The Laryngoscope

Cluster Analysis of Auditory and Vestibular Test Results in Definite Menière's Disease

Lourdes Montes-Jovellar, MD; Francisco Guillen-Grima, MD; Nicolas Perez-Fernandez, MD

Objectives/Hypothesis: To determine whether patients with Menière's disease can be grouped into distinct subtypes based on a cluster analysis of distinct disease parameters.

Study Design: Prospective study at a tertiary center associated with a university hospital.

Methods: The study included 153 patients diagnosed with unilateral definite Menière's disease. The main variables employed were taken from auditory, vestibular, posturographic, and disability assessments.

Results: A four-cluster solution best fitted the data. Each cluster represented a distinct patient profile. Cluster 1 patients (13.1%) were the eldest, with the worst hearing bilaterally and good vestibular function but with a significant postural impact and a low level of disability. Cluster 2 patients (41.2%) were the least affected in all the parameters that were close to normal. Cluster 3 patients (34.6%) were the most affected, experiencing frequent and intense vertigo attacks, and they were visually dependent. Cluster 4 patients (11.1%) had strong asymmetric hearing between both ears and the most uncompensated vestibular deficit; they were moderately disabled.

Conclusions: We have identified four distinct profiles of patients with definite Menière's disease that we consider as ''mildly active elderly,'' ''mildly active young,'' ''active compensated,'' and ''active uncompensated.'' We have demonstrated that only in a restricted population of patients can the American Academy of Otolaryngology–Head and Neck Surgery staging system provide analysis of subtypes of the disease.

Key Words: Vertigo, dizziness, caloric test, posturography, rotatory chair test, disability.

Level of Evidence: 2b.

***Laryngoscope,* 121:1810–1817, 2011**

INTRODUCTION

Menière's disease (MD) is an idiopathic inner ear disorder characterized by episodic vertigo, aural fullness, tinnitus, and fluctuating hearing loss. In 1995, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) introduced a revised diagnostic scale for MD based on clinical criteria. This staging reflected the hearing threshold and level of disability and included a method for reporting the results of therapy according to the frequency of vertigo attacks.[1] Although this is the most frequently used method of diagnosis, several authors have developed individual solutions to the problem of classifying and staging the disease. Some use a complex symptom scoring system[2–4] or require specific auditory or vestibular examination,[5–7] and other systems have received limited attention.[8] However there is a general consensus that definite MD is a highly heterogeneous disorder in terms of its progression,[9] diagnosis and staging, and response to treatment.

The variability between patients with definite MD suggests that disease subtypes probably exist, the origins of which are poorly understood. Genetic heterogeneity and a specific inner ear conformation are likely to be linked to the development of clinical subtypes, together with additional variables relating to both the subject and his or her environment.[10]

Various strategies to subgroup these patients have been described, all of which involve assigning particular importance to a specific variable. However, cluster analysis (CA) is a statistical tool that helps to avoid such bias and enhances the subgrouping procedure. This objective method classifies and groups patients without assuming which variables are most important, and it has previously been used to identify subgroups of tinnitus patients.[11] Groups are constructed such that members of the same cluster have a high degree of association, while those in different clusters are weakly associated. The main purpose of our study was to determine whether CA can group patients with definite MD according to basic audiometric, vestibular, and posturographic variables and disability. Two secondary aims were to characterize the main clinical manifestations of each of the resultant subtypes and to compare our results with those following the more extended staging method of the AAO-HNS.[1]

From the Department of Otorhinolaryngology (L.M.-J., N.P.-F.) and the Department of Preventive Medicine (F.G.-G.), Clínica Universidad de Navarra-Facultad de Medicina University of Navarra, Navarra, Spain.

Editor's Note: This Manuscript was accepted for publication on March 15, 2011.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Dr. Nicolas Perez-Fernandez, Dpto. de ORL-Clínica Universitaria, Pio XII 36, 31008 Pamplona, Navarra, Spain. E-mail: nperezfer@unav.es

DOI: 10.1002/lary.21844

MATERIALS AND METHODS

Patients

Patients who met the following conditions were included in the study between 1998 and 2003: 1) a clinical diagnosis of "definite MD" according to the criteria described in the 1995 AAO-HNS guidelines for reporting results in the treatment of MD[1]; 2) a complete same-day assessment that included audiometric, vestibular, and posturographic tests and the completion of disability questionnaires; 3) the absence of evidence of MD in the contralateral ear; and 4) no signs or symptoms suggesting central nervous system involvement in the disease. The subjects in this study were followed up until 2009 to confirm the absence of clinical symptoms in the contralateral ear.

Methods

Clinical evaluation and bedside testing. In this study, we focused on the time since the first vertigo attack, in combination with the fluctuations in hearing and tinnitus (duration of disease), the time since the last vertigo attack, the number of vertigo attacks in the 6 months before the study (as defined in the AAO-HNS guidelines), and the existence of Tumarkin attacks. Patients underwent a complete neurotologic examination, paying particular attention to spontaneous and horizontal post–head-shaking nystagmus behind Frenzel glasses and/or any hypometric response to the head-thrust maneuver.

Auditory and vestibular evaluation. Audiometric findings were reported in terms of the 0.25-kHz and 6-kHz pure-tone thresholds, pure-tone average (PTA) (calculated by taking the average of the readings at 4 frequencies: 0.5, 1, 2, and 3 kHz), the speech-recognition threshold (SRT) and the speech discrimination score (SDS) of the ipsilateral or symptomatic (*s*) ear and of the contralateral or asymptomatic (*as*) ear.

The Fitzgerald and Hallpike bithermal caloric test was used, in which eye movements were recorded using a video-based system (Ulmer VNG, v. 1.4; Synapsis, Marseille, France). Each ear was irrigated alternately for 40 seconds with a constant water flow at temperatures of 30°C and 44°C. The maximum slow-phase velocity of nystagmus ($^\circ s^{-1}$) was calculated after each irrigation, and canal paresis (CP) and directional preponderance were determined according to Jongkees formula. The caloric test was considered abnormal if CP was >20%.

Rotational chair tests were performed with a rotary chair (Chartr RVT system; ICS Medical Corporation, Schaumburg, IL) housed in a structure that enables the test to be performed in the dark. The subject's head was positioned and restrained so that both the lateral semicircular canals were close to the plane of stimulus (i.e., at the gravitational horizontal). During the test, the subject was maintained in an alert state, and eye movements were recorded by electrooculography. In the sinusoidal harmonic acceleration test, the subject underwent sinusoidal oscillation about a yaw axis at various frequencies (0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz) and with a peak angular velocity of $50^\circ\ s^{-1}$. From the chair velocity and slow-phase velocity, three parameters of the VOR (vestibule-ocular reflex) were calculated (phase, gain, and symmetry), and the subjects were assigned a normal or pathologic score. In this study, the limits of normality were set at the mean +2 standard deviations (SDs) of the results obtained in a group of normal subjects studied in our laboratory. A test was considered abnormal when measurements at three adjacent frequencies were abnormal in terms of phase, gain, or symmetry. A second test was performed, the impulsive rotational test, in which the patient was subjected to velocity steps to the right and left. The velocity step involved the patient undergoing an angular acceleration of $100^\circ\ s^{-1}$ for 1 second, rotation at a constant velocity for 60 seconds, and finally deceleration to $0^\circ\ s^{-1}$ within 1 second. The results were analyzed as the gain (G) and time constant (TC) of the VOR for rotation toward the side of the ipsilesional or symptomatic ear (G*s* and TC*s*) and of the contralesional or asymptomatic ear (G*as* and TC*as*). In assessing the gain, the results were considered normal if both the G*s* and G*as* were >0.45 and asymmetry was <15%. The time constant was considered normal if TC*s* and TC*as* were both >10 seconds and asymmetry was <20%.

Posturography. Computerized dynamic posturography (CDP) testing was performed using a CDP system (Equitest; NeuroCom International, Inc., Clackamas, OR) with four symmetrically positioned force transducers that measure the vertical pressure applied to the support surface by a person when standing. In the Sensory Organization Test (SOT), patients were asked to maintain their balance under six different conditions. The first three conditions (SOT 1, SOT 2, and SOT 3) provided accurate uninterrupted foot support surface information. In SOT 1, patients kept their eyes open, and in SOT 2 their eyes were closed. In SOT 3, patients kept their eyes open, but the surroundings moved in a pattern stimulated by the anterior-posterior (A-P) swaying movements that he or she continuously performed. In conditions SOT 4, SOT 5, and SOT 6, the visual scenarios corresponded to those described for SOT 1, 2, and 3, respectively, but in each case the A-P sway movement of the patient drove the movement of the supporting surface in an axis parallel to the ankle joint. Several trials were performed for each SOT condition, and the A-P sway was measured in each. A value was calculated relative to a sway of 12.5°, considered to be the maximum A-P sway in the ankle joint of normal subjects. Patients were assessed in terms of general performance and received a composite score, an estimate of postural stability, and a weighted average of the results of the different trials with special emphasis placed on conditions SOT 3 through SOT 6.

Disability and handicap assessment. The questionnaires were explained to the patient by the doctor immediately before vestibular testing and were subsequently completed.[12] Where necessary, the technician in charge of the vestibular tests (who was well versed in the scope of the work and had considerable experience in the vestibular laboratory) helped to clarify some issues. Specifically, the dizziness handicap index (DHI) questionnaire was translated and adapted to Spanish following the method of cross-translation. The reliability of the scale was evaluated, and a Cronbach alpha coefficient of 0.9226 was determined for this version of the DHI. The questionnaire contained 25 items, and the total score used in this study ranged from 0 to 100. The UCLA Dizziness Questionnaire contains five items that allow the patients to characterize dizziness. However, for this study we used the global score or "dizziness index" (DI), obtained by multiplying item H1 (frequency of vertigo) by H2 (intensity), which gives a result ranging from 1 to 25. Another questionnaire, the Vertigo Symptom Scale, is useful to provide a measure of the severity of vertigo (Y*Sev*) and of somatic anxiety (Y*Sanx*). It is comprised of 19 items that measure the severity of vertigo and 15 items that measure somatic anxiety. The possible answers to each item range from 0 (never) to 4 (very often and on average more than once a week). The Functional Level Score (FLS) comprises six possible situations that the patient identifies as representative of the functional limitations of the disease.[1]

Statistical Analysis

All analyses were performed using the SPSS 15.0 statistical software (SPSS Inc., Chicago, IL). A P value of <.05 was

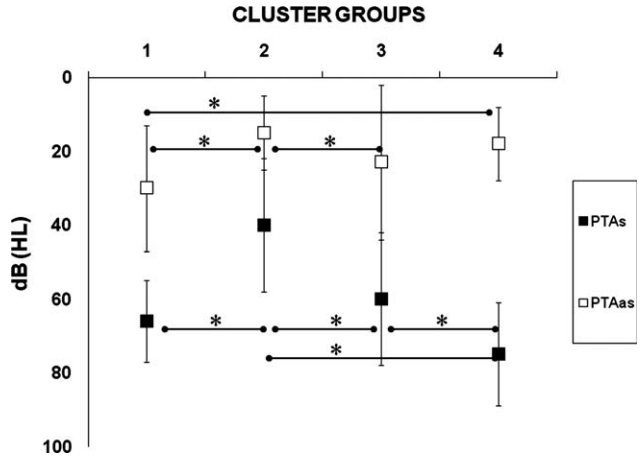

Fig. 1. Audiometric results (pure tone average [PTA]) for symptomatic (*s*) and asymptomatic (*as*) ears, by clusters. HL = hearing level. * = existence of a significant difference ($P < 0.05$).

considered to be statistically significant. We calculated frequencies, means, and ranges for the variables studied. A hierarchical CA of the subjects was performed by the between-groups linkage using squared Euclidian distance as a measure. Differences between the clusters obtained were analyzed using the χ^2 test, Student t test, Mann-Whitney U test, or one-way analysis of variance test coupled to Bonferroni or Tamhane tests depending on the homogeneity of the variance. A discriminant analysis was performed with the most relevant variables using two methods, the "enter independents together" and "stepwise" methods. With these analyses, we calculated a formula for each cluster, which provided a measure of sensitivity and specificity and of the positive and negative predictive value. To record and analyze the relation between the two variables (cluster solution and AAO-HNS staging system), contingency tables were used, and the measure of association was carried out with the χ^2. The Spearman's rank correlation coefficient (rho) was the nonparametric measure used to assess statistical dependence between the two variables. Adjusted standardized residuals were computed to detect those cells that were significant. A cell was significant when the absolute value of its residual was higher than 1.96; the positive or negative value indicated that the number of observed cases was higher or lower than the expected number for this cell.

RESULTS

Patients

The final study population consisted of 153 patients: 70 (45.8%) females and 83 (54.2%) males, with a mean age of 52 years. In this cohort, the mean disease duration was 5.4 years (95% confidence interval [CI]: 1-15), the mean time since the last vertigo spell was 50 days (CI: 25-61), and the mean number of vertigo attacks in the 6-month period before diagnosis was eight (CI: 1-15). Following the first visit and diagnosis, 75 patients were treated with oral medication, 77 were treated with intratympanic gentamicin, and one patient was treated surgically (labyrinthectomy). On vestibular examination, spontaneous nystagmus was evident in 63 (41.2%) patients, there was positive head-shaking nystagmus in 58 (37.9%) patients, and the head-impulse test was abnormal in 47 (30.7%) patients (with head thrusts to the ipsilesional side). The FLS results were distributed as follows: 9 × FLS = 1; 37 × FLS = 2; 31 × FLS = 3; 36 × FLS = 4; 36 × FLS = 5; and 4 × FLS = 6. The mean DHI total score was 43 ± 21, DI was 8 ± 5, Y*Sev* was 10 ± 4, and Y*Sanx* was 15 ± 10. In audiometry tests, the mean PTA*s* was 54 ± 21 dB, and the PTA*as* was 20 ± 13 dB. The mean SRT*s* was 52 ± 22 dB, SRT*as* was 14 ± 12 dB, SDS*s* was 80 ± 20%, and SDS*as* was 96 ± 6%. Caloric test results were abnormal in 61% of patients, and the sinusoidal harmonic acceleration test result was considered abnormal in 42% of patients. The G*s* was 0.44 ± 0.15 and G*as* was 0.44 ± 0.15; the TC*s* was 15.6 ± 8.4 seconds and the TC*as* was 16.2 ± 8.4 seconds. Similarly, posturography testing with the SOT was abnormal in 42% of patients. The most frequent abnormal patterns were a vestibular deficit and the combined

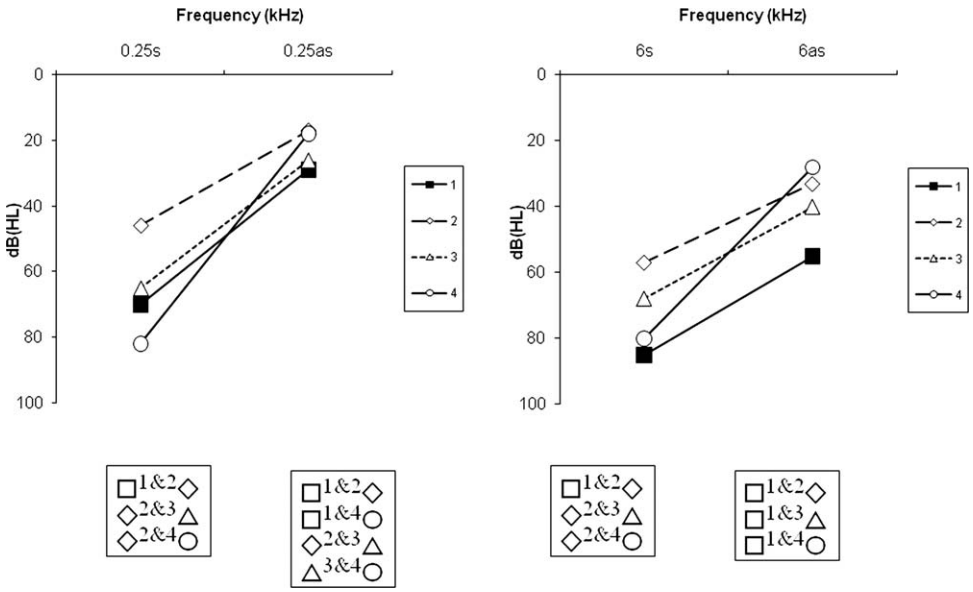

Fig. 2. Audiometric results (0.25 and 6 kHz) for symptomatic (*s*) and asymptomatic (*as*) ears, by clusters. The tables inserted show the significant differences between clusters. HL = hearing level; 1 = cluster 1; 2 = cluster 2; 3 = cluster 3; 4 = cluster 4.

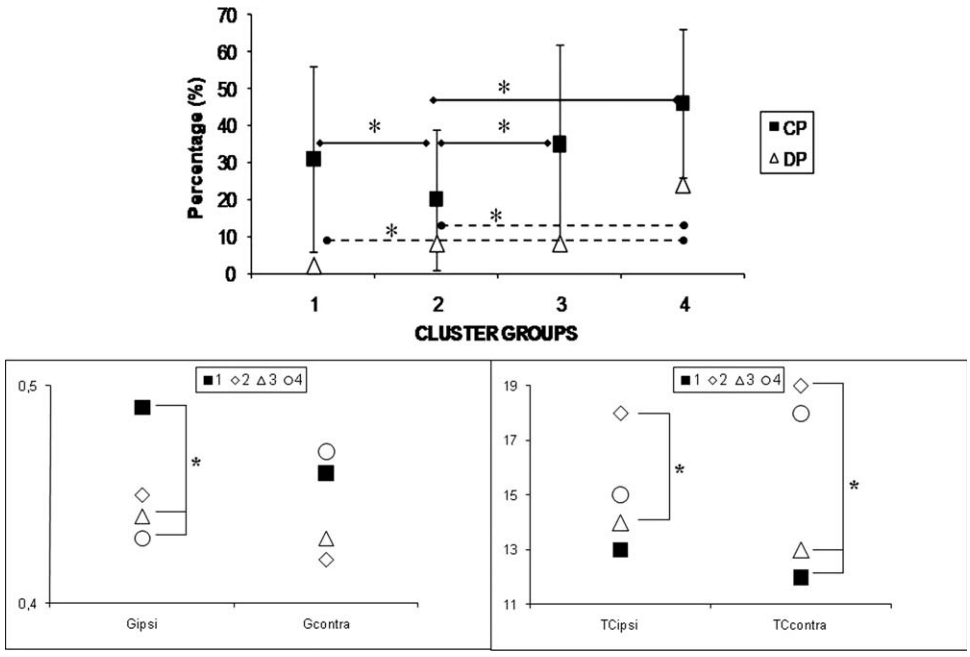

Fig. 3. Results of vestibular tests by clusters: canal paresis (CP), directional preponderance (DP), gain (G), and time constant (TC) for the symptomatic and asymptomatic ears. ipsi = ipsilesional; contra = contralesional. * = existence of a significant difference ($P < 0.05$).

vestibular and visual deficit, which were found in 38% of patients. Visual preference in the SOT of the dynamic posturography was identified in 10% of patients.

Analysis of the Clusters

After performing the CA, four groups were obtained, and in Figures 1 through 5 , we present the values and levels of significance of the between-group analyses for each of the different variables studied.

Cluster 1. Cluster 1 comprised 20 patients (13.1%). These patients had severe hearing loss in the symptomatic ear and, moreover, the highest level of hearing loss in the asymptomatic ear, as seen by the PTA*as*, particularly at the 6-kHz threshold. The level of CP was moderate, and the directional preponderance score was the lowest of the four groups. In the rotatory stimulation, the G*s* value was the highest of the four clusters, and the TC*s* and TC*as* values, and consequently TC asymmetry, were the lowest observed. In terms of posturography, this cluster showed a vestibular deficiency pattern with clear abnormalities in SOT conditions 5 and 6. According to all the measures of disability, these patients were the least disabled.

Cluster 2. Cluster 2 comprised 63 patients (41.2%). These patients showed the weakest hearing loss, both in the symptomatic and asymptomatic ears, and most of the parameters measured differed significantly from those in the other groups, with the exception of the PTA*as* score in cluster 4. In terms of CP, almost all patients had normal caloric values, and the level of CP was significantly lower than in other clusters. TC*s* and TC*as* values were higher than in all the other groups. This cluster showed better posturography results than clusters 1 and 3, similar to those of cluster 4; according to their disability measures, these patients were not excessively disabled.

Cluster 3. Cluster 3 comprised 53 patients (34.6%). According to the audiometric results in both the symptomatic and asymptomatic ears, the patients classified in this cluster were very similar to those in cluster 1, except for the 6-kHz threshold of the asymptomatic ear. CP was high, and the gain in VOR (both G*s* and G*as*) and its time constant (both TC*s* and TC*as*) were low. In posturography, this cluster showed similar results to cluster 1, with the exception of SOT conditions 2 and 3, which were significantly lower. The disability of these patients' measures was most severe, with significant differences when compared to the other clusters in all the questionnaires employed.

Cluster 4. Cluster 4 comprised 17 patients (11.1%). Based on audiometric findings (the PTA and SDS), this cluster showed the most severe hearing loss of all the groups in the symptomatic ear, but hearing was close to normal in the asymptomatic ear. The level of CP was also the highest of all the clusters, as was the directional preponderance. The G*s* and TC*s* values were lower than

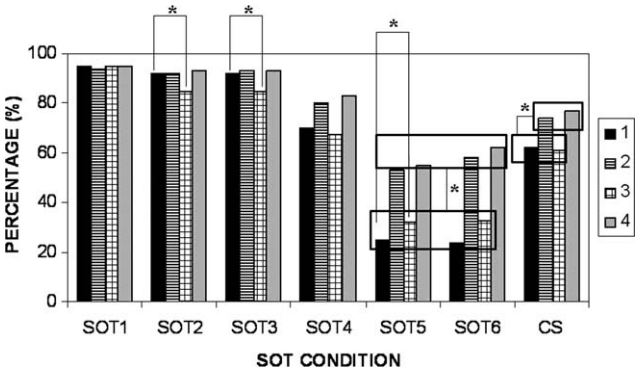

Fig. 4. Results of sensory organization test (SOT) under each condition (1–6) and the composite score (CS) for each cluster (1–4). * = existence of a significant difference ($P < 0.05$).

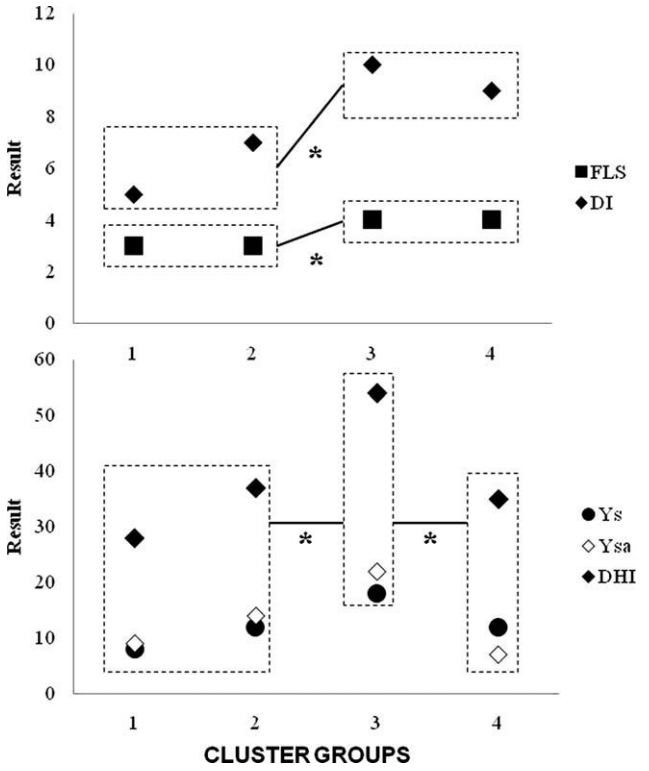

Fig. 5. Disability measures: FLS (functional level score), DI (dizziness index), severity of vertigo (Y*s*), somatic anxiety (Y*as*), and dizziness handicap index (DHI) for each cluster. * = existence of a significant difference ($P < 0.05$).

those of G*as* and TC*as*, and posturography testing in this cluster revealed similar results to cluster 2 for all SOT conditions. The disability determined by FLS was similar to that in cluster 3, although others' questionnaire responses showed closer similarities to clusters 1 and 2.

Discriminant Function

The discriminant function was determined for each cluster (Table I), along with the respective measures of sensitivity and specificity, and positive and negative predictive values. The most relevant variables in each cluster were the following: cluster 1, SOT6; clusters 2 and 4, PTA*s*; and cluster 3, Y*Sanx*.

Clinical Characteristics of the Individual Clusters

The clinical data pertaining to each cluster was also assessed (Table II). The age of the patients in cluster 1 differed from that in clusters 2, 3, and 4. Similarly, clusters 1 and 2 differed from 3 and 4 in terms of both the number of vertigo attacks in the 6 months before examination and in the time since the last vertigo attack. Differences in the treatment proposed were identified between clusters 1 and 3, 2 and 3, and 2 and 4. Moreover, on examination, the number of patients with an abnormal result in the head-impulse test differed significantly in clusters 1 and 2.

Comparison Cluster Solution to AAO-HNS Staging System

Following the PTA*s*, 22 (14.4%) patients were included in group 1, 15 (9.8%) in group 2, 87 (56.9%) in group 3, and 29 (19%) in group 4. In Figure 6 we present the number of patients in each of the clusters by their classification following the AAO-HNS staging system. After clinical characterization of the clusters, we can say that clusters 2, 3, and 4 are closely related by age and report to function, probably representing a progression in the disease. Thus we decided to proceed in our analysis in two ways: the first with all 4 clusters and the second excluding cluster 1. In either of them, both methods of classification (cluster solution, AAO-HNS staging system) are considered independent according to χ^2 test ($P = 0$). To determine which cells of the contingency table contribute most to the statistical significance of the χ^2 test, the percentage of patients in each group and the adjusted residuals are shown in Table III, highlighting the most relevant whose adjusted residuals are higher than 2. In Table III, we present the four-cluster solution, and in Table IV without cluster 1; the Spearman correlation coefficient for the four-cluster solution and for that without cluster 1 was 0.28 and 0.6, respectively.

DISCUSSION

The results of our study revealed that the patients could be grouped into four clusters with unique disease profiles under the general diagnosis of "unilateral definite MD." A CA is an objective means of classifying patients

TABLE I.
The Discriminant Function Obtained for Each Cluster.

Cluster	Discriminant Function	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	4.178-0.39*PTA*s*-0.04*SOT3+0.03*SOT6+0.064**YSev*	90	85.7	48.6	98.3
2	1.736+0.041*PTA*s*+0.013*CP+2.09*G*as*-0.048*TC*as*-0.051*SOT3-0.023*SOT6+0.316*FLS	84.1	93.3	89.9	89.4
3	-6.248-0.015*(0.25kHzs) +1.215Gs+0.028*TC*s*+0.034*TC*as*+0.035*CS+0.055*SOT3-0.057*DI-0.066**YSanx*-0.204*FLS	88.7	89	81	93.7
4	-2.201-0.026*(0.25kHzs)+0.044*PTA*s*+0.022*DP+0.017*SOT6-0.037**YSanx*	100	91	58.6	100

PPV = positive predictive value; NPV = negative predictive value; PTA*s* = pure tone average for symptomatic ear; SOT = sensory organization test; Y*Sev* = severity of vertigo; CP = canal paresis; G*as* = gain of the vestibule-ocular reflex for rotation toward the side of the asymptomatic ear; TC*as* = time constant of the vestibule-ocular reflex for rotation toward the side of the asymptomatic ear; FLS = Functional Level Score; G*s* = gain of the vestibule-ocular reflex for rotation toward the side of the symptomatic ear; TC*s* = time constant of the vestibule-ocular reflex for rotation toward the side of the symptomatic ear; CS = composite score; DI = dizziness index; Y*Sanx* = severity of somatic anxiety; DP = directional preponderance; kHzs = kilohertz.

TABLE II.
Clinical Data for Each Cluster.

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Sex (female/male)	7/13	28/35	26/27	4/13
Age (yr)	63 ± 10	48 ± 11	53 ± 13	50 ± 10
DisDur (yr)	5 ± 3	5 ± 5	6 ± 5	6 ± 4
Tlv (d)	60 ± 49	40 ± 44	25 ± 24	22 ± 21
N	5 ± 4	7 ± 7	11 ± 10	10 ± 5
Tumarkin (%)	10	11	26	18
Tt (med/GIT)	13/7	43/20	16/36/1(lab)	3/14
SpNyst (%)	50	36.5	45.3	35.3
HSNyst (%)	50	32	40	65
HIT (%)	65	14	34	41

DisDur = duration of disease; time in years since the first typical attack; Tlv = time since the last vertigo attack; N = number of vertigo attacks in the previous 6 months; Tumarkin = percentage of patients experiencing Tumarkin attacks; Tt = treatment proposed; med = oral medication; GIT = intratympanic gentamicin; lab = labyrinthectomy; SpNyst = percentage of patients with spontaneous nystagmus; HSNyst = percentage of patients with post–head-shaking nystagmus; HIT = percentage of patients with abnormal head-impulse response.

into subtypes, and the system described here comprehensively encompasses audiometric and vestibular test results, as well as posturography findings and disability.

Before interpreting the results of this study, some of its limitations should be taken into consideration. First, some potentially relevant variables were not included in the study. For example, vestibular evoked myogenic potentials were not included, as the characteristics of the stimuli and the system to register these potentials changed during the period of patient inclusion, introducing a new source of variability. Second, the audiometric data pertaining to the asymptomatic ear are not recognized in any classification system. However, we considered it important to introduce these data as it permits additional tracking of age, as well as the effects of environmental acoustic exposure in individual patients. Furthermore, it is well known that the asymptomatic ear of patients with unilateral ear disease is frequently abnormal. This phenomenon has been demonstrated

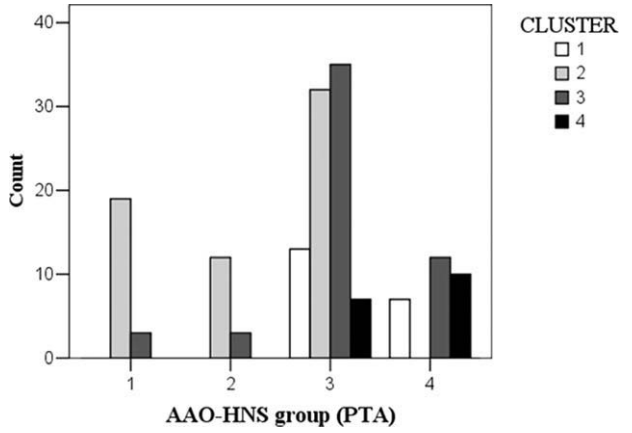

Fig. 6. Number of patients in each cluster according to the corresponding group from the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) staging system based on pure tone average (PTA) in decibels.

TABLE III.
Percentage of Patients in Each of the Clusters by Their Group According to the American Academy of Otolaryngology–Head and Neck Surgery Staging System.

	AAO-HNS Group	Cluster 1	Cluster 2	Cluster 3	Cluster 4
1	Percentage in AAO-HNS group	0	86.4	13.6	0
	Adjusted residual	−2	4.7	−2.2	−1.8
2	Percentage in AAO-HNS group	0	80	20	0
	Adjusted residual	−1.6	3.2	−1.3	−1.4
3	Percentage in AAO-HNS group	14.9	36.8	40.2	8
	Adjusted residual	0.8	−1.3	1.7	−1.4
4	Percentage in AAO-HNS group	24.1	0	41.4	34.5
	Adjusted residual	2	−5	0.8	4.4

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery.

histologically,[13] using various audiometric measures[14] and using electrocochleographic tests, whose positive predictive rates and specificity are increased by including the results from the asymptomatic ear.[15] Third, despite the potential of CA to identify distinct subtypes of the disease, a comparison of different CA studies is difficult owing to methodologic differences, as well as limitations related to the patients and testing. For example, our subjects were patients attending a tertiary referral center (which clearly influences the PTA subgroups), and the tests performed have a moderate degree of redundancy.

Some other limitations related to the test results should also be noted, such as the significant differences we found in the PTA that were relevant to the definition of the four clusters. However, speech audiometry results were of little help in building the clusters; this finding was surprising given the damage to the spiral ganglion cells found in MD models, a feature often considered central to the pathophysiology of the disease.[16,17] The characterization of this feature in individual clusters may be improved by using electrocochleography and/or auditory evoked potentials. Vestibular function was measured using caloric and rotational chair tests, and the results of these tests should be interpreted in conjunction with

TABLE IV.
Percentage of Patients in Clusters 2, 3, and 4 by Their Group According to the American Academy of Otolaryngology–Head and Neck Surgery Staging System.

	AAO-HNS Group	Cluster 2	Cluster 3	Cluster 4
1	Percentage in AAO-HNS group	86.4	13.6	0
	Adjusted residual	4	−2.7	−2
2	Percentage in AAO-HNS group	80	20	0
	Adjusted residual	2.7	−1.7	−1.6
3	Percentage in AAO-HNS group	43.2	47.3	9.5
	Adjusted residual	−1.1	2	−1.3
4	Percentage in AAO-HNS group	0	54.5	45.5
	Adjusted residual	−4.9	1.5	5

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery.

those of the clinical bedside evaluation. In particular, it is noteworthy that as a group, all patients displayed a moderate degree of CP that influences the results of the rotational chair tests considerably.

The four-cluster solution prompted the categorization of MD patients into the following subgroups: 1) mildly active elderly, 2) mildly active young, 3) active compensated, and 4) active uncompensated. The cluster of mildly active elderly (cluster 1) is a special subset of MD patients because MD in the elderly can occur as a de novo disease or as the reactivation of a previous disorder.[18] We did not record a higher incidence of Tumarkin attacks in this cluster, as expected from previous studies of elderly MD patients. However, a trend toward an abnormal result in the bedside examination was evident in this group. This cluster was defined most clearly by the hearing level in both ears and the results of the vestibular tests. Discriminant analysis also identified the SOT condition 6 in the CDP test as a novel variable that should to be taken into consideration when defining this cluster, as the patients in this cluster performed particularly poorly in this test and fell most frequently. This is in agreement with the increased swaying in SOT conditions 3 and 6 displayed by elderly patients when compared to normal elderly subjects who sway more intensely in SOT conditions 4,5, and 6 owing to their age.[19] This increased swaying can ultimately lead to the patient falling into the safety harness of the CDP when displacement approaches the limits of stability. To avoid falling, elderly patients use hip movements and strategies more than ankle strategies in SOT conditions 5 and 6.[20] The limited capacity to shift between strategies to correctly match the demands of the environment and the support surface explains why some older adults are more prone to falling.[21] This limitation could be caused by the difficulty experienced by MD patients in matching the acceleration to which they are subjected when perturbations in the environment or support surface occur.

To define the other three clusters, we characterized the disease in terms of the DI (frequency and intensity of the vertigo attacks) and the time since the last vertigo attack.[7] According to these analyses, cluster 2 differed significantly from clusters 3 and 4; hence, cluster 2 was characterized as mildly active, while clusters 3 and 4 were considered to be associated with strong activity.

Cluster 2 (mildly active young) is best defined by a low frequency of vertigo attacks, a long period of time since the last attack, and the lowest PTA*s* score that is significantly better than in other clusters and that approaches the PTA*as*. This finding correlates with the low level of vestibular deficit in this cluster and the high level of postural stability, which is evident through the equilibrium maintained in the CDP test. Interestingly, these findings do not reflect the evolution of the process, as no significant differences in disease duration were found between clusters. Furthermore, at earlier stages of the disease, the levels of auditory and vestibular deficiency are low or unrelated.[9] Thus, the symptoms in these patients are independent of disease duration, with attacks inflicting less damage to vestibular function and hearing.

Among the four groups, clusters 3 and 4 comprised patients with a very active disorder, as reflected by their DI scores. These were considered as active clusters, in which a correlation between auditory and vestibular deficiency was observed, indicating intense damage to structures in the inner ear. The discompensation measured in the vestibular tests was greater in cluster 4 patients, including head-shaking nystagmus, directional preponderance of the caloric test, and gain and time constant asymmetry in rotations toward the symptomatic and asymptomatic ear. As such, cluster 3 was termed active compensated and cluster 4 was termed active uncompensated. Interestingly, patients in the active compensated cluster were significantly more disabled than those of the active uncompensated cluster, particularly in terms of levels of somatic anxiety. We propose that this finding is linked to the results of CDP, whereby these patients display a significant degree of disequilibrium and are visually dependent. In MD, visual dependence is very relevant as visual stimulation is deleterious in 15% of patients.[22] Furthermore, this effect is not correlated with age, sex, or clinical variables, shifts to nonvisual dependence after vestibular neurectomy,[23] yet it is related to somatic anxiety. A study of a subset of MD patients who experience Tumarkin attacks produced similar results, indicating that the impact of the disease on somatic anxiety is fundamental.[12] Patients in the active uncompensated cluster had severe hearing loss in the symptomatic ear and an intense vestibular deficit in the caloric test, although the disease had little impact on postural control when assessed by CDP. Thus, like the low active cluster, PTA*s* is the most significant defining parameter for this cluster.

The staging system by the AAO-HNS and our cluster solution are both methods to categorize MD patients into different subtypes. The former is based on the assumption that some specific degree of hearing loss (decided a priori without statistical support) marks the difference between the different subtypes. In terms of hearing loss, our solution does not provide a cutoff point between subtypes in which we see some overlap in PTA; this is because it has been constructed with the information from several variables. However, its value relies also on the objective methodology used, which will indirectly help to evaluate the clinical properties of the AAO-HNS staging system. We must say that both methods are independent ways of classifying MD patients, and the reason relies on the distribution of patients in clusters 2 and 4, as shown in Table III. But the amount of correlation between them is very low (Spearman rho of 0.28). Thus, the AAO-HNS categorizes patients only by hearing loss, which is insufficient to provide significant clinical information on the disease.

A detailed evaluation of the cluster solution shows some order in classification, a staging in functionality, as patients can move from a mildly active young stage to an active one and vice versa, and in the latter, they can be compensated or not also occasionally moving from one to another. The AAO-HNS staging system and this particular three-cluster solution are still independent, and now the difference is due to the three clusters (shown in Table IV), but the correlation is moderately high

(Spearman rho of 0.6). According to these findings, we can say that in a restricted population of patients with MD, staging by hearing level is not only a correct means of obtaining subtypes of the disease, but with clinical information as mildly active young persons belong to AAO-HNS groups 1, 2, and 3, active compensated to groups 2, 3, and 4, being active uncompensated mainly in groups 3 and 4. This finding is in accordance with what is expected when patients are followed over a long period and probably reflects the progressive damage that occurs in the inner ear. However, in elderly patients, the amount of age-related hearing loss or presbyacusis probably exceeds the amount of disease-related hearing loss, precluding of the use of the AAO-HNS staging system.

In classifying and characterizing definite MD according to distinct parameters, the CA offers some advantages over other methods. Principal component and factor analyses[24] produce linear combinations of variables, and they reduce their number by identifying two or three new domains comprised of combinations of old variables. The discriminant analysis[25] begins with known groups and finds scaled combinations of measured variables that best distinguish those groups. The CA reduces the number of patients (in our case 153) by placing them into groups (4-solution clusters). We believe that the identification of different subtypes will allow research efforts to focus on specific homogeneous subgroups.

Our work was performed without any predetermined criteria for the classification of the different bedside and instrumental test results, which reinforces its relevance. This is of special interest, as the four-cluster solution has a functional meaning that was not searched for in the initial approach to the problem of finding subgroups of patients with MD. This statistical methodology could be useful for the evaluation of patients with other diseases that share a similar clinical heterogeneity and complexity in test results, as occurs in vestibular migraine. Previous work using multivariate analysis allows for differentiation between MD and migraine based on rotatory chair testing and caloric test results.[26] An interesting observation from both studies is the different importance that rotatory chair and posturography test results have for the differentiation of the clusters in MD and between MD and migraine-associated dizziness. To differentiate between diseases, rotatory chair test results are of great value but not the posturography data; contrary to this, according to our findings, for the differentiation between clusters, rotatory chair test results are of limited value, but posturography (in particular SOT condition 6) is very relevant.

This work is one step forward in the process of elucidating the basis of the disease by allowing us to focus in clinical subtypes on the findings of more complex analysis as genetic association studies. In a similar way, it would allow for the development of tailored therapeutic strategies that offer a better prognosis to MD patients.

CONCLUSION

We have identified four groups of MD patients defined according to auditory and vestibular examinations, posturographic analysis, and disability measures. These findings provide important information to help identify strategies targeting specific subgroups of MD patients. We have demonstrated that in a restricted population of patients, the AAO-HNS staging system can provide analysis of subtypes of the disease.

BIBLIOGRAPHY

1. Committee on Hearing and Equilibrium: Guidelines for diagnosing the evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg* 1995;113:181–185.
2. Stalhe J, Arenberg IK, Goldman G. Staging Meniere's disease: description of a vertigo-disability profile. *Am J Otol* 1981;2:357–364.
3. Arenberg IK, Micalco LL. Inner ear disease typing for Meniere's disease with audiometric and electrocochleographic correlates. In: Hohmann D (ed). *EcoG, OAE and Intraoperative Monitoring: Proceedings of the First International Conference*. Wurzburg, Germany, September 20–24, 1992. Amsterdam/New York: Kugler Publ; 1993:131–132.
4. Van de Heyning PH, Wuyts FL, Claes J, Koekelkoren E, Van Laer C, Valcke H. Definition, classification and reporting of Meniere's disease and its symptoms. *Acta Otolaryngol Suppl* 1997;526:5–9.
5. Shea JJ. Classification of Meniere's disease. *Am J Otol* 1993;14:224–229.
6. Gibson WPR. The ten point score for the clinical diagnosis of Meniere's disease. In: Kaufman Arenberg I (ed). *Inner Ear Surgery.* Amsterdam/New York: Kugler Publ; 1992:109–113.
7. Soto A, Labella T, Santos S, et al. The usefulness of computerized dynamic posturography for the study of equilibrium in patients with Meniere's disease: correlation with clinical and audiologic data. *Hear Res* 2004; 196:26–32.
8. Olson JE, Wolfe JW. Comparison of subjective symptomatology and responses to harmonic acceleration in patients with Meniere's disease. *Ann Otol Rhinol Laryngol Suppl* 1981;90(4 pt 3):15–17.
9. Perez-Garrigues H, Lopez-Escamez JA, Perez P, et al. Time course of episodes of definitive vertigo in Meniere's disease. *Arch Otolaryngol Head Neck Surg* 2008;134:1149–1154.
10. Gates GA. Meniere's disease review 2005. *J Am Acad Audiol* 2006;17: 16–26.
11. Tyler R, Coelho C, Tao P, et al. Identifying tinnitus subgroups with cluster analysis. *Am J Audiol* 2008;17:S176–S184.
12. Perez-Fernandez N, Montes-Jovellar L, Cervera-Paz J, Domenech-Vadillo E. Auditory and vestibular assessment of patients with Meniere's disease who suffer Tumarkin attacks. *Audiol Neurootol* 2010;15:399–406.
13. Kariya S, Cureoglu S, Fukushima H, et al. Histopathologic changes of contralateral human temporal bone in unilateral Meniere's disease. *Otol Neurotol* 2007;28:1063–1068.
14. House JW, Doherty JK, Fisher LM, Derebery MJ, Berliner KI. Meniere's disease: prevalence of contralateral ear involvement. *Otol Neurotol* 2006;27:355–361.
15. Hwang JH, Ho HC, Hsu CJ, Yang WS, Liu TC. Diagnostic value of combining bilateral electrocochleography results for unilateral Meniere's disease. *Audiol Neurootol* 2008;13:365–369.
16. Momin SR, Melki SJ, Alagramam KN, Megerian CA. Spiral ganglion loss outpaces inner hair cell loss in endolymphatic hydrops. *Laryngoscope* 2010;120:159–165.
17. Megerian CA, Semaan MT, Aftab S, et al. A mouse model with postnatal endolymphatic hydrops and hearing loss. *Hear Res* 2008;237:90–105.
18. Ballester M, Liard P, Vibert D, Hausler R. Meniere's disease in the elderly. *Otol Neurotol* 2002;23:73–78.
19. Mirka A, Black FO. Clinical application of dynamic posturography for evaluating sensory integration and vestibular dysfunction. *Neurol Clin* 1990;8:351–359.
20. Liaw MY, Chen CL, Pei YC, Leong CP, Lau YC. Comparison of the static and dynamic balance performance in young, middle-aged, and elderly healthy people. *Chang Gung Med J* 2009;32:297–304.
21. Fulk GD, Robinson CJ, Mondal S, Storey CM, Hollister AM. The effects of diabetes and/or peripheral neuropathy in detecting short postural perturbations in mature adults. *J Neuroeng Rehabil* 2010;7:44.
22. Rama-Lopez J, Perez-Fernandez N. Characterisation of the influence exerted by the visual factor in patients with balance disorders [in Spanish]. *Rev Neurol* 2004;39:513–516.
23. Lacour M, Barthelemy J, Borel L, et al. Sensory strategies in human postural control before and after unilateral vestibular neurotomy. *Exp Brain Res* 1997;115:300–310.
24. Perez N, Garmendia I, Garcia-Granero M, Martin E, Garcia-Tapia R. Factor analysis and correlation between Dizziness Handicap Inventory and Dizziness Characteristics and Impact on Quality of Life scales. *Acta Otolaryngol Suppl* 2001;545:145–154.
25. Sanchez-Ferrandiz N, Fernandez-Gonzalez S, Guillen-Grima F, Perez-Fernandez N. Intractable Meniere's disease. Modelling of the treatment by means of statistical analysis. *Auris Nasus Larynx* 2010;37: 409–414.
26. Dimitri PS, Wall C, 3rd, Oas JG, Rauch SD. Application of multivariate statistics to vestibular testing: discriminating between Meniere's disease and migraine associated dizziness. *J Vestib Res* 2001;11:53–65.