Accepted: 30 January 2017

DOI: 10.1111/coa.12844

ORIGINAL ARTICLE

WILEY

Extended phenotype and clinical subgroups in unilateral Meniere disease: A cross-sectional study with cluster analysis

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Funding information
Instituto de Salud Carlos III, Grant/Award Number: PI13/1242; FEDER Funds, Grant/Award Number: PI13/1242; EU

Objectives: To define clinical subgroups by cluster analysis in patients with unilateral Meniere disease (MD) and to compare them with the clinical subgroups found in bilateral MD.

Design: A cross-sectional study with a two-step cluster analysis.

Settings: A tertiary referral multicenter study.

Participants: Nine hundred and eighty-eight adult patients with unilateral MD. Main outcome measures: best predictors to define clinical subgroups with potential different aetiologies.

Results: We established five clusters in unilateral MD. Group 1 is the most frequently found, includes 53% of patients, and it is defined as the sporadic, classic MD without migraine and without autoimmune disorder (AD). Group 2 is found in 8% of patients, and it is defined by hearing loss, which antedates the vertigo episodes by months or years (delayed MD), without migraine or AD in most of cases. Group 3 involves 13% of patients, and it is considered familial MD, while group 4, which includes 15% of patients, is linked to the presence of migraine in all cases.

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Group 5 is found in 11% of patients and is defined by a comorbid AD. We found significant differences in the distribution of AD in clusters 3, 4 and 5 between patients with uni- and bilateral MD.

Conclusions: Cluster analysis defines clinical subgroups in MD, and it extends the phenotype beyond audiovestibular symptoms. This classification will help to improve the phenotyping in MD and facilitate the selection of patients for randomised clinical trials.

1 | INTRODUCTION

Meniere's disease (MD) is a chronic disorder of the inner ear characterised by episodes of spontaneous vertigo, with fluctuating low-to-medium frequency sensorineural hearing loss (SNHL), tinnitus and aural fullness.[1] It is associated with the accumulation of endolymph, a histopathological finding also called endolymphatic hydrops.[2] Diagnosis is based on the characteristic presentation of the different clinical symptoms mentioned. The prevalence of MD is higher in European than Asian and African populations with a range of 10-225 cases/100 000 individuals. Most of the patients suffer SNHL just in one ear, but it can appear in the contralateral ear after several years in 25%-40% of cases (metachronic SNHL).[3]

Patients with MD may exhibit a partial syndrome at their onset. So, vertigo, tinnitus and SNHL only occurs simultaneously in 38% of patients at the onset of the disease,[4] but isolated symptoms such fluctuating SNHL or episodic vertigo can be observed several months or years before the patient develops the complete syndrome. This, along with the fact that MD may show overlapping symptoms with vestibular migraine (VM), makes the diagnosis a challenge in its initial course.[5]

Genetic factors may contribute to the development of MD.[6,7] Familial MD has been found in 10% of cases;[8] most of these families have an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity. Using exome sequencing, six genes have been involved in familial MD.[9-12]

Key Points

- Unilateral Meniere disease is a set of rare disorders and five clinical subgroups have been identified.
- Delayed Meniere disease, familial cases, migraine and autoimmune diseases are the major predictors to define clinical subgroups.
- A detailed phenotyping beyond audiovestibular symptoms is needed to define clinical subgroups.

Some comorbidities, such as migraine or autoimmune disorders (AD), have been associated with MD in epidemiological studies.[13,14] Proteomics studies support autoimmunity as a potential mechanism in MD.[15] However, the relationship between migraine and MD is not clear. Although migraine is a common condition affecting 19% of women and 9% of men,[16] migraine is found in more than 30% of MD patients.[17] Furthermore, 45% of patients with MD experienced at least one migraine symptom during the episode of vertigo[14] and 8% of patients with MD experiences migraine-type headache during the attacks.[18] Moreover, VM involves 1% of the population,[19] and it may also occur in patients with MD.[20]

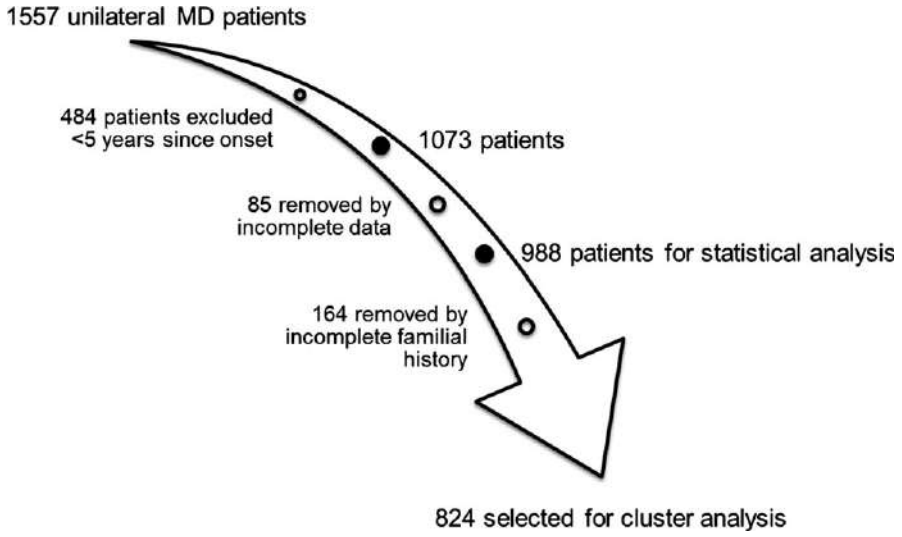


FIGURE 1 Flow chart showing the selection of patients with unilateral MD in this study

In a previous study, we performed a cluster analysis in patients with bilateral MD (BMD) and defined five clinical variants: metachronic SNHL (BMD type 1), synchronic SNHL (BMD type 2), familial MD (BMD type 3), MD with migraine (BMD type 4) and MD with AD (BMD type 5).[21]

In this work, our first objective was to perform a cluster analysis in patients with unilateral MD to define clinical subgroups. For this, we considered the clinical predictors that we found to be relevant in BMD; the second objective was to compare the clinical features between the clusters found in patients with unilateral MD (UMD) and BMD.

2 | METHODS

2.1 | Subjects

A multicenter, cross-sectional, retrospective study was designed including patients with UMD. For this, the clinical records of a total of 1557 patients diagnosed with definite unilateral MD from 21 clinical centres were reviewed in June 2016. MD diagnosis was defined according to the criteria of the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS).[22] To consider familial MD, another relative (first or second degree) has to fulfil all the criteria of definite or probable MD.[1] Patients with a previous history of SNHL (months or years) before the onset of vertigo episodes were defined as delayed MD.[1]

Patients with unilateral MD with <5 years since the onset of the symptoms were excluded, remaining 1073 individuals. This study was approved by the Institutional Review Board for Clinical Research (PI-13-1242). Every patient underwent a complete neuro-otological evaluation, a pure-tone audiometry and caloric testing. A brain MRI was performed to rule out any concomitant neurological lesions. The clinical variables studied were age, gender, duration of disease, age of onset, delayed MD, familial MD, hearing threshold at diagnosis, hearing stage defined as four pure-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, vascular risk factors (dyslipidaemia, hypertension, type 2 diabetes and smoking), Tumarkin crisis and the functional scale of the AAO-HNS.[22]

Four hundred and five patients with BMD with >5 years of evolution, previously selected for cluster analysis,[21] were used to compare the clinical variables between UMD and BMD.

2.2 | Statistical analysis

A descriptive statistical analysis of anonymised data was performed using SPSS software (SPSS Inc, Chicago, IL, USA). Data are shown as means with their standard deviations (SD). Quantitative variables were compared using Student's unpaired *t*-test. Qualitative variables were compared using cross-tables and Fisher's exact test. Nominal *P*-values <.05 were considered statistically significant.

We carried out a two-step cluster analysis using log-likelihood distance measures, as previously described.[21] The final cluster analysis was applied using only four categorical variables: history of autoimmune disease, delayed MD, Familial Meniere disease (FMD) or sporadic cases, and migraine.

3 | RESULTS

Figure 1 shows a flow chart with the patients included in this study. Our cohort consisted of 852 sporadic cases and 122 individuals with FMD (12.5%), and the familial history was not available in 14 cases. We observed significant differences in hearing threshold at diagnosis, which was 51±18 dB HL in sporadic cases and 31±28 dB HL in FMD ($P=2.4\times10^{-11}$). Furthermore, the prevalence of AD was higher in sporadic cases (*P*=.029, Table 1). Table S1 lists the 183 patients

TABLE 1 Clinical phenotype in sporadic and familial Meniere disease with at least 5 y since the onset of the disease

Variables	FMD (n=122)	SMD (n=852)	*P*-value
Age, Mean (SD)	59.3 (12.3)	57.8 (12.1)	.2
Gender (%women)	74 (60.7)	478 (56.1)	.38
Age of onset (SD)	45.3 (13.6)	45.6 (12.5)	.82
Age of onset ≤40, n (%)	47 (38.5)	306 (36.0)	.62
Time course (years), mean (SD)	14.0 (9.2)	11.7 (7.2)	**.011**
Hearing loss at diagnosis, mean (SD)	31.3 (28.0)	50.9 (17.8)	**2.40E-11**
Delayed MD, n (%)	12 (9.9)	61 (7.5)	.37
Headache, n (%)	49 (40.2)	267 (32.1)	.08
Migraine, n (%)	25 (20.7)	149 (18.0)	.45
Autoimmune disease, n (%)	13 (11.0)	146 (19.4)	**.029**
Hearing stage, n (%)			
1	3 (2.5)	64 (7.8)	**.045**
2	19 (15.6)	171 (20.9)	
3	70 (57.4)	430 (52.5)	
4	30 (24.6)	154 (18.8)	
Cardiovascular risk			
High blood pressure, n (%)	41 (33.6)	286 (34.2)	.92
Dyslipidaemia, n (%)	55 (45.5)	307 (37.2)	.09
Type 2 diabetes, n (%)	14 (11.7)	84 (10.1)	.63
Smoking, n (%)	23 (19.5)	185 (22.3)	.55
Tumarkin crisis, n (%)	22 (18.8)	150 (18.1)	.9
Functional scale, n (%)			
1	52 (45.2)	188 (23.0)	**7.00E-06**
2	24 (20.9)	251 (30.7)	
3	13 (11.3)	207 (25.3)	
4	16 (13.9)	107 (13.1)	
5	9 (7.8)	54 (6.6)	
6	1 (0.9)	11 (1.3)	

SMD, Sporadic Meniere disease; FMD, Familial Meniere disease.
Bold P-values indicate statistically significant differences.

TABLE 2 Clinical features of sporadic and familial unilateral Meniere disease stratified by the presence of autoimmune disease (AD)

	Sporadic MD			Familial MD		
Variables	**AD+ (n=146)**	**AD− (n=607)**	***P*-value**	**AD+ (n=12)**	**AD− (n=107)**	***P*-value**
Age, Mean (SD)	56.8 (11.4)	58.2 (12.1)	.19	54.7 (13.7)	59.8 (12.1)	.16
Gender (%women)	83 (56.8)	337 (55.5)	.78	8 (61.5)	64 (61.0)	1.0
Age of onset (SD)	43.2 (10.7)	45.9 (12.6)	**.007**	42.4 (16.4)	46 (12.9)	.35
Age of onset≤40, n (%)	55 (37.7)	213 (35.1)	.57	6 (46.2)	39 (37.1)	.56
Time course (years), mean (SD)	13.5 (8.0)	11.5 (7.1)	**.009**	12.9 (6.6)	13.6 (8.8)	.77
Hearing loss at diagnosis, mean (SD)	53.7 (16.8)	50.3 (17.8)	**.035**	48 (20.5)	28.7 (28.4)	**.007**
Delayed MD, n (%)	7 (4.9)	50 (8.8)	.17	1 (7.7)	11 (10.5)	1.0
Headache, n (%)	67 (45.9)	184 (30.5)	**5.90E-04**	4 (30.8)	43 (41.0)	.56
Migraine, n (%)	52 (35.6)	86 (14.4)	**2.44E-08**	2 (15.4)	23 (22.1)	.7
Hearing stage, n (%)						
1	4 (2.8)	46 (7.7)	.11	1 (7.7)	1 (1.0)	.25
2	27 (18.6)	131 (21.8)		3 (23.1)	15 (14.3)	
3	83 (57.2)	315 (52.5)		6 (46.2)	63 (60.0)	
4	31 (21.4)	108 (18.0)		3 (23.1)	26 (24.8)	
Cardiovascular risk factors						
High blood pressure, n (%)	59 (40.7)	202 (33.9)	.15	2 (15.4)	36 (34.3)	.22
Dyslipidaemia, n (%)	62 (42.5)	224 (38.3)	.39	5 (38.5)	47 (44.8)	.77
Type 2 diabetes, n (%)	9 (6.2)	66 (11.1)	.09	3 (25.0)	9 (8.6)	.11
Smoking, n (%)	27 (18.5)	146 (24.5)	.13	2 (15.4)	21 (20.4)	1.0
Tumarkin crisis, n (%)	30 (20.7)	115 (19.5)	.73	3 (23.1)	19 (18.6)	.71
Functional scale, n (%)						
1	11 (7.7)	115 (19.6)	**1.14E-07**	3 (23.1)	48 (48.0)	.061
2	39 (27.5)	199 (34.0)		3 (23.1)	21 (21.0)	
3	67 (47.2)	131 (22.4)		2 (15.4)	11 (11.0)	
4	18 (12.7)	87 (14.8)		3 (23.1)	12 (12.0)	
5	7 (4.9)	44 (7.5)		1 (7.7)	8 (8.0)	
6	0 (0.0)	10 (1.7)		1 (7.7)	0 (0.0)	

Bold P-values indicate statistically significant differences.

showing a comorbid AD found in sporadic and FMD, being autoimmune hypothyroidism the most common disease in our cohort.

We analysed patients with sporadic MD according to the presence or absence of AD. We found an earlier age of onset (*P*=.007), worse hearing loss at diagnosis (*P*=.035), worse score in the vertigo functional scale (1.14×10^{-7}) and higher prevalence of migraine (36%, $P=2.44\times10^{-8}$) in patients with sporadic UMD and AD when they were compared with cases without AD (Table 2).

We also compared the clinical features of patients with delayed MD (N=75, 7.6% patients) with the rest of patients with non-delayed MD (N=913, 92.4% patients, Table 3). The hearing loss at diagnosis was worse in patients with delayed MD compared with non-delayed MD (*P*=.006). Of note, there was no difference in the prevalence of vascular risk factors between both groups.

We carried out a cluster analysis to identify subgroups of patients with common clinical features in UMD. Two hundred forty-nine patients remained unclassified because of incomplete clinical data (25% of our cohort). Figure 2 shows the size of the clusters and the contribution of each predictor to define the cluster. The predictors were ranked according to its importance to define each cluster, being delayed MD and FMD the most relevant (Figure 3).

We have identified five clusters for UMD. Cluster 1 is the most common, including 53.4% of patients, and it is defined by sporadic UMD without migraine, delayed MD and no AD. Cluster 2 (8.4%) groups all patients with delayed MD, being 83% sporadic and 17% FMD. Cluster 3 (12.7%) includes patients with FMD, without AD in most cases (90%) and no migraine in 78% of them. Cluster 4 (14.9%) includes patients with sporadic UMD and migraine, without delayed MD or autoimmune history in 40% of cases. Cluster 5 (10.6%) consists of UMD patients with AD, without migraine or delayed MD.

Table 4 shows the five groups found and the main clinical differences within all groups. We observed that cluster 4 has an earlier age of onset than the rest of groups (*P*=.001). Moreover, according to the functional scale of the AAO-HNS, we observe that groups 4 and 5 have more vertigo attacks (9.33×10^{-11}) than the other

TABLE 3 Clinical features of patients with and without delayed Meniere disease (DMD)

Variables	DMD (n=75)	NO DMD (n=913)	*P*-value
Age, Mean (SD)	55.7 (12.8)	58.1 (12.0)	.1
Gender (%women)	41 (54.7)	526 (57.5)	.63
Age of onset (SD)	45.6 (13.1)	45.4 (12.5)	.89
Age of onset≤40, n (%)	24 (32.0)	334 (36.6)	.46
Time course (years), mean (SD)	10.3 (6.1)	12.2 (7.7)	**.036**
Hearing loss at diagnosis, mean (SD)	54.9 (24.1)	47.4 (20.3)	**.006**
Headache, n (%)	25 (33.8)	306 (34.5)	1.0
Migraine, n (%)	12 (16.2)	169 (19.2)	.64
Family history, n (%)	27 (37.0)	341 (38.8)	.8
FMD, n (%)	12 (16.4)	109 (12.7)	.37
Autoimmune disease, n (%)	8 (11.3)	156 (19.5)	.11
Hearing stage, n (%)			
1	2 (2.8)	66 (7.5)	.08
2	19 (26.8)	175 (19.8)	
3	31 (43.7)	473 (53.6)	
4	19 (26.8)	168 (19.0)	
Cardiovascular risk			
High blood pressure, n (%)	18 (24.7)	307 (34.1)	.12
Dyslipidaemia, n (%)	33 (45.2)	325 (36.9)	.17
Type 2 diabetes, n (%)	6 (8.3)	86 (9.7)	.84
Smoking, n (%)	17 (23.0)	191 (21.9)	.88
Tumarkin crisis, n (%)	17 (23.9)	161 (18.0)	.21
Functional scale, n (%)			
1	12 (18.8)	233 (26.4)	.16
2	21 (32.8)	253 (28.7)	
3	11 (17.2)	209 (23.7)	
4	12 (18.8)	112 (12.7)	
5	8 (12.5)	61 (6.9)	
6	0 (0.0)	14 (1.6)	

Bold P-values indicate statistically significant differences.

groups. Delayed MD, FMD, migraine and AD strongly differ among groups, and these variables are the foundation to assign a given patient to each cluster.

Next, we compared the clinical features of patients with UMD against patients with BMD included in clusters 3-5 that were previously reported[21] (Table S2). Thereby, individuals with BMD in cluster 3 (FMD) showed an earlier age of onset (*P*=.03), worse hearing loss at diagnosis (1.04×10^{-8}) and worse score in the AAO-HNS functional scale (*P*=.02) than patients with UMD type 3. However, patients with UMD in cluster 3 presented an AD in 11.4% of cases unlike BMD group.

Patients with BMD in cluster 4 (migraine) showed a worse hearing stage (*P*=.03) and more Tumarkin crisis (*P*=.04), probably associated with a longer duration of the disease (*P*=.004). However, patients with UMD type 4 presented a comorbid AD in 40.7% of cases ($P=2.16\times10^{-7}$). This finding was not observed in patients with BMD and migraine, where none of them showed AD.

Finally, patients with UMD in cluster 5 had a worse score on the functional scale (*P*=.002), while patients with BMD in cluster 5 also had a longer disease duration (*P*=.001) and it was associated with migraine in 38% ($P=9.46\times10^{-9}$), type 2 diabetes in 36% (7.6×10^{-5}) and FMD in 29% (1×10^{-6}) of cases.

4 | DISCUSSION

4.1 | Extended phenotype in MD

The epidemiological association of MD with migraine and several AD, including rheumatoid arthritis or psoriasis, supports the hypothesis of an extended phenotype, beyond audio-vestibular symptoms.[13] The diagnostic criteria for definite UMD formulated by the Classification Committee of the Bárány Society in 2015 are based on the observation of recurrent episodes of vertigo associated with low-to-middle frequency SNHL and fluctuating aural symptoms (hearing loss, tinnitus or aural fullness) in the involved ear.[1] Although these criteria increase the accuracy in clinical diagnosis for UMD, for example isolated high-frequency hearing loss with vestibular episodic symptoms is excluded,[23] they do not consider some comorbidities commonly observed in some patients such AD or migraine.

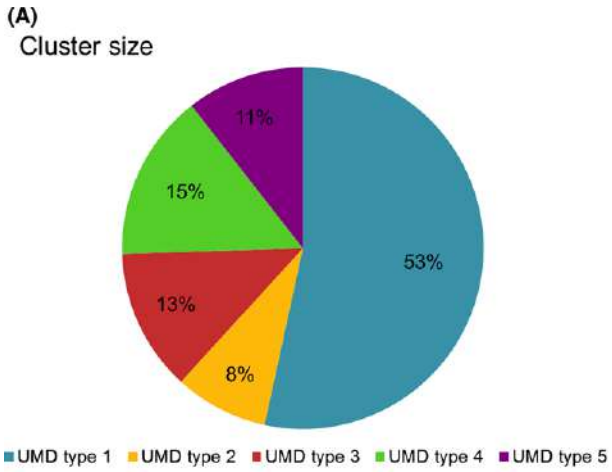
4.2 | Unilateral MD is a heterogeneous disorder

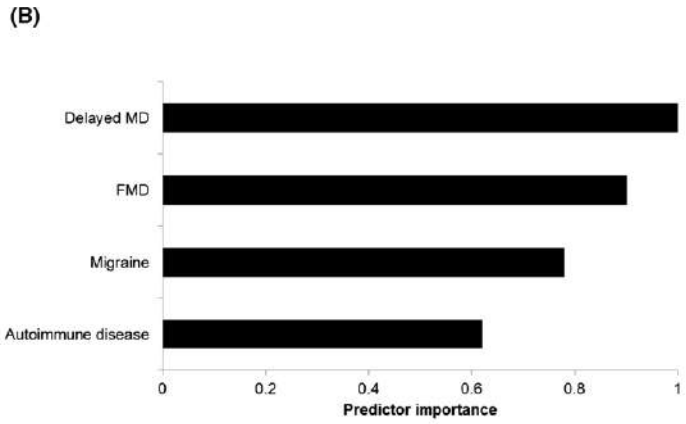
We have used cluster analysis previously to define subsets of patients with BMD,[21] as it allows the inclusion of quantitative and categorical variables to define clusters. According to four clinical predictors: delayed MD, history of FMD, migraine and history of AD, we have identified five subgroups of patients with UMD with strong potential aetiological implications, and three of these subgroups were also found in BMD (type 3 FMD, type 4 BMD with migraine and type 5 BMD with AD). These clinical variants observed in UMD and BMD confirm previous epidemiological studies,[13] but they also suggest a separate role for genetics and autoimmunity as factors contributing to the development of MD. The role of migraine also deserves attention, but further studies are needed in this specific subgroup to clarify the relationship UMD-migraine-AD.

4.3 | Clinical subgroups in UMD

As we have previously observed in BMD, the five subgroups of patients with UMD, each subgroup has its own set of predictors to define it. To keep the coherence with the subgroups previously defined for BMD, we have maintained the nomenclature for types 3, 4 and 5 for UMD.

UMD type 1 or 'classic MD phenotype' is the most common clinical variant, and it includes patients with Sporadic Meniere disease (SMD) without migraine or AD. The mean age of onset was 46 years old, comparable to the age of onset observed in the rest of the groups, with the exception of UMD type 4 (with migraine), which





(C)

VARIABLES	UMD type 1	UMD type 2	UMD type 3	UMD type 4	UMD type 5
N, (%)	440 (53.4)	69 (8.4)	105 (12.7)	123 (14.9)	87 (10.6)
SMD (%)	100	82.6	0	100	100
FMD (%)	0	17.4	100	0	0
Delayed MD (%)	0	100	0	0	0
Migraine (%)	0	17.4	21.7	100	0
Autoimmune disease (%)	0	11.6	11.4	40.7	100

FIGURE 2 Summary of cluster analysis in unilateral Meniere disease (UMD). A. Pie chart showing five groups or clinical variants in UMD. B. Bar chart ranking the importance of predictors to define the groups. C. Classification of UMD in five clinical variants according to its observed frequency and lead predictor: Type 1, classical MD; Type 2, delayed MD; Type 3, familial Meniere disease (FMD); Type 4, migraine; Type 5, autoimmune disease

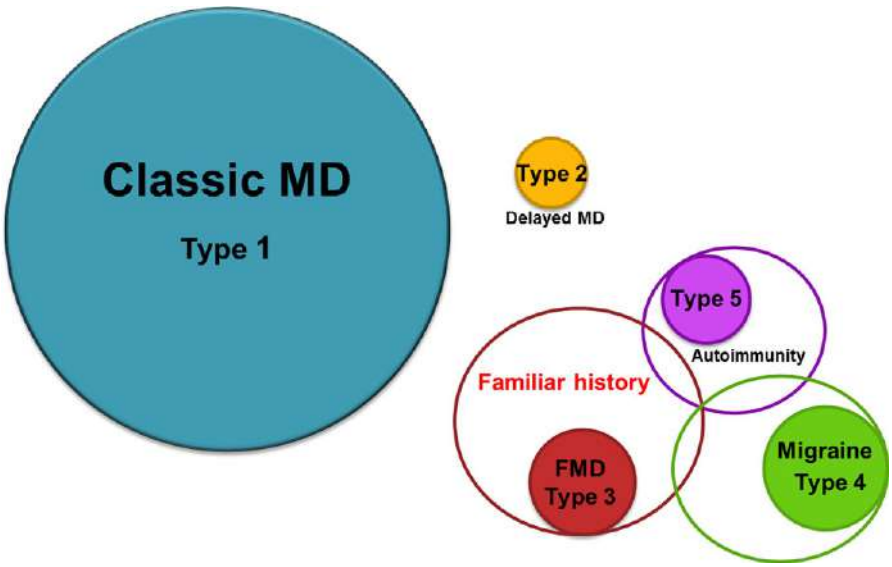


FIGURE 3 Schematic diagram of all five subgroups observed in UMD. Circle areas are proportional to the frequency observed in each group.

TABLE 4 Comparison of the main variables in each clinical subgroups defined by two-step cluster analysis in unilateral Meniere disease (UMD)

Variables	UMD type 1 (n=440)	UMD type 2 (n=69)	UMD type 3 (n=105)	UMD type 4 (n=123)	UMD type 5 (n=87)	*P*-value
Group predictor	Classical MD	Delayed MD	FMD	Migraine	AD	
Age, Mean (SD)	59.1 (12.2)	56.5 (12.7)	60.0 (11.7)	54.2 (10.9)	56.9 (11.0)	**3.09E-04**
Gender (%women)	237 (53.9)	36 (52.2)	64 (61.0)	86 (69.9)	46 (52.9)	**.02**
Age of onset (SD)	46.3 (12.6)	46.2 (13.1)	46.0 (13.0)	**41.2 (11.1)**	44.1 (10.3)	**.0012**
Age of onset≤40, n (%)	153 (34.8)	20 (29.0)	39 (37.1)	**61 (49.6)**	27 (31.0)	**.01**
Time course (years), mean (SD)	11.9 (7.1)	**10.6 (6.3)**	13.9 (12.6)	12.6 (7.9)	12.5 (7.8)	**.04**
Hearing loss at diagnosis, mean (SD)	50.1 (16.8)	54.7 (24.9)	**28.7 (27.5)**	52.0 (17.5)	52.9 (18.1)	**7.74E-24**
Delayed MD, n (%)	0 (0.0)	**69 (100.0)**	0 (0.0)	0 (0.0)	0 (0.0)	**4.86E-177**
Headache, n (%)	83 (18.9)	23 (33.3)	42 (40.0)	123 (100.0)	15 (17.2)	**3.18E-62**
Migraine, n (%)	0 (0.0)	12 (17.4)	23 (21.7)	**123 (100.0)**	0 (0.0)	**4.33E-138**
Family history, n (%)	90 (20.7)	24 (34.8)	105 (100.0)	59 (48.4)	47 (54.7)	**3.14E-50**
FMD, n (%)	0 (0.0)	12 (17.4)	**105 (100.0)**	0 (0.0)	0 (0.0)	**2.04E-159**
Autoimmune disease, n (%)	0 (0.0)	8 (11.6)	12 (11.4)	50 (40.7)	**87 (100.0)**	**1.54E-110**
Hearing stage, n (%)						
1	31 (7.1)	2 (3.0)	2 (1.9)	9 (7.4)	3 (3.4)	.14
2	84 (19.3)	18 (26.9)	16 (15.2)	25 (20.5)	19 (21.8)	
3	246 (56.4)	28 (41.8)	62 (59.0)	64 (52.5)	46 (52.9)	
4	75 (17.2)	19 (28.4)	25 (23.8)	24 (19.7)	19 (21.8)	
Cardiovascular risk						
High blood pressure, n (%)	156 (35.5)	18 (26.1)	36 (34.3)	43 (35.2)	35 (40.2)	.47
Dyslipidaemia, n (%)	167 (38.9)	31 (44.9)	46 (43.8)	39 (32.0)	39 (44.8)	.23
Type 2 diabetes, n (%)	50 (11.5)	6 (8.8)	9 (8.6)	7 (5.7)	5 (5.7)	.23
Smoking, n (%)	110 (25.3)	15 (21.7)	20 (19.4)	20 (16.5)	19 (21.8)	.28
Tumarkin crisis, n (%)	77 (17.7)	7 (25.4)	16 (15.7)	25 (20.5)	22 (25.6)	.24
Functional scale, n (%)						
1	88 (20.5)	12 (20.3)	48 (47.1)	16 (13.6)	6 (6.9)	**9.33E-11**
2	143 (33.3)	20 (33.9)	22 (21.6)	34 (28.8)	24 (27.6)	
3	96 (22.3)	9 (15.3)	12 (11.8)	**41 (34.7)**	**42 (48.3)**	
4	61 (14.2)	11 (18.6)	13 (12.7)	17 (14.4)	10 (11.5)	
5	35 (8.1)	7 (11.9)	6 (5.9)	7 (5.9)	5 (5.7)	
6	7 (1.6)	0 (0.0)	1 (1.0)	3 (2.5)	0 (0.0)	

started 5 years earlier. UMD type 1 has no FMD or autoimmune disorder, and patients do not have migraine, so further studies are required to investigate this large subgroup of SMD to determine its contributing factors.

UMD type 2 is defined as delayed MD (previously known as delayed hydrops), and it is a rare condition. No other subgroup presented any patient with delayed MD, so this single predictor defines the group. Most of patients were SMD and do not have migraine (83%). The AD was only observed in 10% of the patients, as expected in the general population. Interestingly, UMD type 2 patients do not show a particular vascular risk profile as the observed frequencies for high blood pressure and dyslipidaemia were not significantly different from those observed in UMD type 1 (which do not differ in age or sex profile to UMD type 2).

UMD type 3 includes all patients with FMD. The mean hearing thresholds observed at diagnosis in FMD were around 30 dB HL, suggesting that subclinical fluctuating hearing loss may go unnoticed in familial recurrent vertigo. We have subtyped them in two subgroups (UMD type 3a without migraine, 78%, and UMD 3b with migraine 22%). FMD is a rare Mendelian disorder, and most of the families show an autosomal dominant inheritance with incomplete penetrance and variable expressivity. So far, six genes have been identified in FMD by exome sequencing: *COCH*, *DPT*, *DTNA*, *FAM136A*, *PRKCB and SEMA3D*.[9,10,12] Of note, these findings resemble BMD type 3 where most of the families do not present migraine.[8,24] According to this subtyping for FMD, there will be two types of FMD, with and without migraine, and they will mirror genetic heterogeneity in autosomal dominant FMD. The families may

include patients with UMD or/and BMD, so epigenetic factors may influence uni- or bilateral involvement.[8,9]

UMD type 4 is defined as SMD plus migraine, and it was found in 15% of cases. Although most of the patients do not show autoimmune background, there is a 41% of UMD type 4 with AD. These individuals with SMD plus migraine and AD represent a challenge for the treatment. This group may overlap with VM and it may share common pathophysiological mechanisms. Patients with MD may show migraine symptoms even during the attacks of vertigo,[18] and this finding could make difficult the differential diagnosis of VM and MD.[1,19] 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).[25]

UMD type 5 could be considered as autoimmune MD, as all patients have another concurrent AD, and all of them are sporadic without migraine.

Our study has several limitations. In spite of our efforts to improve phenotyping in patients with UMD, we could not classify 249 patients with UMD in any cluster and they were excluded from the model. In fact, the largest group (UMD type 1) remains poorly characterised, as it is not associated with any particular clinical feature or aetiological factor. The role of allergy in MD deserves more research efforts, as a high prevalence of sensitisation to inhalant or food allergens has been reported in MD.[26] Finally, UMD type 3 and type 5 overlap in 10% of cases (FMD with AD without migraine).

However, the recognition of different subgroups of patients in UMD or BMD is the first step not only to improve the selection of patients for genetic and immunological studies, but also for randomised clinical trials (RCT). Most of the RCT performed in MD were not able to demonstrate any effects of diuretics,[27] betahistine or steroids;[28] these results could be explained by a biased selection of patients with different aetiologies. Further phenotyping of these clinical variants is needed for a better understanding of the clinical heterogeneity observed in MD.

ACKNOWLEDGEMENTS

We acknowledge to all members of the *Meniere disease's Consortium (MeDiC)*, a network of clinical and research centres contributing to the study of Meniere's disease. List of participants in *MeDiC*: Oscar Alemán (Hospital General Universitario de Alicante, Spain), Mario S. Almeida-Branco (Hospital de Poniente, El Ejido, Almería, Spain), Juan Carlos Amor-Dorado (Hospital Can Misses Ibiza, Spain), Ismael Aran (Complexo Hospitalario de Pontevedra, Spain), Angel Batuecas-Caletrio (Hospital Universitario Salamanca, Spain), Jesus Benitez (Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas de Gran Canaria, Spain), Emilio Dominguez (Hospital Infanta Luisa, Sevilla), Juan Manuel Espinosa-Sanchez (Hospital San Agustin Linares, Spain), Jesus Fraile (Hospital Miguel Servet, Zaragoza, Spain), Ana María García-Arumi (Hospital Universitario Vall d'Hebron, Barcelona, Spain), Rocío González-Aguado (Hospital Universitario Marqués de Valdecilla, Santander), Antonio Jimenez-Luna (Hospital Universitario Reina Sofia, Córdoba), Jennifer Knäpper (Centro Médico Teknon, Barcelona), Jose Antonio Lopez-Escamez (Complejo Hospitalario Universidad de Granada, Spain), Raquel Manrique Huarte, Nicolas Perez-Fernandez (Clinica Universidad de Navarra, Spain), Pedro Marques (Centro Hospitalar de S.João, Porto, Portugal), Eduardo Martin-Sanz, Ricardo Sanz (Hospital Universitario de Getafe, Madrid, Spain), Manuel Oliva Dominguez (Hospital Costa del Sol Marbella, Spain), Paz Perez (, Hospital Cabueñes, Asturias, Spain), Herminio Perez-Garrigues, Vanesa Perez-Guillén (Hospital La Fe, Valencia, Spain), Sofia Santos-Perez, Andres Soto-Varela (Complexo Hospitalario Universitario, Santiago de Compostela, Spain), Maria Cruz Tapia (Instituto Antolí Candela, Madrid, Spain), Roberto Teggi (San Raffaelle Scientific Institute, Milan, Italy) and Gabriel Trinidad (Complejo Hospitalario Badajoz, Spain).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LF and JALE conceived and designed the study. ASV, SSP, ABC, VPG, HPG, JF, EMS, MCT, GT, AMGA, RGA, JMES, PM, PP, JB and JALE collected clinical information. LF and JALE analysed the data and drafted the manuscript. LF, ASV, SSP, ABC, VPG, HPG, JF, EMS, MCT, GT, AMGA, RGA, JMES, PM, PP, JB and JALE revised and approved the final version of the manuscript.

FUNDING

This study was funded by a PI13/1242 Grant from ISCIII by FEDER Funds from the EU.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Frejo L, Martin-Sanz E, Teggi R, et al. Extended phenotype and clinical subgroups in unilateral Meniere disease: A cross-sectional study with cluster analysis. *Clin Otolaryngol*. 2017;00:1–9.