	Bilateral Meniere disease
BMD type 1	Metachronic hearing loss
BMD type 2	Synchronic hearing loss
BMD type 3	Familial Meniere disease
BMD type 4	Meniere disease + migraine
BMD type 5	Meniere disease + autoimmune disease
FMD	Familial Meniere disease
MD	Meniere disease
MRI	Magnetic resonance imaging
RCT	Randomized clinical trials
SNHL	Sensorineural hearing loss
SMD	Sporadic Meniere disease

**TABLE 2 | Clinical phenotype in sporadic and familial Meniere disease with at least 5 years since the onset of the disease.**

Variables	FMD (n = 52)	SMD (n = 258)	p-value
Age, mean (SD)	55.5 (12.7)	61.5 (11.1)	<b>0.001</b>
Gender (% women)	34 (65.4)	147 (57.0)	0.28
Age of onset (SD)	39 (12.9)	44.8 (13.1)	<b>0.003</b>
Age of onset ≤40, n (%)	28 (53.8)	96 (37.2)	<b>0.03</b>
Time course (years), mean (SD)	16.3 (8.7)	16.3 (9.4)	0.96
Synchronic, n (%)	11 (21.6)	72 (27.9)	0.39
Metachronic, n (%)	40 (78.4)	186 (72.1)	
Hearing loss at diagnosis, mean (SD)	51.9 (15.5)	56.6 (17.8)	0.092
Headache, n (%)	23 (44.2)	92 (36.1)	0.27
Migraine, n (%)	13 (25.0)	44 (17.3)	0.24
Rheumatoid history, n (%)	10 (20.4)	25 (9.8)	<b>0.048</b>
Hearing stage, n (%)			
1	0 (0.0)	4 (1.6)	0.58
2	9 (17.6)	35 (13.6)	
3	28 (54.9)	131 (51.0)	
4	14 (27.5)	87 (33.9)	
Cardiovascular risk			
High blood pressure, n (%)	13 (26.5)	93 (39.7)	0.1
Dyslipidemia, n (%)	21 (42.0)	111 (47.6)	0.53
Type 2 diabetes, n (%)	12 (24.0)	41 (17.4)	0.32
Smoking, n (%)	15 (30)	53 (21.5)	0.2
Tumarkin crisis, n (%)	17 (35.4)	63 (25.5)	0.16
Functional Scale, n (%)			
1	9 (17.6)	53 (21.3)	0.81
2	15 (29.4)	71 (28.5)	
3	10 (19.6)	58 (23.3)	
4	7 (13.7)	35 (14.1)	
5	7 (13.7)	25 (10.0)	
6	3 (5.9)	7 (2.8)	

SMD, sporadic Meniere disease; FMD, familial Meniere disease. Significant p values in bold.



**TABLE 3 | Autoimmune diseases and other rheumatoid conditions observed in patients with bilateral Meniere disease.**

Autoimmune diseases	N
Rheumatoid arthritis	10
Fibromyalgia	6
Arthrosis	5
Ankylosing spondylitis	5
Psoriasis	4
Hypothyroidism	3
Sjogren syndrome	3
Type 1 diabetes	2
Rosacea	2
Graves-Basedow disease	2
Systemic lupus erythematosus	2
Psoriatic arthritis	1
Autoimmune inner ear disease	1
Polymyalgia rheumatica	1
Inflammatory bowel disease	1
Cogan syndrome	1
Hip synovitis	1
Carpal tunnel syndrome	1
Undetermined	10

*DTNA* and *FAM136A* genes involved in autosomal dominant familial MD (50).

The aim of this study is to describe the phenotype of patients with BMD, including comorbidities such as autoimmune diseases or familial aggregation, and to perform a cluster analysis to identify clinical variants in BMD.

## MATERIALS AND METHODS

### Subjects

A multicenter, cross-sectional retrospective study was designed, including patients with BMD diagnosed and tracked by the Meniere’s Disease Consortium. For this, the clinical records of a total of 405 patients diagnosed with definite BMD from 16 clinical centers in Spain and Portugal were reviewed in March 2016. MD diagnosis was established according to the diagnostic scale of the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) (51). Familial MD (FMD) was defined if at least another relative (first or second degree) fulfilled all the criteria of definite or probable MD, according to the criteria established by the Barany Society International Classification for Vestibular Disorders (1). Patients with unilateral MD or bilateral BMD with less than 5 years of evolution were excluded of the study. Seven patients were excluded because of inconsistent data. This study was approved by the Institutional Review Board for Clinical Research (PI-13-1242).

Every patient underwent a complete neuro-otological evaluation, including a pure-tone audiometry, an otoscopy, nystagmus examination, and a caloric testing. A brain MRI was performed to exclude any other possible cause of neurological symptoms. Patients with simultaneous SNHL in both ears were considered to have synchronic SNHL, while metachronic SNHL was considered if an interval longer than 1 month between the first and the second ear was observed.

**TABLE 4 | Clinical features of sporadic and familial bilateral Meniere disease stratified by the presence of autoimmune disease (AD).**

Variables	Sporadic MD			Familial MD		
	AD+ (n = 25)	AD- (n = 230)	p-value	AD+ (n = 10)	AD- (n = 39)	p-value
Age, mean (SD)	61.7 (9.1)	61.6 (11.2)	0.94	56.5 (13.8)	55 (12.4)	0.74
Gender (% women)	18 (72.0)	128 (55.7)	0.14	6 (60.0)	26 (66.7)	0.72
Age of onset (SD)	43.4 (11.0)	45.2 (13.2)	0.5	35.9 (12.3)	40.5 (13.0)	0.31
Age of onset ≤40, n (%)	11 (44.0)	82 (35.7)	0.51	6 (60.0)	19 (48.7)	0.73
Time course (years), mean (SD)	17.4 (8.7)	16.1 (9.6)	0.52	20.7 (8.9)	14 (7.0)	<b>0.01</b>
Hearing loss at diagnosis, mean (SD)	57.5 (18.3)	56.7 (17.8)	0.83	52.3 (15.2)	52 (15.9)	0.96
Headache, n (%)	15 (62.5)	77 (33.5)	<b>0.007</b>	8 (80.0)	14 (35.9)	<b>0.03</b>
Migraine, n (%)	8 (33.3)	36 (15.7)	<b>0.044</b>	5 (50.0)	7 (17.9)	<b>0.05</b>
Hearing stage, n (%)						
1	0 (0.0)	4 (1.7)	0.37	0 (0.0)	0 (0.0)	0.32
2	5 (20.0)	30 (13.1)		1 (11.1)	8 (20.5)	
3	9 (36.0)	119 (52.0)		4 (44.4)	23 (59.0)	
4	11 (44.0)	76 (33.2)		4 (44.4)	8 (20.5)	
Cardiovascular risk factors						
High blood pressure, n (%)	13 (59.1)	80 (37.7)	0.07	2 (20.0)	10 (27.0)	1
Dyslipidemia, n (%)	12 (50.0)	97 (46.9)	0.83	4 (40.0)	16 (42.1)	1
Type 2 diabetes, n (%)	8 (33.3)	33 (15.8)	<b>0.046</b>	5 (50.0)	7 (18.4)	0.09
Smoking, n (%)	6 (28.6)	47 (21.0)	0.41	3 (30.0)	12 (30.8)	1
Tumarkin crisis, n (%)	6 (27.3)	57 (25.3)	0.8	5 (50.0)	12 (32.4)	0.46
Functional Scale, n (%)						
1	4 (17.4)	48 (21.3)	0.94	2 (20.0)	7 (17.9)	<b>0.007</b>
2	7 (30.4)	64 (28.4)		4 (40.0)	11 (28.2)	
3	6 (26.1)	52 (23.1)		1 (10.0)	8 (20.5)	
4	2 (8.7)	33 (14.7)		0 (0.0)	6 (15.4)	
5	3 (13.0)	22 (9.8)		0 (0.0)	7 (17.9)	
6	1 (4.3)	6 (2.7)		3 (30.0)	0 (0.0)	

Significant *p* values in bold.

Clinical variables studied were as follows: gender, duration of disease, age of onset, family history of MD, hearing loss at diagnosis, hearing stage defined as four-tone average of 0.5, 1, 2, and 3 kHz according to the AAO-HNS criteria (stage 1, ≤25 dB; stage 2, 26–40 dB; stage 3, 41–70 dB, and stage 4, >70 dB), type of headache (migraine, tension-type headache), history of autoimmune disease (AD), cardiovascular risk factors (high blood pressure, type 2 diabetes, dyslipidemia, and smoking), Tumarkin crisis, and the Functional Scale of the AAO-HNS.

## Statistical Analysis

A descriptive statistical analysis was carried out using SPSS software v.22 (SPSS Inc., Chicago, IL, USA). Data are shown as means with their SDs. Quantitative variables were compared using Student's unpaired *T*-test. Qualitative variables were compared using crosstabs and Fisher's exact test. Nominal *p*-values <0.05 were considered statistically significant.

We carried out a two-step cluster analysis using log-likelihood distance measures, which can detect relationships within a complex dataset between patients with multiple distinct characteristics. It tries to identify homogenous groups of cases based on the distribution of some variables (input variables). The method identifies the groups by running pre-clustering first and then by using hierarchical methods to classify and to find the optimal number of clusters.

Initially, we selected variables showing differences between the clinical groups during the descriptive analysis to test its relevance as predictors of clusters. The procedure was iterated several times

until we found the minimum number of homogenous clusters. The final cluster analysis was applied using the four following categorical variables: history of autoimmune disease, onset of hearing loss (synchronic/metachronic), FMD or sporadic cases, and migraine. The four variables included produced a silhouette of cohesion and division of 0.8, indicative of good data partitioning. Two additional variables were added to the model: age of onset <40 years old and gender, although their contribution to refine the clustering was limited.

## RESULTS

Three hundred ninety-eight patients with BMD were included in the study. There were 258 sporadic cases and 52 individuals with FMD (20%). Although apparently there were no clinical differences in the phenotype between sporadic and familial cases, FMD had an earlier age of onset (*p* = 0.003) and a higher prevalence of autoimmune comorbidities (Table 2). So, the distribution of frequencies for the age of onset showed that the number of patients starting before 40 years old was significantly higher in the FMD (Figure 1). Table 3 lists the autoimmune comorbid conditions found, being rheumatoid arthritis the most common in our cohort.

The clinical features in patients with sporadic and FMD were stratified according to the presence or absence of autoimmune comorbidities. In the sporadic cases, headache and migraine were most commonly observed in patients with autoimmune background (62.5 and 33%, respectively) compared with patients without autoimmune comorbidities (33 and 16%), suggesting

a potential association between migraine and autoimmunity in patients with sporadic BMD (Table 4).

We also compared patients according to the onset of hearing loss (Table 5). One hundred three (26%) individuals developed simultaneous hearing loss in both ears (synchronic hearing loss, either symmetric or asymmetric), while 291 (73%) patients started with hearing loss in one ear and developed

the hearing loss in the contralateral ear (metachronic hearing loss). Figure 2 compares the distribution of frequencies for the age of onset in patients with synchronic or metachronic hearing loss. There were no clinical differences between them, but the occurrence of headache was most commonly observed in synchronic hearing loss ( $p = 0.0004$ ), and the worst hearing stage was observed in patients with metachronic hearing loss ( $p = 0.004$ ).

We performed cluster analysis to identify groups of patients with common clinical features in BMD. Figure 3 shows the size of the clusters, the relevance of predictors, and the contribution of each predictor to define the cluster. The best predictors for clustering were autoimmune history, FMD, migraine, and the onset of hearing loss (synchronic/metachronic). Ninety-five patients remained unclassified because of incomplete clinical data.

We have defined five clusters for BMD and ranked them according to its relative frequency (Figure 4). Cluster 1 is the most common, including 46.5% of patients, and it is defined by metachronic hearing loss without migraine, sporadic BMD, and no autoimmune history. Cluster 2 (17.5%) includes patients with synchronic hearing loss, sporadic BMD, no migraine, and no autoimmune history. Cluster 3 (12.9%) includes patients with FMD without migraine in 82% of patients. Cluster 4 (11.9%) consists of patients with migraine and sporadic BMD. Cluster 5 (11.2%) groups all patients with autoimmune comorbidities, being 71% sporadic and 29% FMD.

Table 6 shows the five groups found and the major clinical differences among the groups. Comparing the age of onset by groups, we observe that groups 3–5 have earlier onsets than groups 1 and 2 ( $p = 0.0003$ ). The type of hearing loss, FMD, migraine, and autoimmune comorbidities strongly differ among groups, and these variables are the basis to assign a given patient to each cluster.

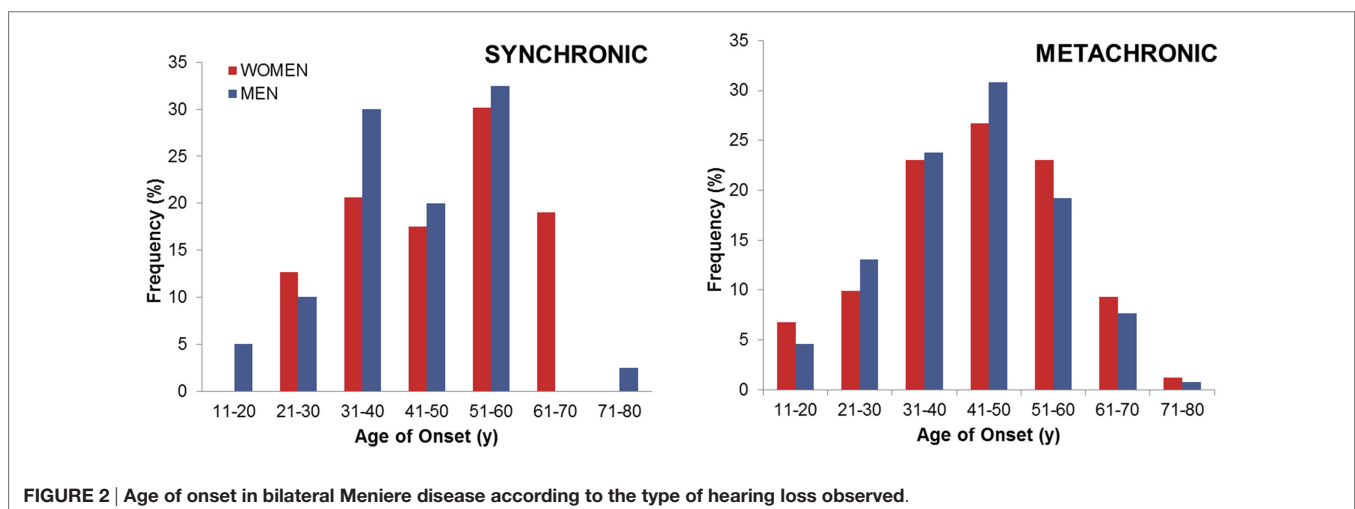
**TABLE 5 | Clinical features in bilateral Meniere disease according to the onset of hearing loss.**

Variables	Synchronic (n = 103)	Metachronic (n = 291)	p-value
Age, mean (SD)	61 (11.0)	60.1 (11.9)	0.49
Gender (% women)	63 (61.2)	161 (55.3)	0.36
Age of onset (SD)	46.1 (12.8)	43.5 (13.2)	0.07
Age of onset ≤40, n (%)	39 (37.9)	118 (40.5)	0.73
Time course (years), mean (SD)	14.4 (8.9)	16.2 (8.9)	0.08
Family history, n (%)	39 (39.8)	119 (43.0)	0.64
FMD, n (%)	11 (13.3)	40 (17.7)	0.39
Hearing loss at diagnosis, mean (SD)	55.1 (17.0)	55.9 (17.0)	0.71
Headache, n (%)	55 (53.4)	96 (33.3)	<b>0.0004</b>
Migraine, n (%)	25 (24.3)	49 (17.0)	0.11
Rheumatoid history, n (%)	15 (15.0)	35 (12.2)	0.49
Hearing stage, n (%)			<b>0.004</b>
1	1 (1.0)	6 (2.1)	
2	27 (26.5)	34 (11.7)	
3	42 (41.2)	152 (52.4)	
4	32 (31.4)	98 (33.8)	
Cardiovascular risk			
High blood pressure, n (%)	47 (51.1)	109 (39.9)	0.068
Dyslipidemia, n (%)	53 (55.2)	121 (45.1)	0.097
Type 2 diabetes, n (%)	13 (13.5)	50 (18.5)	0.35
Smoking, n (%)	22 (21.8)	68 (24.5)	0.68
Tumarkin crisis, n (%)	24 (25.8)	69 (24.9)	0.89
Functional Scale, n (%)			
1	14 (14.0)	73 (26.0)	0.11
2	29 (29.0)	77 (27.4)	
3	26 (26.0)	55 (19.6)	
4	12 (12.0)	40 (14.2)	
5	16 (16.0)	27 (9.6)	
6	3 (3.0)	9 (3.2)	

Significant p values in bold.

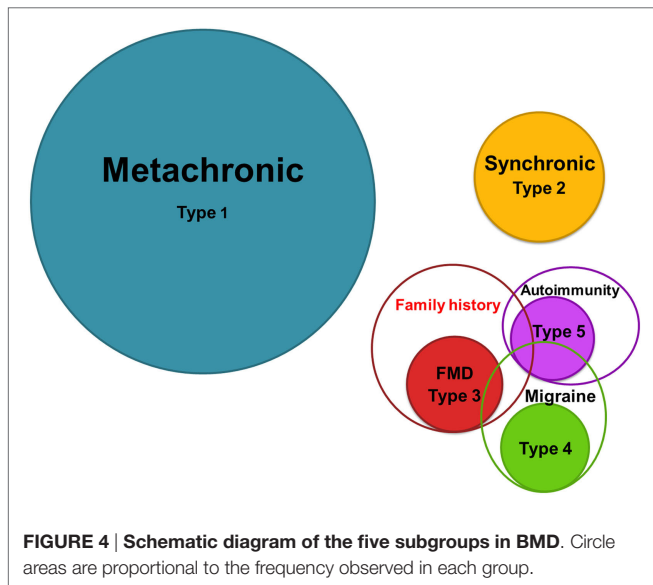
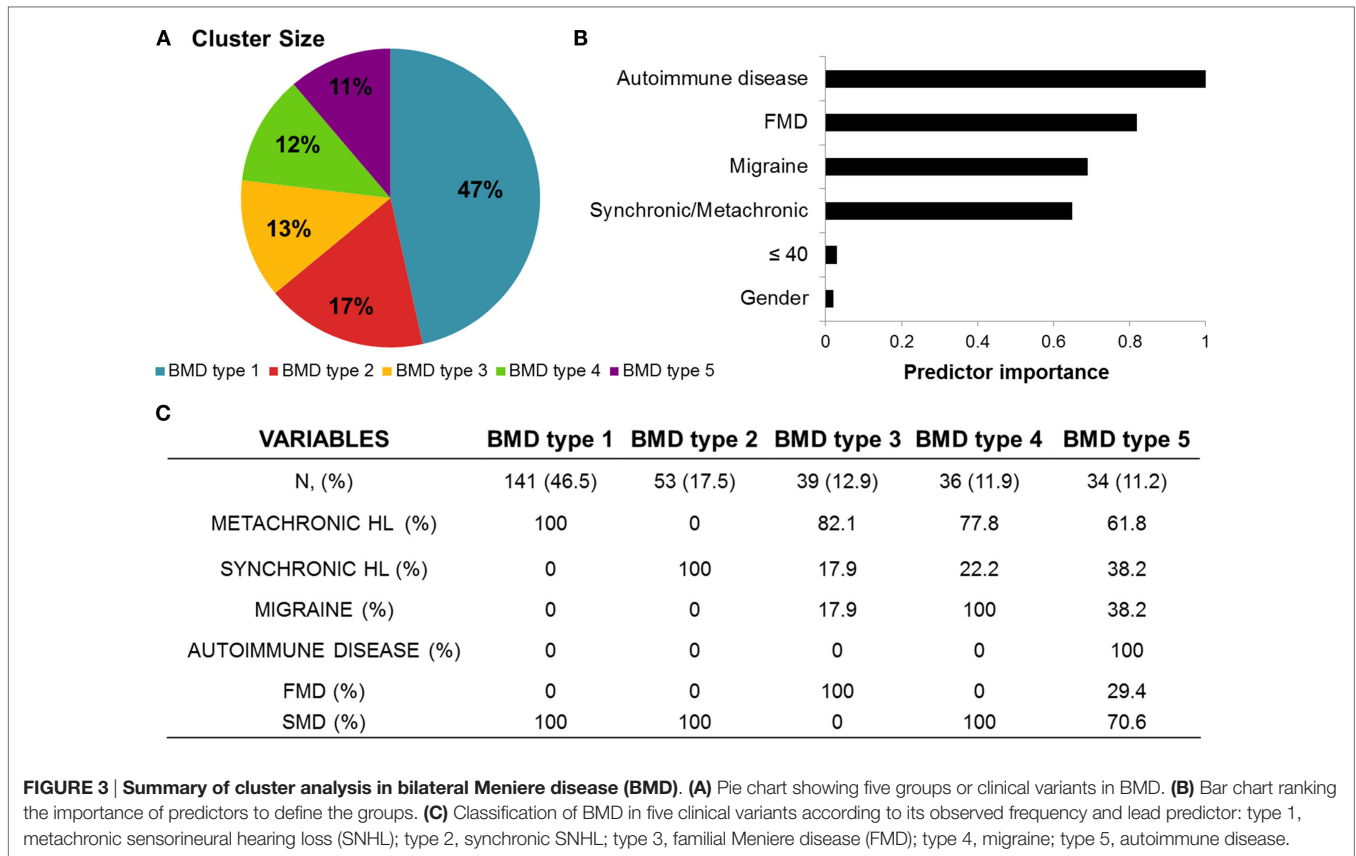
## DISCUSSION

The diagnostic criteria for MD formulated by the Classification Committee of the Bárány Society state that bilateral involvement is determined by hearing loss defined in the audiogram



**FIGURE 2 | Age of onset in bilateral Meniere disease according to the type of hearing loss observed.**





(1). So, if the absolute thresholds for bone-conducted sound are  $\geq 35$  dB HL at each of two contiguous frequencies below 2000 Hz in both ears, and the patient has experienced  $\geq 2$  episodes of spontaneous vertigo each lasting 20 min to 12 h associated with fluctuating aural symptoms, the diagnosis of definite BMD is established. The notes added to the definition also describe a

second clinical variant when the patient develops simultaneous bilateral SNHL (symmetric or asymmetric) (1, 52), but no further clinical information was included in the definition.

Our study demonstrates that BMD is a heterogeneous disorder, and two-step cluster analysis is a very useful tool to define groups of patients with BMD according to four clinical predictors: FMD, autoimmune history, migraine, and the type of onset for hearing loss. We selected this method since it allows the inclusion of quantitative and categorical variables to define clusters (53).

We present a new classification for BMD in five groups of patients with potential etiological implications, which probably will improve the diagnostic workflow and the management of patients with BMD. Previous studies in patients with BMD were focused in the diagnosis by electrocochleography or MRI (54–56), but they did not consider the comorbidities commonly observed, such as migraine or AD in some cases. The phenotype of a patient with an episodic vestibular syndrome should not be limited to the description of the inner ear symptoms, skipping crucial information such as the familiar history of MD or migraine. Furthermore, the comorbidities of migraine or AD may explain the perception of MD as a continuum, which overlaps with migraine (57) or autoimmune inner ear disease (1, 58, 59).

The most remarkable finding in our study is that the five groups of patients identified do not overlap themselves, and each of them has a set of features able to define the group.

Bilateral MD type 1 is the most common clinical variant, and it includes patients with MD in one ear (unilateral MD), and

**TABLE 6 | Clinical variants in bilateral Meniere disease (BMD) defined by two-step cluster analysis.**

Variables	BMD type 1 (n = 141)	BMD type 2 (n = 53)	BMD type 3   (n = 39)	BMD type 4 (n = 36)	BMD type 5 (n = 34)	p-value
Group predictor	Metachronic SNHL	Synchronic SNHL	FMD	Migraine	AD	
Age, mean (SD)	63.3 (11.0)	62.4 (9.5)	54.7 (13.2)	54.1 (11.5)	59.7 (11.1)	<b>0.00001</b>
Gender (% women)	73 (51.8)	30 (56.6)	26 (66.7)	25 (69.4)	24 (70.6)	0.11
Age of onset (SD)	46.4 (13.1)	47.9 (12.0)	40 (14.5)	<b>37 (12.5)</b>	39.8 (11.3)	<b>0.0003</b>
Age of onset ≤40, n (%)	46 (32.6)	15 (28.3)	19 (48.7)	21 (58.3)	16 (47.1)	<b>0.011</b>
Synchronic, n (%)	0 (0.0)	53 (100.0)	7 (17.9)	8 (22.2)	13 (38.2)	<b>3.39 × 10<sup>-42</sup></b>
Metachronic, n (%)	141 (100.0)	0 (0.0)	32 (82.1)	28 (77.8)	21 (61.8)	
Family history, n (%)	18 (12.8)	7 (13.2)	39 (100.0)	7 (19.4)	19 (55.9)	<b>1.81 × 10<sup>-27</sup></b>
FMD, n (%)	0 (0.0)	0 (0.0)	39 (100.0)	0 (0.0)	10 (29.4)	<b>4.10 × 10<sup>-53</sup></b>
Headache, n (%)	22 (15.6)	20 (37.7)	14 (35.9)	36 (100.0)	23 (67.6)	<b>4.88 × 10<sup>-20</sup></b>
Migraine, n (%)	0 (0.0)	0 (0.0)	7 (17.9)	36 (100.0)	13 (38.2)	<b>1.21 × 10<sup>-44</sup></b>
Rheumatoid history, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	34 (100.0)	<b>2.44 × 10<sup>-64</sup></b>
Cardiovascular risk factors						
High blood pressure, n (%)	46 (34.3)	23 (50.0)	10 (27.0)	11 (34.4)	15 (46.9)	0.15
Dyslipidemia, n (%)	58 (45.3)	26 (53.1)	16 (42.1)	13 (43.3)	15 (45.5)	0.86
Type 2 diabetes, n (%)	23 (17.8)	9 (18.4)	7 (18.4)	1 (3.2)	12 (36.4)	<b>0.019</b>
Smoking, n (%)	31 (22.6)	10 (18.9)	12 (30.8)	6 (17.1)	9 (29.0)	0.53

Significant p values in bold.

they develop the hearing loss in the contralateral ear (conversion from unilateral to BMD). The mean age of onset was 46 years old, comparable to BMD type 2, but it is significantly higher than it was observed in the rest of the groups (types 3, 4, or 5). BMD type 1 has no familial or autoimmune history, and patients do not have migraine, so further studies are required to investigate other concurrent comorbidities to determine contributing factors.

Bilateral MD type 2 is the second most frequently observed clinical variant, and fluctuating bilateral SNHL loss may resemble AIED, since simultaneous SNHL with vestibular symptoms can occur in 50% patients with AIED (58). However, these patients do not have any autoimmune comorbid conditions, migraine, or familial history of MD. Interestingly, BMD type 2 patients show a vascular risk profile, since 50% of them show high blood pressure, and 53% have dyslipidemia. When we compared these frequencies with BMD type 1, which do not differ in age or sex profile to BMD type 2, they were not significantly different ( $p = 0.078$ ), but further studies should assess the role of vascular risk factors in labyrinthine microcirculation in MD.

Comparing the hearing stage for the worst ear, it seems to be worse in BMD type 1 (metachronic SNHL) than in type 2 (synchronic SNHL). Since both groups do not differ for the age of onset, duration of disease, or gender distribution, we cannot determine the reason for the severe SNHL in the first ear in BMD type 1.

Bilateral MD type 3 includes all patients with familial history of MD, and we could subtype them in two subgroups (3a with migraine, 82%, and 3b BMD without migraine 18%). These findings confirm the early description of families with MD co-segregating migraine and MD (60) and the more recent description of FMD without migraine (2, 61, 62). According to this subtyping for FMD, there will be two types of families with MD, with and without migraine, and they reflect the genetic heterogeneity in FMD. The families include patients with uni and BMD, so epigenetic factors may influence uni or bilateral

involvement. Most of the described families have an autosomal dominant pattern of inheritance, and the participation of several genes indicate a genetic heterogeneity in FMD (2, 50). Although variable expressivity and incomplete penetrance was observed, we did not find cases with episodic ataxia in the families.

Bilateral MD type 4 is associated with migraine in all cases, but they do not have familial history of MD. This group may overlap with VM, and it may share common pathophysiological mechanisms (63). Patients with MD may show migraine symptoms even during the attacks of vertigo (57), and this finding could make difficult the differential diagnosis of VM and MD. Magnetic resonance imaging may be useful in the diagnostic evaluation of patients with the spectrum of VM/MD (MD with concurrent migraine or in cases VM and auditory symptoms) (64).

Bilateral MD type 5 could be considered as autoimmune MD, since all patients have another concurrent AD. However, this group is heterogeneous and includes patients with sporadic (71%), FMD (29%), migraine (38%), and both synchronic (38%) and metachronic SNHL (62%). Patients with BMD type 5 and migraine may have either synchronic or metachronic SNHL.

Our study has several limitations. Despite our efforts to improve phenotyping in patients with BMD, we could not classify 95 patients with BMD in any cluster, and they were excluded of the model. In fact, the largest group (BMD type 1) remains poorly characterized, since it is not associated with any particular clinical feature or etiological factor. The role of allergy in MD deserves more research efforts, since a high prevalence of sensitization to inhalant or food allergies have been reported in MD (65–67).

However, the recognizing of different subgroups of patients and the definition of clinical variants in BMD is not only the first step to improve the selection of patients for genetic and immunological studies but also for randomized clinical trials (RCT). Most of the RCT performed in MD, were not able to demonstrate any effects of diuretics (68) or betahistine (69) and had limited

effectiveness for intratympanic gentamicin (70) or steroids (71), and these results could be explained by a biased selection of patients with different etiologies. Further phenotyping of these clinical variants are needed for a better understanding of the clinical heterogeneity observed in BMD.

## AUTHOR CONTRIBUTIONS

LF and JL-E conceived and designed the study. AS-V, SS-P, AB-C, VP-G, HP-G, JF, EM-S, MT, GT, AG-A, RG-A, JE-S, PM, PP, JB, and JL-E collected clinical information. LF and JL-E analyzed the data and drafted the manuscript. LF, AS-V, SS-P, AB-C, VP-G, HP-G, JF, EM-S, MT, GT, AG-A, RG-A, JE-S, PM, PP, JB, and JL-E revised and approved the final version of the manuscript.

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