ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:328-335; doi: 10.14639/0392-100X-1121

Vestibology

Italian survey on benign paroxysmal positional vertigo

Survey italiana sulla vertigine parossistica posizionale

A. MESSINA[1], A.P. CASANI[2], M. MANFRIN[3], G. GUIDETTI[4]

[1] Otoneurology and Tinnitus Unit, Chair of Audiology, P. Giaccone University Hospital, Palermo; [2] Department of Surgical, Medical and Critical Care Pathology, University of Pisa; [3] ENT Clinic, IRCCS Policlinico San Matteo, Pavia; [4] Vertigo Center, Poliambulatorio Chirurgico Modenese, Modena

SUMMARY

Benign paroxysmal positional vertigo (BPPV) is the most common type of peripheral vertigo. BPPV often relapses after the first episode, with a recurrence rate between 15% and 50%. To date both the aetiopathogenetic processes that lead to otoconia detachment and the factors that make BPPV a relapsing disease are still unclear, but recent epidemiological studies have shown a possible association with cardiovascular risk factors. The aim of the present study (Sesto Senso Survey) was to evaluate in the Italian population through an observational survey, the main demographic and clinical characteristics of patients with BPPV (first episode or recurrent) with particular focus on the potential cardiovascular risk factors. The survey was conducted in 158 vestibology centres across Italy on 2,682 patients (mean age 59.3 ± 15.0 years; 39.1% males and 60.9% females) suffering from BPPV, from January 2013 to December 2014. The results showed a high prevalence of cardiovascular risk factors such as high blood pressure (55.8%), hypercholesterolaemia (38.6%) and diabetes (17.7%), as well as a family history of cardiovascular disease (49.4%). A high percentage of patients also had hearing loss (42.9%), tinnitus (41.2%), or both (26.8%). The presence of hypertension, dyslipidaemia and pre-existing cardiovascular comorbidities were significantly related to recurrent BPPV episodes (OR range between 1.84 and 2.31). In addition, the association with diabetes and thyroid/autoimmune disease (OR range between 1.73 and 1.89) was relevant. The survey results confirm the significant association between cardiovascular comorbidities and recurrent BPPV and identify them as a potential important risk factor for recurrence of BPPV in the Italian population, paving the way for the evaluation of new therapeutic strategies in the treatment of this disease.

KEY WORDS: Benign paroxysmal positional vertigo • Risk factors • Cardiovascular diseases • Therapy

RIASSUNTO

La vertigine parossistica posizionale benigna (VPPB) è il tipo più comune di vertigine periferica. Frequentemente dopo il primo episodio la VPPB presenta recidive, con un tasso di ricorrenza tra il 15% ed il 50%. Ad oggi non vi è chiarezza sui processi eziopatogenetici che portano al distacco degli otoconi né su quali siano i fattori che rendono la VPPB una patologia recidivante, ma recenti studi epidemiologici hanno evidenziato una possibile associazione con fattori di rischio cardiovascolari. Lo scopo del presente studio (Sesto Senso Survey) è stato quello di valutare nella popolazione italiana, attraverso un'indagine osservazionale, le principali caratteristiche demografiche e cliniche dei pazienti con VPPB (primo episodio o ricorrente), con particolare attenzione ai potenziali fattori di rischio cardiovascolare. L'indagine è stata condotta in 158 centri di Vestibologia in tutta Italia su 2.682 pazienti (età media 59,3 ± 15,0 anni; 39,1 maschi e 60,9% femmine) affetti da VPPB, da gennaio 2013 a dicembre 2014. I risultati hanno mostrato in questi pazienti l'alta prevalenza di fattori di rischio cardiovascolari come ipertensione arteriosa (55,8%), ipercolesterolemia (38,6%) e diabete (17,7%), oltre ad una elevata familiarità per malattie cardiovascolari (49,4%). In un'elevata percentuale di pazienti si è inoltre registrata la presenza di ipoacusia (42,9%), acufeni (41,2%) o entrambi (26,8%). Significativamente correlata agli episodi di recidiva di VPPB è risultata la presenza di ipertensione arteriosa, dislipidemia e comorbidità cardiovascolare accertata (range OR tra 1,84 e 2,31). Rilevanti anche le associazioni con diabete e patologie tiroidee e autoimmuni (range OR tra 1,73 e 1,89). I risultati dell'indagine confermano la significativa associazione tra comorbidità cardiovascolari e VPPB recidivanti e le identificano come importante potenziale fattore di rischio per le recidive di VPPB nella popolazione italiana, aprendo la strada alla valutazione di nuove strategie terapeutiche nel trattamento di questa patologia.

PAROLE CHIAVE: *Vertigine parossistica posizionale benigna • Fattori di rischio • Patologie cardiovascolari • Terapia*

Acta Otorhinolaryngol Ital 2017;37:328-335

Introduction

Benign paroxysmal positional vertigo (BPPV) is a clinical syndrome characterised by brief recurrent episodes of vertigo, triggered by changes in head position with respect to gravity and due to abnormal stimulation of the cupula of one of the three semicircular canals, most frequently the posterior one. The excitatory response of the cupula is generated by otoliths that detach from the macula of the utricle and move into the lumen of the semicircular canal in response to movements of the head; otoliths then reach the cupula that is stimulated abnormally by the small crystals, thus causing vertigo and nystagmus. Otoliths, which have been observed during surgery, may in some cases adhere to the cupula, generating a form of BPPV called cupulolithiasis [1 2]. The characteristic signs of BPPV are evoked when the subject's head is positioned so that the plane of the semicircular canal is aligned with gravity, generating nystagmus and vertigo. The duration, frequency and intensity of symptoms can vary. Autonomic manifestations (nausea, vomiting) or a persistent residual dizziness can be also present [1 2].

BPPV is the most common type of peripheral vertigo, with a reported prevalence of 11 to 64 cases per 100,000 persons, with a peak in the 50-70 age group; a higher prevalence is reported among women [1 3].

BPPV often relapses after the first episode, with a recurrence rate of between 15% and 50%, and the episode usually reoccurs within a few months [1 4].

To date both the aetiopathogenetic processes that lead to otoconia detachment and the factors that make BPPV a recurrent disease are unclear. In recent years, various epidemiological studies have analysed family history data in order to highlight any comorbidities that might be related to recurrences of BPPV [3-6]. Between 2007 and 2009, the Revert international registry collected data from over 4000 consecutive cases of vertigo observed in 618 vestibology centres in 13 countries around the world [7]. This and other studies demonstrated an association between recurrent BPPV and arterial hypertension (present in 52% of cases), hyperlipidaemia (up to 55% of cases), thyroid dysfunction (up to 21.3% of cases) and a significant prevalence of diabetes in patients with BPPV compared with the general population [4 6 8]. In a recent observational study, hypertension and diabetes were shown to be significantly related to risk of recurrent BPPV, with increased risk if both comorbidities were present at the same time [5]. The Revert registry showed that 46.3% of BPPV subjects had cardio-vascular comorbidities, and 17.2% hormonal dysfunctions [7]. This is consistent with the hypothesis that both arterial hypertension and hyperlipidaemia can cause vascular damage in the inner ear. Furthermore, it is known that BPPV may follow an ischaemic event around the anterior vestibular artery which would facilitate otoconia detachment from the utricle. Additionally, vertebrobasilar ischaemia has been suggested as a predisposing factor for BPPV and some data sustain a correlation between BPPV and stroke [4]. A recent retrospective nationwide population study in Taiwan examined data from the National Health Research Institute (NHRI) to assess cerebrovascular risk in patients with BPPV compared with a control group. Over a period of 9 years, the risk of stroke in BPPV subjects was 1.4-fold higher than the risk in subjects without BPPV ($p = 0.001$) [9].

The aim of the present study was to evaluate in the Italian population, through an observational survey, the main demographic and clinical characteristics of patients with BPPV (first episode or recurrent) with particular focus on potential cardiovascular risk factors.

Materials and methods

Our investigation is a multicentric observational study. We collected patient history and diagnostic and clinical assessments on 2,682 patients who had referred to 158 Italian vestibology out-patient clinics belonging to the "Sesto Senso Study Group" from January 2013 to December 2014. The inclusion criterion was a diagnosis of BPPV, either initial episode or recurrence. We considered recurrent BPPV the new clinical manifestation of vertigo signs and symptoms after the resolution of the previous episode, diagnosed according to the standard practice of each centre.

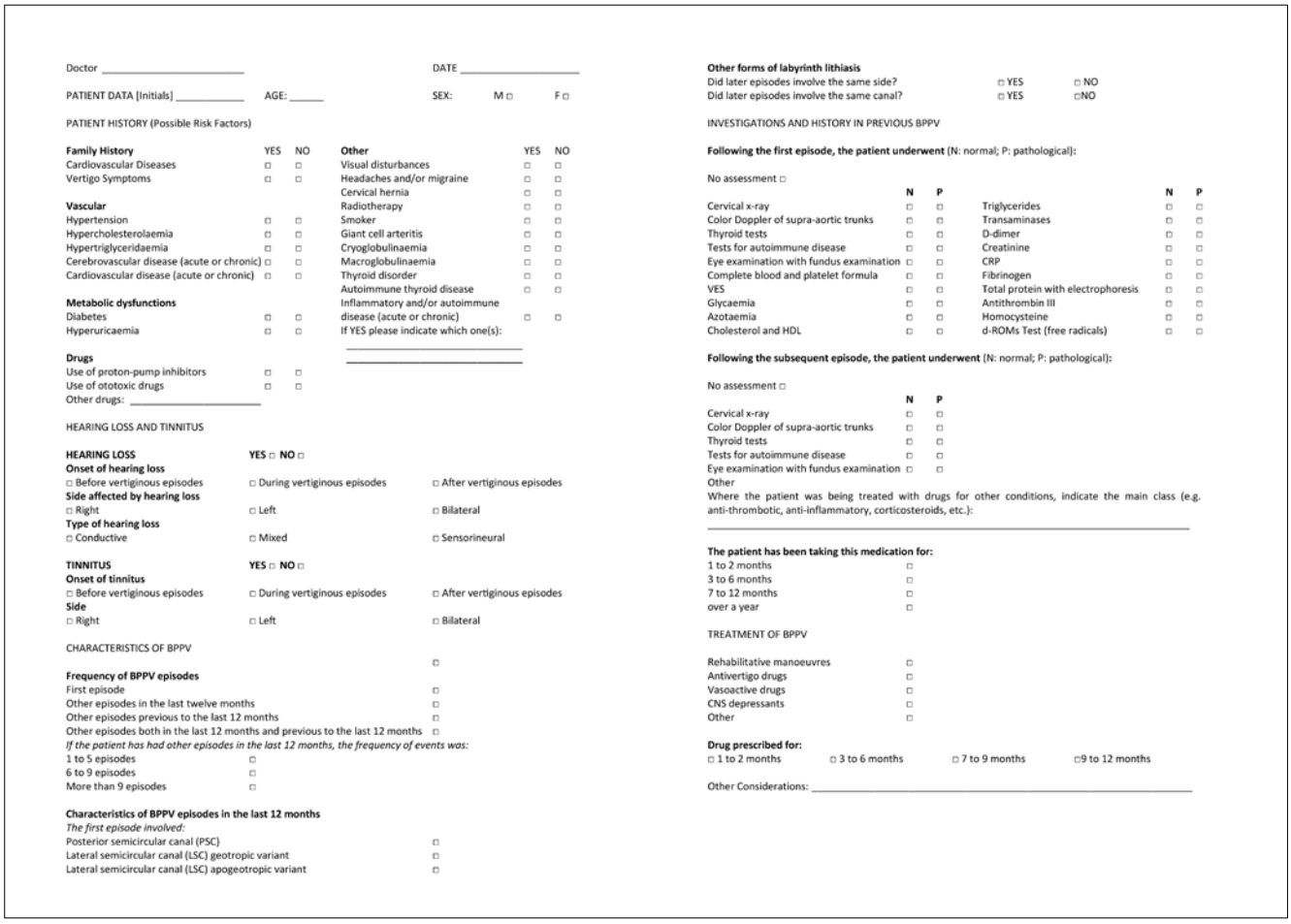
The data were registered using a form divided into four sections (Fig. 1):

1. Patient history (possible risk factors): family history of vertigo and cardiovascular disease, vascular and metabolic risk factors (hypertension, hypercholesterolaemia, hypertriglyceridaemia, acute or chronic cerebrovascular disease, acute or chronic cardiovascular disease, diabetes, hyperuricaemia), use of drugs and/or other comorbidities.
2. Hearing loss and tinnitus: reported audiological symptoms associated with episodes of BPPV.
3. Characteristics of BPPV, first episode or recurrence: number and frequency of episodes, canal involved.
4. Treatment of first BPPV episode and any subsequent episodes: description of the treatment used; in the event of pharmacological treatment, duration of therapy.

The demographic and clinical data were summarised in frequency tables or central tendency and dispersion tables, using the most suitable indicators for the variables (mean, standard deviation).

The discrete data were summarised as absolute frequencies and relative frequency percentages. Missing values were not considered for calculation of the relative frequency percentages.

The analysis of the association between recurrence and possible risk factors was performed through the χ^2 test and the odds ratios (OR) with 95% confidence intervals.



Doctor _____ DATE _____

PATIENT DATA [Initials] _____ AGE: _____ SEX: M □ F □

PATIENT HISTORY (Possible Risk Factors)

Family History	YES	NO	Other	YES	NO
Cardiovascular Diseases	□	□	Visual disturbances	□	□
Vertigo Symptoms	□	□	Headaches and/or migraine	□	□
			Cervical hernia	□	□
Vascular			Radiotherapy	□	□
Hypertension	□	□	Smoker	□	□
Hypercholesterolaemia	□	□	Giant cell arteritis	□	□
Hypertriglyceridaemia	□	□	Cryoglobulinaemia	□	□
Cerebrovascular disease (acute or chronic)	□	□	Macroglobulinaemia	□	□
Cardiovascular disease (acute or chronic)	□	□	Thyroid disorder	□	□
			Autoimmune thyroid disease	□	□
Metabolic dysfunctions			Inflammatory and/or autoimmune		
Diabetes	□	□	disease (acute or chronic)	□	□
Hyperuricaemia	□	□	If YES please indicate which one(s):		
			_____		
Drugs			_____		
Use of proton-pump inhibitors	□	□			
Use of ototoxic drugs	□	□			
Other drugs: _____					

HEARING LOSS AND TINNITUS

HEARING LOSS **YES □ NO □**

Onset of hearing loss
□ Before vertiginous episodes □ During vertiginous episodes □ After vertiginous episodes

Side affected by hearing loss
□ Right □ Left □ Bilateral

Type of hearing loss
□ Conductive □ Mixed □ Sensorineural

TINNITUS **YES □ NO □**

Onset of tinnitus
□ Before vertiginous episodes □ During vertiginous episodes □ After vertiginous episodes

Side
□ Right □ Left □ Bilateral

CHARACTERISTICS OF BPPV

□

Frequency of BPPV episodes
First episode □
Other episodes in the last twelve months □
Other episodes previous to the last 12 months □
Other episodes both in the last 12 months and previous to the last 12 months □
If the patient has had other episodes in the last 12 months, the frequency of events was:
1 to 5 episodes □
6 to 9 episodes □
More than 9 episodes □

Characteristics of BPPV episodes in the last 12 months
The first episode involved:
Posterior semicircular canal (PSC) □
Lateral semicircular canal (LSC) geotropic variant □
Lateral semicircular canal (LSC) apogeotropic variant □

Other forms of labyrinth lithiasis
Did later episodes involve the same side? □ YES □ NO
Did later episodes involve the same canal? □ YES □NO

INVESTIGATIONS AND HISTORY IN PREVIOUS BPPV

Following the first episode, the patient underwent (N: normal; P: pathological):

No assessment □

	N	P		N	P
Cervical x-ray	□	□	Triglycerides	□	□
Color Doppler of supra-aortic trunks	□	□	Transaminases	□	□
Thyroid tests	□	□	D-dimer	□	□
Tests for autoimmune disease	□	□	Creatinine	□	□
Eye examination with fundus examination	□	□	CRP	□	□
Complete blood and platelet formula	□	□	Fibrinogen	□	□
VES	□	□	Total protein with electrophoresis	□	□
Glycaemia	□	□	Antithrombin III	□	□
Azotaemia	□	□	Homocysteine	□	□
Cholesterol and HDL	□	□	d-ROMs Test (free radicals)	□	□

Following the subsequent episode, the patient underwent (N: normal; P: pathological):

No assessment □

	N	P
Cervical x-ray	□	□
Color Doppler of supra-aortic trunks	□	□
Thyroid tests	□	□
Tests for autoimmune disease	□	□
Eye examination with fundus examination	□	□

Other
Where the patient was being treated with drugs for other conditions, indicate the main class (e.g. anti-thrombotic, anti-inflammatory, corticosteroids, etc.):
_____

The patient has been taking this medication for:
1 to 2 months □
3 to 6 months □
7 to 12 months □
over a year □

TREATMENT OF BPPV

Rehabilitative manoeuvres □
Antivertigo drugs □
Vasoactive drugs □
CNS depressants □
Other □

Drug prescribed for:
□ 1 to 2 months □ 3 to 6 months □ 7 to 9 months □9 to 12 months

Other Considerations: _____

Fig. 1. Data collection form.

Statistical analysis was performed using SPSS Statistical Package, ver. 16.0.
In the event of missing data, no replacement approach was applied.

Results

Demographic data

A total of 2,682 valid forms were collected for statistical processing (Table I).
Most patients were women (60.9%). The mean age at diagnosis was 59.3 years (SD ± 15.0), with a percentage of over 65 of 38.3%. The 60-69 age group was the most frequent (26.6%), while only 0.2% were under 18 years of age.

Medical history and comorbidities

The possible risk factors are shown in Table II. 55.8% of patients had high blood pressure and nearly half (49.4%) had a family history of cardiovascular disease. Hypercholesterolaemia and hypertriglyceridaemia were found, respectively, in 38.6% and 21.1% of patients, and diabetes in 17.7%. At anamnesis, 12.3% of the sample reported a previous diagnosis of cardiovascular disease and 12.6% a cerebrovascular disease. The frequency of thyroid pa-

Table I. Demographic data.

Patients	**N = 2,682**
Gender (n = 2,579) *	**n (%)**
Males	1008 (39.1%)
Females	1571 (60.9%)
Age (n = 2621)†	**n (%)**
Mean (± SD)	59.3 ± 15.0
Over 65	1004 (38.3%)
Age groups	
< 18	6 (0.2%)
18-29	84 (3.2%)
30-39	204 (7.8%)
40-49	418 (15.9%)
50-59	486 (18.5%)
60-69	698 (26.6%)
70-79	535 (20.4%)
≥ 80	190 (7.2%)

**103 missing data on gender.*
† 61 missing data on age.

Table II. Medical history and possible risk factors.

Family history	n / N (%)
Cardiovascular diseases	1253 / 2538 (49.4%)
Vertigo symptoms	401 / 2318 (17.3%)
Risk factors and vascular disorders	
Hypertension	1416 / 2537 (55.8%)
Hypercholesterolaemia	917 / 2377 (38.6%)
Hypertriglyceridaemia	477 / 2266 (21.1%)
Cerebrovascular disease (acute or chronic)	277 / 2196 (12.6%)
Cardiovascular disease	268 / 2185 (12.3%)
Metabolic disorders	
Diabetes	419 / 2363 (17.7%)
Hyperuricaemia	72 / 2193 (3.3%)
Drugs	
Use of proton-pump inhibitors (PPI)	638 / 2279 (28.0%)
Use of ototoxic drugs	193 / 2122 (9.1%)
Other	
Headaches and/or migraine	668 / 2202 (30.3%)
Smoker	665 / 2216 (30.0%)
Visual disturbances	473 / 2163 (22.0%)
Cervical hernia	311 / 2111 (14.7%)
Thyroid dysfunction	298 / 2102 (14.2%)
Autoimmune disease	100 / 2024 (4.9%)
Inflammatory and/or autoimmune disease (acute or chronic)	79 / 1958 (4.0%)
Radiotherapy	71 / 2066 (3.4%)
Giant cell arteritis	37 / 2046 (1.8%)
Macroglobulinaemia	19 / 2022 (0.9%)
Cryoglobulinaemia	8 / 2031 (0.4%)
HEARING LOSS	**1131 / 2637 (42.9%)**
Onset	
Before episode of BPPV	811 / 1010 (80.3%)
During episode of BPPV	115 / 1010 (11.4%)
After episode of BPPV	81 / 1010 (8.0%)
Side	
Right side	121 / 1020 (11.9%)
Left side	107 / 1020 (10.5%)
Bilateral	792 / 1020 (77.6%)
Type	
Conductive	24 / 929 (2.6%)
Mixed	112 / 929 (12.1%)
Sensorineural	793 / 929 (85.4%)
TINNITUS	**1027 / 2494 (41.2%)**
Onset	
Before episode of BPPV	631 / 902 (69.9%)
During episode of BPPV	156 / 902(17.3%)
After episode of BPPV	115 / 902(12.8%)
Side	
Right side	221 / 848 (26.1%)
Left side	184 / 848 (21.7%)
Bilateral	443 / 848 (52.2%)
HEARING LOSS and TINNITUS *	**719 (26.8%)**

** We considered all patients (n=2682), counting those who answered "Yes" to "Hearing loss" and "Tinnitus".*

thology was 14.2%; 28% of patients used proton-pump inhibitors and 30% were smokers.

Hearing loss and tinnitus

In most cases, BPPV was associated with audiological symptoms (Table II). 42.9% of patients presented hearing loss, 80.3% of whom reported onset before the episode of BPPV and 85.4% of cases were of a sensorineural nature. 41.2% of patients had tinnitus, 69.9% of whom reported onset before the episode of BPPV and in 52.2% of cases this was bilateral. 26.8% of the sample presented hearing loss and tinnitus simultaneously. The patients who had hearing loss were older ($p < 0.001$). In particular, the average age of the patients with hearing loss (n = 1131) was of 66.4 years (SD 12.4), while the average age of patients without hearing loss (n = 1506) was 53.8 years (SD 14.4).

Characteristics of BPPV

The clinical features of BPPV episodes are shown in Table III. A near-uniform distribution was recorded between the first episode of BPPV (47.5%) and recurrent BPPV (52.5%). In terms of the frequency of recurring episodes, 1-5 episodes per year was the most commonly reported range (84.3%), while 15.7% reported 6 or more episodes per year. The canal most commonly involved in the first episode of BPPV was the posterior semicircular canal (57.4%), and most relapses involved the same canal (49.2%).

Treatment of vertigo

The treatment of BPPV, reported in Table IV, is based on rehabilitative manoeuvres (85.9%), followed by vasoactive drugs (35.9%). Use of antivertigo drugs was found in roughly one-third of the total sample (32.7%). Only in 4.4% of cases were central nervous system (CNS) depressants used.

In most cases, medical treatment lasted between 1 and 2 months (64.7%), while in about one-third of patients (30%) it was 3-6 months and only in 5.3% of cases did treatment continue for over 6 months.

Association between recurrence and comorbidities

In addition to the descriptive research, statistical processing of the data was performed in order to analyse the association between recurrent BPPV and possible risk factors (Table V, Fig. 2). The following significant correlations were found: family history of vertigo associated with cardiovascular disease (OR = 1.5, $p < 0.001$ and OR = 1.46, $p < 0.005$), hypertension (OR = 2.05, $p < 0.001$), hypercholesterolaemia (OR = 1.84, $p < 0.001$), hypertriglyceridaemia (OR = 2.11, $p < 0.001$), cerebrovascular disease (OR = 1.88, $p < 0.001$) and cardiovascular disease (OR = 2.31, $p < 0.001$). In addition, the association with diabetes was significant (OR = 1.73, $p < 0.001$). Finally, a correlation with the use of proton-pump inhibitors and

Table III. Characteristics of BPPV episodes.

	No. (%)
Patients - BPPV*	**2638**
First Episode	1252 (47.5%)
Recurrences	1386 (52.5%)
Other episodes in the last twelve months (< 12 months)	781 (56.4%)
Other episodes prior to the last 12 months (> 12 months)	326 (23.5%)
Other episodes both in the last 12 months and prior to the last 12 months	279 (20.1%)
Frequency of BPPV recurrence in the last 12 months†	
1 to 5 episodes	840 (84.3%)
6 to 9 episodes	101 (10.1%)
More than 9 episodes	56 (5.6%)
Canal affected in the first episode of BPPV‡	
The posterior semicircular canal (PSC)	1356 (57.4%)
The lateral semicircular canal (LSC) geotropic variant	681 (28.8%)
The lateral semicircular canal (LSC) apogeotropic variant	214 (9.1%)
Other forms of labyrinth lithiasis	112 (4.7%)
Canal affected in subsequent BPPV episodes	
Same canal	682 / 1386 (49.2%)

** 44 missing data for BPPV features.*
† 63 missing data for number of BPPV episodes in the 1060 (781 + 279) patients who reported episodes in the last twelve months.
‡ 319 missing data for canal affected in the first episode of BPPV

Table IV. Treatment of BPPV.

	No. (%)
Treatment used for BPPV episodes	
Rehabilitative manoeuvres	2305 (85.9%)
Antivertigo drugs	878 (32.7%)
Vasoactive drugs	964 (35.9%)
CNS depressants	118 (4.4%)
Total patients treated with drugs*	**1571 (58.6%)**
Duration of drug therapy†	
1 to 2 months	841 (64.7%)
3 to 6 months	390 (30.0%)
7 to 9 months	26 (2.0%)
9 to 12 months	43 (3.3%)

** 365 out of 1,571 (23.2%) patients used more than one drug.*
† Of the 1,571 patients with prescribed medications, 271 had missing data for "Duration of drug therapy."

with the use of ototoxic drugs was also found (OR 1.81, $p < 0.001$ and OR 1.96, $p < 0.001$, respectively).

Discussion

To date it is still unclear what is the aetiopathogenetic mechanism of BPPV and whether there are any other diseases related to the recurrence of BPPV. Recent epidemiological studies have shown a possible association with cardiovascular risk factors [3 5-7 9].

In the present observational study, cardiovascular history was assessed for 2,682 patients diagnosed with BPPV, both

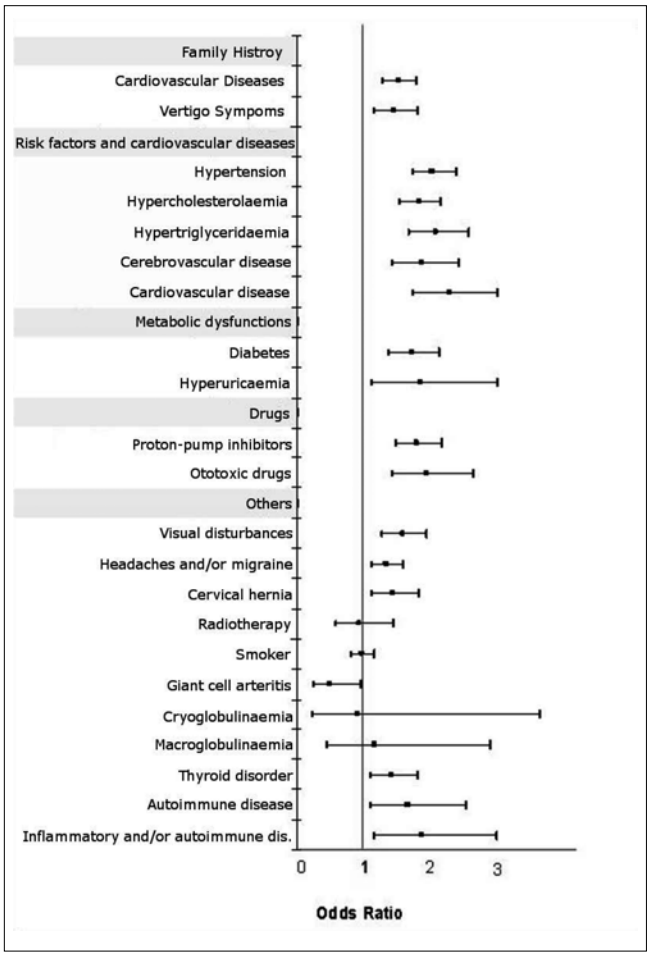


Fig. 2. Association between recurrent BPPV and comorbidities, medications, lifestyles: Crude OR and 95% Confidence Intervals.

Table V. Association between the first episode of BPPV or recurrent BPPV and comorbidities, drugs and lifestyles.

	BPPV				
	Patients at first episode	Patients with recurrences	Crude OR	CI 95%	p (*)
Family history					
Cardiovascular diseases	526 (44.1%)	715 (54.7%)	1.54	1.31-1.80	< 0.001
Dizziness symptoms	159 (14.6%)	239 (20.0%)	1.46	1.17-1.82	< 0.005
Risk factors and vascular disorders					
Hypertension	557 (46.9%)	844 (64.4%)	2.05	1.75-2.41	< 0.001
Hypercholesterolaemia	348 (31.2%)	558 (45.5%)	1.84	1.55-2.18	< 0.001
Hypertriglyceridaemia	157 (14.8%)	314 (26.8%)	2.11	1.70-2.61	< 0.001
Cerebrovascular disease (acute or chronic)	96 (9.2%)	178 (15.9%)	1.88	1.44-2.45	< 0.001
Cardiovascular disease	82 (7.9%)	183 (16.5%)	2.31	1.76-3.05	< 0.001
Metabolic disorders					
Diabetes	152 (13.6%)	261 (21.5%)	1.73	1.39-2.16	< 0.001
Hyperuricaemia	24 (2.3%)	47 (4.2%)	1.86	1.13-3.06	< 0.05
Drugs					
Use of proton-pump inhibitors (PPI)	234 (21.9%)	396 (33.7%)	1.81	1.50-2.19	< 0.001
Use of ototoxic drugs	63 (6.2%)	124 (11.5%)	1.96	1.43-2.69	< 0.001
Other					
Visual disturbances	180 (17.9%)	288 (25.6%)	1.59	1.29-1.96	< 0.001
Headaches and/or migraine	279 (27.0%)	377 (33.1%)	1.34	1.12-1.61	< 0.01
Cervical hernia	122 (12.4%)	187 (17.0%)	1.44	1.13-1.84	< 0.025
Radiotherapy	35 (3.6%)	36 (3.4%)	0.93	0.58-1.45	ns
Smoker	316 (30.3%)	338 (29.6%)	0.97	0.81-1.16	ns
Giant cell arteritis	24 (2.5%)	13 (1.2%)	0.49	0.25-0.97	< 0.05
Cryoglobulinaemia	4 (0.4%)	4 (0.4%)	0.92	0.23-3.69	ns
Macroglobulinaemia	8 (0.8%)	10 (1.0%)	1.17	0.45-2.94	ns
Thyroid disfunction	118 (11.9%)	174 (16.1%)	1.42	1.10-1.82	< 0.025
Autoimmune disease	35 (3.7%)	63 (6.0%)	1.68	1.10-2.57	< 0.05
Inflammatory and/or autoimmune disease (acute or chronic)	26 (2.8%)	52 (5.2%)	1.89	1.17-3.04	< 0.05

Crude Odds Ratio (OR) and 95% Confidence Intervals (95%) and their p-values.
**χ2 Test.*

initial episodes and recurrences, who had referred to 158 Italian vestibology out-patient clinics from January 2013 to December 2014. Most patients were over 40 years old (88.6%), with a prevalence of women (60.9%) and a BPPV recurrence rate of 52.5%, in line with data reported in literature [1 3]. With regards to the prevalence of recurrent BPPV, only the Ogun et al. survey conducted in the United States has until now registered a higher frequency (76.3%), but this, as reported by the authors, may be due to the survey procedures used which favoured selection of patients with recurrent BPPV [6].

Our survey showed a high prevalence of cardiovascular risk factors such as high blood pressure (55.8%), hypercholesterolaemia (38.6%) and diabetes (17.7%), as well as family history of cardiovascular disease (49.4%). A comparison of the relative frequencies of these risk factors in the study sample with the data available for the general population highlighted the higher prevalence of these parameters in patients with BPPV vs. the general population (Fig. 3) [10].

A high proportion of patients had hearing loss and/or tinnitus (up to 42.9%), a result consistent with Ogun et al. study in which 41.9% of subjects displayed hearing loss, suggesting that audiological symptoms in BPPV patients are potential markers of vascular pathophysiology in the inner ear that should be validated [11].

Analysis of correlations also suggests that cardiovascular risk factors expose the BPPV subject to a risk of relapse with OR values that sometimes are higher than 2. Specifically, the presence of arterial hypertension, dyslipidaemia and established cardiovascular comorbidities (OR range between 1.84 and 2.31) would seem to be significantly related to episodes of recurrent BPPV, and association with diabetes and thyroid/autoimmune disease (OR range between 1.42 and 1.89) would seem to be relevant.

These results support the hypothesis of a vascular role in

	Survey Data	General population data*
Family History Of Cardiovascular Diseases	49.4%	40%
Hypertension	55.8%	32%
Hypercholesterolaemia	38.6%	23%
Hypertriglyceridaemia	21.1%	24%
Diabetes	17.70%	8%

** From Guidetti G. La terapia della vertigine vascolare nella pratica ambulatoriale: esperienza multicentrica (VascVert Study). Otorinolaringol. 2005;55:237-46*

Fig. 3. Prevalence of vascular risk factors in the study sample and the general population.

the aetiopathogenesis of BPPV and its recurrence. Moreover, the link between inflammation and vascular pathophysiology of the inner ear and audio-vestibular disorders has already been pointed out [10-13]. As is known, the blood supply to the inner ear is a terminal circulation and given the lack of collateral circulation, any even partial occlusion of the AICA (anterior inferior cerebellar artery) or VBA (vertebrobasilar artery) can cause an ischaemic event in the inner ear [11]. Recently, patients with idiopathic sudden hearing loss were shown to have significantly lower flow-mediated dilation of the brachial artery than controls (5.6 ± 1.6 vs. 7.7 ± 3.7; $p < 0.01$) [14], significantly lower levels ($p = 0.018$) of endothelial progenitor cells [15] and increased plasma levels of adhesion molecules, which is an early sign of endothelial dysfunction [16].

The data have also suggested an unexpected correlation between the recurrence of BPPV and use of proton-pump inhibitors, and confirmed a possible correlation between recurrence of BPPV and the use of ototoxic drugs. These data stimulate further specific studies.

Finally, it is interesting to note that in our sample more than 80% of patients reported hearing loss or tinnitus prior to the episode of BPPV. At the same time, it should also be underlined the fact that patients with hearing loss were significantly older. For these reasons, and given the importance of the issue, to evaluate the possible correlation between hearing loss and BPPV it would be necessary in the future perform a specific study, which evaluates in detail the various characteristics of the hearing loss in BPPV for classes of age and comparing such data with an adequate sample of subjects not suffering from BPPV.

The survey results also suggests some considerations regarding therapeutic strategies adopted in the treatment of BPPV. Standard treatment generally involves rehabilitation therapy based on liberatory or repositioning manoeuvres that are effective in resolving symptoms in up to 90% of cases within 24 hours [17]. However, the number of manoeuvres needed to achieve resolution can vary and the incidence of residual dizziness after treatment is high (60%) and long-term (13-16 days), thus complicating complete resolution of symptoms [18 19]. The use of vasoactive drugs could therefore be of help, especially to contrast any pathogenetic mechanism with a microcirculatory component. Specifically, treatment could include not only drugs to reduce the impact of known risk factors (antihypertensives, statins, antidiabetics) but also more specific vascular drugs to counteract "causal" damage generated on the endothelial wall in the inner ear, such as glycosaminoglycans (GAGs), which exert anti-inflammatory and antithrombotic actions on the endothelial wall [10 20-24]. In this regard, our study showed that antivertigo drugs were prescribed in almost 33% of cases and vasoactive drugs in about 36%, thus demonstrating that specialists are aware of vascular risk factors.

Our study has some limitations. For example, many parameters have not been evaluated, including brain MRI, post-traumatic vertigo and psychiatric disorders. Furthermore, the study did not have an appropriate control of the population without BPPV. Finally, the observational nature of the study, obviously, did not allow definitive answers about the investigated correlations, which require appropriate studies, but that nonetheless gave, albeit partial, a significant picture of the Italian real-life situation on BPPV helping to increase knowledge about the comorbidity in BPPV also investigated recently in other studies [25-27].

Conclusions

In conclusion, the present study investigated the demographic and clinical characteristics of 2,682 Italian patients with BPPV. In particular, the results have highlighted a population of patients with 60 years on average, a prevalence of women (60.9%) and a high BPPV recurrence rate (52.5%). Finally, the study seems to confirm the prevalence of cardiovascular comorbidities in patients suffering from BPPV and identify them as potential important risk factors for recurrent BPPV in the Italian population, paving the way for the evaluation of new therapeutic strategies.

References

1. Kim JS, Zee DS. *Benign paroxysmal positional vertigo.* N Engl J Med 2014;370:1138-47.
2. Fife TD, Iverson DJ, Lempert T, et al. *Practice parameter: therapies for benign paroxysmal positional vertigo (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology*. Neurology 2008;70:2067-74.
3. Saxena A, Prabhakar MC. *Performance of DHI Score as a predictor of benign paroxysmal positional vertigo in geriatric patients with dizziness/vertigo: a cross-sectional study*. PLoS One 2013;8:e58106.
4. von Brevern M, Radtke A, Lezius F, et al. *Epidemiology of benign paroxysmal positional vertigo: a population based study*. J Neurol Neurosurg Psychiatry 2007;78:710-5.
5. De Stefano A, Dispenza F, Suarez H, et al. *A multicenter observational study on the role of comorbidities in the recurrent episodes of benign paroxysmal positional vertigo*. Auris Nasus Larynx 2014;41:31-6.

[6] Ogun OA, Janky KL, Cohn ES, et al. *Gender-based comorbidity in benign paroxysmal positional vertigo*. PLoS One 2014;9:e105546.

[7] Agus S, Benecke H, Thum C, et al. *Clinical and demographic features of vertigo: findings from the REVERT Registry*. Front Neurol 2013;4:48.

[8] Papi G, Guidetti G, Corsello SM, et al. *The association between benign paroxysmal positional vertigo and autoimmune chronic thyroiditis is not related to thyroid status*. Thyroid 2010;20:237-8.

[9] Kao CL, Cheng YY, Leu HB, et al. *Increased risk of ischemic stroke in patients with benign paroxysmal positional vertigo: a 9-year follow-up nationwide population study in Taiwan*. Front Aging Neurosci 2014;6:108.

[10] Guidetti G. *La terapia della vertigine vascolare nella pratica ambulatoriale: esperienza multicentrica (VascVert Study)*. Otorinolaringol 2005;55:237-46.

[11] Lee H. *Recent advances in acute hearing loss due to posterior circulation ischemic stroke*. J Neurol Sci 2014;38:23-9.

[12] Trune D. *Vascular pathophysiology in hearing disorders*. Semin Hear 2012;33:242-50.

[13] Faralli M, Ricci G, Molini E, et al. *Paroxysmal positional vertigo: the role of age as a prognostic factor*. Acta Otorhinolaryngol Ital 2006; 26:25-31.

[14] Ciccone MM, Cortese F, Pinto M, et al. *Endothelial function and cardiovascular risk in patients with idiopathic sudden sensorineural hearing loss*. Atherosclerosis 2012;225:511-6.

[15] Quaranta M, Ramunni A, De Luca C, et al. *Endothelial progenitor cells in sudden sensorineural hearing loss*. Acta Otolaryngol 2011;131:347-50.

[16] Quaranta M, Ramunni A, Brescia P, et al. *Soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 in sudden hearing loss*. Otol Neurol 2008;29:470-4.

[17] Mandalà M, Santoro GP, Asprella Libonati G, et al. *Double-blind randomized trial on short-term efficacy of the Semont maneuver for the treatment of posterior canal benign paroxysmal positional vertigo*. J Neurol 2012;259:882-5.

[18] Seok JI, Lee HM, Yoo JH, et al. *Residual dizziness after successful repositioning treatment in patients with benign paroxysmal positional vertigo*. J Clin Neurol 2008;4:107-10.

[19] Leopardi G, Chiarella G, Serafini G, et al. *Paroxysmal positional vertigo: short- and long-term clinical and methodological analyses of 794 patients*. Acta Otorhinolaryngol Ital 2003;23:155-60.

[20] Ferrari G, Agnese A, Cavallero A, et al. *Medical and surgical treatmets for tinnitus: the efficacy of combined treatment with sulodexide and melatonin*. J Neurosurg Sci 2015;59:1-9.

[21] Coccheri S, Mannello F. *Development and use of sulodexide in vascular diseases: implications for treatment*. Drug Des Dev Ther 2014;8:49-65.

[22] Neri G, De Stefano A, Baffa C, et al. *Treatment of central and sensorineural tinnitus with orally administered melatonin and sulodexide: personal experience from a randomized controlled study*. Acta Otorhinolaryngol Ital 2009;29:86-91.

[23] Panu F, Manca T, Cauli S, et al. *Efficacia del trattamento con sulodexide nei pazienti affetti da vertigine di origine vascolare*. Otorinolaringol 2008;58:159-64.

[24] Tirelli G, Zarcone O, Giacomarra V, et al. *La vertigine da causa vascolare. Ipotesi patogenetiche e considerazioni terapeutiche.* Otorinolaringol 2001;51:61-8.

[25] Babac S, Djeric D, Petrovic-Lazic M, et al. *Why do treatment failure and recurrences of benign paroxysmal positional vertigo occur?* Otol Neurotol 2014;35:1105-10.

[26] Picciotti PM, Lucidi D, De Corso E, et al. *Comorbidities and recurrence of benign paroxysmal positional vertigo: personal experience*. Int J Audiol 2016;55:279-84.

[27] Choi SJ, Lee JB, Lim HJ, et al. *Clinical features of recurrent or persistent benign paroxysmal positional vertigo*. Otolaryngol Head Neck Surg 2012;147;919-24.

Received: February 25, 2016 - Accepted: March 21, 2017

Address for correspondence: Aldo Messina, Otoneurology and Tinnitus Unit, Chair of Audiology, P. Giaccone University Hospital, Palermo, Italy. Tel. +39 091 6554250. E-mail: aldo_odecon@libero.it