Clinical Features, Familial History, and Migraine Precursors in Patients With Definite Vestibular Migraine: The VM-Phenotypes

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Research Submissions

Clinical Features, Familial History, and Migraine Precursors in Patients With Definite Vestibular Migraine: The VM-Phenotypes Projects

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Objective.—The aim of this work was to assess through a questionnaire the features of vertiginous episodes, accompanying symptoms, familial history, and migraine precursors in a sample of 252 subjects with a diagnosis of definite vestibular migraine.

Background.—Migraine is a common neurological disorder characterized by episodic headaches with specific features. About two-thirds of cases run in families, and patients may refer symptoms occurring in infancy and childhood, defined as

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episodic syndromes that may be associated with migraine. Migraine is associated with episodic vertigo, called vestibular migraine, whose diagnosis mainly relies on clinical history showing a temporary association of symptoms.

Methods.—In this cross-sectional multicentric study, 252 subjects were recruited in different centers; a senior specialist through a structured questionnaire assessed features of vestibular symptoms and accompanying symptoms.

Results.—The age of onset of migraine was 23 years, while onset of vertigo was at 38 years. One hundred and eighty-four subjects reported internal vertigo (73%), while 63 subjects (25%) reported external vertigo. The duration of vertigo attacks was less than 5 minutes in 58 subjects (23%), between 6 and 60 minutes in 55 (21.8%), between 1 and 4 hours in 29 (11.5%), 5 and 24 hours in 44 (17.5%), up to 3 days in 14 (5.5%), and more than 3 days in seven (2.8%); 14 subjects (5.5%) referred attacks lasting from less than 5 minutes and up to 1 hour, nine (3.6%) referred attacks lasting from less than 5 minutes and up to 1 to 4 hours, six (2.4%) referred attacks lasting from less than 5 minutes and up to 5 to 24 hours, and five (2%) cases referred attacks lasting from less than 5 minutes and up to days. Among accompanying symptoms, patients referred the following usually occurring, in order of frequency: nausea (59.9%), photophobia (44.4%), phonophobia (38.9%), vomiting (17.8%), palpitations (11.5%), tinnitus (10.7%), fullness of the ear (8.7%), and hearing loss (4%). In total, 177 subjects referred a positive family history of migraine (70.2%), while 167 (66.3%) reported a positive family history of vertigo. In the sample, 69% of patients referred at least one of the pediatric precursors, in particular, 42.8% of subjects referred motion sickness. The age of onset of the first headache was lower in the subsample with a familial history of migraine than in the total sample. Among the pediatric precursors, benign paroxysmal vertigo – BPV, benign paroxysmal torticollis, and motion sickness were predictive of a lower age of onset of vertigo in adulthood; cyclic vomiting was predictive for vomiting during vertigo attacks in adults.

Conclusions.—Our results may indicate that vestibular symptoms in pediatric patients may act as a predisposing factor to develop vestibular migraine at an earlier age in adulthood.

Key words: vestibular migraine, vertigo, headache, migraine, clinical diagnosis, vestibular disorders

Abbreviations: BPV benign paroxysmal vertigo, BPPV benign paroxysmal positional vertigo, ICHD International Classification of Headache Disorders, MD Ménière's disease, VM vestibular migraine

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INTRODUCTION

The association between migraine and vertigo is frequently observed in clinical practice and the complaint of vertigo and dizziness is more elevated in migraineurs than in the general population, ranging between 30% and 50%.[1,2] In previous years, various terms such as migraine-associated dizziness, migraine-related vertigo, and migrainous vertigo have been used to describe episodic vestibular symptoms in patients with migraine when an alternative diagnosis has been ruled out.[3,4] Since clinical examination is usually normal during the vertigo-free period,[5] the diagnosis mainly relies on clinical history. Recently, a joint committee between the International Headache Society and the Bárány Society established the following diagnostic criteria for both the definite and probable nosological disorder called vestibular migraine (VM) in which migraine per se is associated with the occurrence of vestibular symptoms.[6]

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Definite VM:

a. At least five episodes with vestibular symptoms of a moderate or severe intensity, lasting 5 minutes to 72 hours.
b. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD).
c. One or more migraine features with at least 50% of the vestibular episodes:
   - Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
   - Photophobia and phonophobia
   - Visual aura
d. Not better accounted for by another vestibular or ICHD diagnosis.

In order to diagnose probable VM, only one of the criteria B or C must be observed.

The diagnostic criteria for definite VM are included in the 3rd edition of the International

Classification of Headache Disorders (ICHD-III), published in 2013, where it appears in the appendix for new disorders.[7]

Familial aggregation has been widely observed in migraine[8] and episodic vertigo,[9] and both disorders may arise from the interplay between genetic predisposition and environmental factors. While different reports have been published on the genetics and familiarity of migraine, the few studies on VM up to the present time have produced inconclusive results.

Finally, ICHD-III included four migraine equivalents in infancy and childhood, defined as "episodic syndromes which may be associated with migraine": cyclic vomiting, abdominal pain, benign paroxysmal vertigo, and benign paroxysmal benign paroxysmal torticollis. For some of them, an involvement of the vestibular system can be proposed. Motion sickness in pediatric subjects, consisting of autonomic signs and symptoms occurring during movement, has also been studied as a possible migraine precursor.[10]

The aim of our work was to assess the features of vertiginous episodes, accompanying symptoms, familial history, and migraine precursors in a large sample of subjects with a diagnosis of definite VM.

MATERIALS AND METHODS

Patients.—In this cross-sectional multicentric study, 252 subjects were recruited in different centers in Italy and Spain between January 2016 and March 2017 among those evaluated during daily clinical practice. Two hundred and sixty-five patients were initially enrolled. A six months' follow-up was requested in order to confirm the diagnosis of definite VM. Thirteen subjects (4.9%) were excluded afterwards since presenting mild low frequencies sensorineural hearing loss. All patients presented a diagnosis of definite VM according to the Bárány/ICHD Society criteria.[6] Of the 252 subjects, 214 (84.9%) were female. The age at inclusion was 45.8 ± 13.6 years (range 19-76 years). All patients were interviewed by a senior neuro-otologist. The centers were tertiary referral outpatient clinics or vertigo clinics in general hospitals in Italy (Milan, Turin, Brescia, Policoro, Pisa, Siena, Chieti, Florence, Naples, and Parma) and Spain (Salamanca, Granada, Madrid). The local ethics committees of all the participating centers approved this study. All patients gave their written informed consent before entering the study. Data were saved on eCRF in our hospital, only senior specialists were given a username/password, and they were asked to include patients evaluated in their clinical activity presenting criteria for definite VM and signing informed consent.

Methods.—A full bedside examination, an audiometric examination, and a CNS MRI was performed before inclusion. Patients with low frequency sensorineural hearing loss were not included, as well as patients with an MRI positive otherwise for microischemic lesions. A diagnosis of migraine was confirmed by a senior neurologist. A structured questionnaire was designed to record the symptoms according to the Bárány Vestibular Symptoms Grid and to characterize the vestibular phenotype.[11] Data regarding migrainous features were also collected; since our paper is mainly focused on vestibular symptoms, they were not included neither were published. In particular, vestibular symptoms were:

- **internal vertigo** is a false sensation of self-motion, when no self-motion is occurring; for internal vertigo, subjects were asked if they had the sensation of spinning or other false sensations such as swaying, tilting, bobbing, bouncing, or sliding.
- **dizziness** is the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion.
- **visuo-vestibular symptoms—external vertigo** is the false sensation that the visual surround is spinning or flowing.
- **postural symptoms** are balance symptoms related to maintenance of postural stability, occurring only while upright (seated, standing, or walking).

The following triggering conditions were also assessed:

- **positional vertigo** is vertigo triggered by and occurring after a change of head position in space relative to gravity.
- **head-motion vertigo** is vertigo occurring only during head motion.

- **visually induced vertigo** is vertigo triggered by a complex, distorted, large field or moving visual stimulus, including the relative motion of the visual surround associated with body movement.

The vestibular symptoms were classified into six groups according to their duration: less than 5 minutes; 6 minutes to less than 1 hour; from 1 to 4 hours; from 5 to 24 hours; up to 3 days; more than 3 days. Regarding vertigo-related symptoms (internal/external vertigo, triggering conditions and duration of attacks), multiple answers were accepted. The questionnaire also included patient's age at onset of vestibular symptoms and headache, and a set of questions to determine the accompanying symptoms occurring during the attacks, ie, vision-related symptoms (photophobia, visual aura, diplopia), hearing-related symptoms (phonophobia, tinnitus, fullness of the ear, hearing loss), vegetative symptoms (nausea, vomiting, palpitations, choking), emotional symptoms (anxiety), and headache. Patients were asked to choose whether accompanying symptoms occurred never, sometimes (<50% of attacks), or usually (≥50% of attacks).

Patients were also asked if any of their family members, ie, another relative in the first or second degree, suffered from migraine and/or vertigo in the family; if a familial history of vertigo was found, patients were asked if they could refer a possible diagnosis, choosing among the following conditions: VM, Ménière's disease, benign paroxysmal positional vertigo (BPPV), vestibular neuritis, unable to respond.

Finally, the following migraine precursors were investigated in the questionnaire: motion sickness, cyclic vomiting, episodic abdominal pain, episodic vertigo, benign paroxysmal torticollis. To diagnose migraine precursors, criteria of ICHD-III beta version were observed.[7]

A positive history for cyclic vomiting has been considered when the patient referred episodes (at least 5) of severe vomiting without apparent cause, lasting for at least 1 hour or days alternating with symptom-free periods and occurring with the same stereotyped symptoms and intensity in childhood. Episodic abdominal pain was considered when patients reported recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2 to 72 hours and with normality between episodes. Benign paroxysmal benign paroxysmal torticollis was diagnosed when the patient reported recurrent and stereotyped episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously occurring in infants and small children, with onset in the first year. BPV was diagnosed in subjects reporting recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.

We included motion sickness among them, although not commonly accepted, and probably better definable as a migraine marker.

Statistical Analysis.—Absolute and relative frequencies of each symptom were calculated and compared between different groups using chi-square statistics. Quantitative variables are presented as mean ± standard deviation and unpaired Student's *t*-tests were used to compare them. A P value $< .05$ was considered to be statistically significant. A Spearman test was performed to investigate the association between different variables. One full regression model was calculated to assess the independent role of migraine precursors on age of onset of vertigo. We used SPSS software version 17.0 (SPSS, Inc., Chicago, IL, USA) for statistical analysis

RESULTS

Descriptive Analyses: Type of Symptoms, Duration, Familial History, and Migraine Precursors.—In total, 252 patients were included in the sample. The age at inclusion was 46 ± 14 years [range 19-76 years], and the female/male ratio was 5.6/1. The duration of vestibular symptoms was 52.8 ± 67.2 months [range 2-360 months]. The age of onset of migraine was 23 ± 9 years [range 11-40 years], while the age at the first vertigo attack was 38 ± 13 years [range 16-60 years]. In total, 16 patients reported synchronous occurrence of headache and vertigo; these patients presented a lower age of onset of both disorders than the remaining population (mean age of 20 ± 2 years, $P = .05$). Demographic data have been summarized in Table 1.

Table 1.—Demographic Data of Our Sample ($n = 252$)

Age at inclusion	46 ± 14 [range 19-76 years]
Sex	214 females (84.9%)
Age of onset of first headache	23 ± 9 [range 11-40 years]
Age of onset of the first vestibular episode	38 ± 13 [range 16-60 years]
Duration of vestibular symptoms	52.8 ± 67.2 months [range 2-360 months]

Internal vertigo was reported by 184 subjects (73%) (Table 1). In this sample, the sensation of spinning was reported by 135 subjects (53.6% of the total sample), while non spinning was reported by 62 patients (24.6%). Positional triggered vertigo was reported by 61 patients (24.2%), and in 48 of them (19.0%), the vertigo was transient. Vertigo was triggered by head motion in 84 cases (33.3%), while it was visually induced in 48 subjects (19%).

Spontaneous dizziness was reported by 119 subjects (47.2%) (Table 1). Among them, 63 patients (25%) had positional vertigo and 53 patients (21%) reported head motion-triggered vertigo, while in 35 (13.9%), it was visually induced.

External vertigo was reported by 63 subjects (25%) (Table 1), and in 10 (4%) of them, the sensation was head motion-dependent.

Finally, postural symptoms were reported by 155 subjects (61.5%). These results are summarized in Table 2.

The duration of vertigo attacks was less than 5 minutes in 58 subjects (23%), in the range between 6 and 60 minutes in 55 (21.8%), between 1 and 4 hours in 29 (11.5%), 5 to 24 hours in 44 (17.5%), 1 to 3 days in 14 (5.5%), and more than 3 days in seven (2.8%); 14 subjects (5.5%) referred attacks lasting from less than 5 minutes and up to 1 hour, nine (3.6%) referred attacks lasting from less than 5 minutes to 1 to 4 hours, six (2.4%) referred attacks lasting from less than 5 minutes to 5 to 24 hours, and five (2%) referred attacks lasting from less than 5 minutes to more than 1 day (Fig. 1).

The accompanying symptoms reported during vertigo attacks and percentages are reported in Table 3.

In total, 177 subjects referred a positive familial history of migraine (70.2%), while 167 (66.3%) reported familial cases of vertigo. When asked about the known diagnoses, 54 (21.4%) reported VM, 22 (8.7%) BPPV, 18 (7.1%) Ménière's disease (MD),

Table 2.—Vertigo Related Symptoms in the Total Sample (252 Subjects)

Vertigo Related Symptoms	Triggering Conditions
Internal Vertigo 184 (73%)	Positional 61 (24.2%) Head Motion 84 (33.3%) Visually Induced 48 (19%)
Spontaneous Dizziness 119 (47.2%)	Positional 63 (25%) Head Motion 53 (21%) Visually Induced 35 (13.9%)
External Vertigo 63 (25%)	Head Motion 10 (4%) Oscillopsia head movement dependent 10 (4%) Oscillopsia non head movement dependent 17 (6.7%)
Postural Symptoms 155 (61.5%)	Unsteadiness 136 (54%) Lateral directional pulsion 50 (19.8%) Antero-retro directional pulsion 38 (15%) Balance associated near fall 55 (21.8%) Balance associated fall 7 (0.3%)

Percentage of the total sample shown in parentheses. Multiple answers were accepted from each subject.

Table 3.—Accompanying Symptoms Reported by Patients During Vertigo Attacks

	Number of Cases (and Percentage)		
Symptoms	Mostly	Sometimes	Never
Vision related			
Photophobia	111 (44%)	109 (43.3%)	32 (12.7%)
Visual aura	–	21 (8.3%)	231 (91.7%)
Diplopia	–	23 (9.1%)	229 (90.9%)
Hearing related			
Phonophobia	98 (38.9%)	80 (31.7%)	74 (29.4%)
Tinnitus	27 (10.8%)	103 (40.8%)	122 (48.4%)
Fullness of the ear	22 (8.8%)	76 (30.1%)	154 (61.1%)
Hearing loss	10 (4%)	38 (15%)	204 (81%)
Vegetative			
Nausea	151 (59.9%)	75 (29.8%)	26 (10.3%)
Vomiting	45 (17.8%)	84 (33.4%)	123 (48.8%)
Palpitations	29 (11.5%)	88 (34.9%)	135 (53.6%)
Choking	13 (5.1%)	36 (14.3%)	203 (80.6%)

Mostly means in more than 50% of attacks, sometimes in less than 50%.

seven (2.8%) vestibular neuritis, while 66 (26.2%) were unable to specify diagnoses.

The total number and percentages of patients referring migraine precursors are reported in Table 4.

Table 4.—Migraine Precursors in Our Sample ($n = 252$); in the Second Column the Total Number (and Percentage) of Patients

Migraine Precursors	
Motion sickness	108 (42.8%)
Cyclic vomiting	24 (9.5%)
Episodic abdominal pain	18 (7.1%)
Episodic vertigo (BPV)	12 (4.8%)
Benign paroxysmal torticollis	12 (4.8%)

Correlations.—No correlation was found between external vertigo/internal vertigo and duration of vertigo/tinnitus, hearing loss, or fullness of the ear. A correlation was found between the age at onset of the first headache and the first vertigo ($r_s = 0.37$, 95% CI 0.25 to 0.46; $P < .0001$). The age at onset of the first headache was lower in the subsample with a familial history of migraine than in the remaining sample (20 ± 11 vs 24 ± 9 years, $t = 2.5$, $P = .01$). Moreover, the age at onset of the first headache in patients with a familial history of VM was lower than in the total sample (19 ± 12 vs 24 ± 9 years, $t = 2.8$, $P = .004$), while age at the first vertigo episode was not significantly different ($P = .1$).

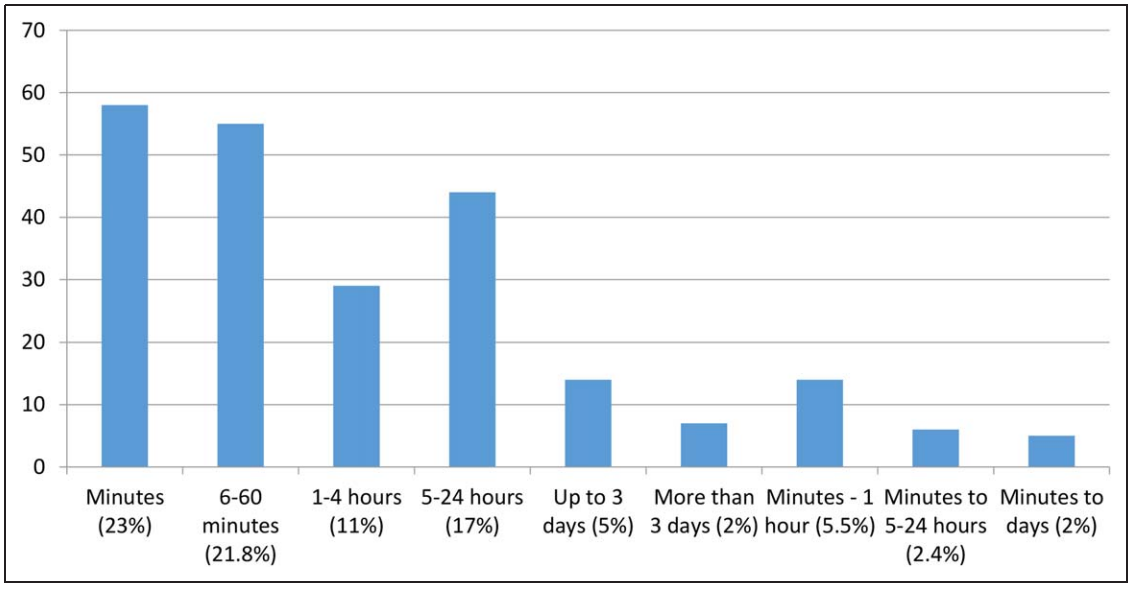

Fig. 1.—Duration of vertigo attacks. Vertical axis shows the number of cases reported; percentage of the total sample (252 subjects) shown in parentheses. [Color figure can be viewed at wileyonlinelibrary.com]

Table 5.—Relative Frequencies of Symptoms Tinnitus, Fullness of the Ear, and Hearing Loss, Occurring During Vertigo in the Subsample of Patients With a Negative and Positive Familial History for MD (Second and Third Columns) and Negative or Positive Familial History for Either VM or MD

	Negative Family History for MD ($n = 234$)	Positive Family History for MD ($n = 18$)	Negative Family History for Either MD or VM ($n = 180$)	Positive Family History for Either MD or VM ($n = 72$)
Tinnitus	Mostly 24 Sometimes 90 Never 120	Mostly 3 Sometimes 13 Never 2 ($X^2 = 10.9$, $P = .004$)	Mostly 10 Sometimes 71 Never 99	Mostly 16 Sometimes 34 Never 22 ($X^2 = 21$, $P = .00003$)
Fullness of the ear	Mostly 20 Sometimes 66 Never 148	Mostly 2 Sometimes 10 Never 6 ($X^2 = 6.7$, $P = .03$)	Mostly 9 Sometimes 50 Never 121	Mostly 13 Sometimes 25 Never 34 ($X^2 = 14$, $P = .0008$)
Hearing loss	Mostly 9 Sometimes 69 Never 156	Mostly 1 Sometimes 7 Never 10 ($P = .2$)	Mostly 8 Sometimes 23 Never 149	Mostly 2 Sometimes 14 Never 56 ($P = .3$)

MD, Ménière's disease; VM, vestibular migraine. Results are shown as total number of patients reporting the symptom mostly (most than 50% of attacks), sometimes (less than 50% of attacks), never, respectively. A chi-square test has been performed to assess differences between groups.

Considering the pediatric precursors, motion sickness was predictive for external vertigo ($X^2 = 4.4$; $P = .04$), and cyclic vomiting was predictive for vomiting during vertigo attacks ($X^2 = 6.1$; $P = .01$).

In Table 5, we present the total number of subjects referring tinnitus, fullness of the ear, and hearing loss in the subset of patients with a negative/positive family history for MD alone and with a positive/negative family history for either MD or VM. Above all, tinnitus and fullness of the ear were more frequently reported by patients with a familial history of MD and VM.

Finally, in order to assess a possible role on the age of onset of migrainous symptoms, a prespecified general linear regression model considering age at onset of vertigo as an dependent variable and pediatric precursors as independent variables demonstrated that BPV, benign paroxysmal torticollis, and motion sickness were predictive for a lower age of onset of vertigo. Above all, the presence of BPV was associated with a 9.8-year reduced age of onset of vertigo, benign paroxysmal torticollis of 11.1, and motion sickness with a 3.9-year lower age of onset. The results and statistics are summarized in Table 6.

DISCUSSION

Vestibular migraine is a common neurotological disorder affecting 1-2% of the European descendant population.[12] The diagnostic criteria for VM has changed in the last 15 years for some aspects; the Lempert and Olesen criteria are at present commonly accepted, and based on clinical history. A validation of these criteria has been recently published.[13] However, a large heterogeneity of symptoms may be observed among different patients. As far as we know, this is the largest sample of patients with definite VM at present and ours is an ongoing project and we are still recruiting clinical data in Italy and Spain to build a large database to characterize the different phenotypes of definite VM.

First, we found that the duration of vertigo attacks is highly variable and our results are in line with those previously published,[14-16] although in our sample, a lower rate (8%) of patients reported

Table 6.—Linear Model Considering the Age of Onset of Vertigo as Dependent Variable and Different Migraine Pediatric Precursors as Independent Variables

	Coefficient	95% CI	t statistic	*P* value
Cyclic vomiting	1.5	−3.5 to 6.5	0.58	.5598
BPV	−9.8	−17.1 to −2.5	−2.67	.008
Benign paroxysmal torticollis	−11.1	−18.3 to −3.7	−2.98	.0032
Abdominal pain	−4.5	−10.7 to 1.8	−1.40	.1640
Motion sickness	−3.9	−7.1 to −0.8	−2.44	.0152

BPV, benign paroxysmal vertigo.

vertigo attacks lasting for more than 1 day and a higher rate of patients reported short vertigo attacks lasting for less than 1 hour (44.8%). Partially diverging from other recent papers are our results on vertiginous symptoms, since we found a higher rate of patients referring internal (73%) rather than external vertigo (25%), whereas in a recent paper, the latter symptom was reported in 53.7% of patients;[17] it should be noted that those authors included a sample of 41 subjects.

Interestingly, the onset of migraine preceded the onset of vertigo by around 15 years, but patients reporting a synchronous presentation were characterized by a lower age at onset of both symptoms. Similarly, the age at onset of migraine was lower in patients with a familial history of migraine and/or episodic vertigo for VM. It is well established that migraine aggregates within families,[18] so it could be speculated that genetic factors may play a significant role in those patients with an early onset of both symptoms and familial history. Since migraine and familial migraine are common disorders, a polygenic contribution with common and rare variants is expected to drive the phenotype.

The second interesting finding in our cohort is that patients with definite VM may experience auditory symptoms such as tinnitus, fullness of the ear, and hearing loss during vertigo attacks, which are more commonly reported in subjects with Ménière's disease (MD). This finding has already been reported previously.[19] In particular, a recent study reported that a subset of patients with definite VM experienced, at least sometimes, tinnitus (46.4%), fullness of the ear (34.5%), and hearing loss (25.7%) during vertigo.[20] Our results confirm these data, although we found a higher rate of patients referring tinnitus (51.5%) and a lower rate referring hearing loss (19%). It could be of some importance to note that patients with a familial episodic vertigo, including familial VM or MD, could present a higher frequency of tinnitus and fullness of the ear during the attacks.

We found a high rate of patients referring a familial history of migraine (73.1%) and episodic vertigo (66.2%), among them VM (21.4% of subjects) and MD (7.1%). Regarding familial migraine, results are overlapping with those of previous works.[18,21] There are few studies showing a familial aggregation of migraine, episodic vertigo and MD.[22-24] It should be noted that diagnoses were referred by patients and could not be confirmed by a medical examination.

It could be speculated that both findings, those concerning accompanying symptoms and family history, may underline some possible overlapping pathophysiological mechanism between MD and VM; it is known for example that MD subjects present a higher rate of migraine than the total population.[25] Conversely, in the early stages of both disorders, differential diagnosis may be a troublesome issue in some cases.[26-28]

Finally, interesting considerations may be drawn from the data on migraine precursors. In our cohort, we found that 69% of patients referred at least one of the pediatric precursors of migraine; in particular, 42.8% of subjects referred motion sickness. Recent studies have emphasized how motion sickness is a common finding in the general population and it has

a strong genetic contribution.[29,30] Our data are in line with a previously published work reporting a rate of migraine equivalents of 70.3% and motion sickness of 40.5% in a sample of over 1000 pediatric patients mostly with migrainous headaches.[31] Another recent review on migraine precursors reported a rate of 1.9-2.3% for cyclic vomiting, 1.7-4.1% for episodic abdominal pain, and 2-2.6% for episodic vertigo in the total pediatric population.[10] Clearly, our rates are higher since our cohort was composed only of migraineurs. Benign paroxysmal torticollis is considered to be linked to a vestibular dysfunction, either peripheral or central.[32,33] Interestingly, patients referring cyclic vomiting when of pediatric age also referred vomiting during vertigo attacks, indicating a possibly more reactive autonomic system.

Among pediatric precursors, motion sickness and in a significantly increased measure, episodic vertigo/benign paroxysmal torticollis, were predictive of a lower age of onset of vertigo in patients with VM in our cohort.

In a retrospective study, it has been reported that benign paroxysmal vertigo in childhood could be a migraine precursor.[34] Our study also supports the view that an association between vestibular symptoms when patients were of pediatric age may act as a predisposing factor to develop VM at an earlier age in adulthood, and suggests the presence of genetic factors predisposing to vestibular disorder in this early onset VM.

Finally, we want to underline some possible limitations of our study. We tried to avoid inclusion of patients only suffering from episodic vertigo and migrainous headaches; for that purpose, a follow-up at 6 months was requested and doubtful cases (ie, probable VM) were excluded. Above all, evaluation of familial cases of vertigo (and their diagnoses) and clinical history of migraine precursors may present some uncertainty, since these data were only collected during the structured interview with the patient.

Regarding precursors, some clinical data might be underestimated; on the opposite, since the specialist was unable to confirm the diagnosis of the vestibular disorders in family trees, these data might present a certain degree of uncertainty.

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Category 3

(a) Final Approval of the Completed Manuscript

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