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A multicenter observational study on the role of comorbidities in the recurrent episodes of benign paroxysmal positional vertigo

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ABSTRACT

Objective: Primary objective of this study was to find a statistical link between the most worldwide comorbidities affecting the elderly population (hypertension, diabetes, osteoarthrosis, osteoporosis and depression) and recurrent episodes of BPPV. Secondary objective was defining possible "groups of risk" for people suffering recurrent positional vertigo related to the presence of a well documented comorbidity.
Methods: This was an observational, cross-sectional, multicenter, spontaneous, non-pharmacological study. The data of 1092 patients suffering BPPV evaluated in 11 different Departments of Otolaryngology, Otoneurology and Neurology, referring Centers for positional vertigo evaluation, were retrospectively collected.
Results: Regarding evaluated comorbidities (hypertension, diabetes, osteoarthrosis, osteoporosis and depression), data analysis showed the presence of at least one comorbid disorder in 216 subjects (19.8%) and 2 or more in 408 subjects (37.4%). Moreover there was a statistical significant difference between the number of comorbidities and the number of recurrences, otherwise said as comorbidity disorders increased the number of relapses increased too.
Conclusion: The presence of a systemic disease may worsen the status of the posterior labyrinth causing a more frequent otolith detachment. This condition increases the risk for patients suffering BPPV to have recurrent episodes, even if correctly managed by repositioning maneuvers. The combination of two or more of aforementioned comorbidities further increases the risk of relapsing BPPV, worsened by the presence of osteoporosis. On the basis of this results it was possible to define "groups of risk" useful for predicting BPPV recurrence in patients with one or more comorbidity.

Abbreviations: BPPV, benign paroxysmal positional vertigo; PSC, posterior semicircular canals; HSC, horizontal semicircular canal; ASC, anterior semicircular canal; OA, osteoarthrosis; CRM, canalith repositioning maneuver; OR, odds ratio.

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1. Introduction

Background

Benign paroxysmal positional vertigo (BPPV) is one of the most common recognized vestibular disorder encountered in a neurotology clinic [1] and it accounts for nearly 20% of all the vestibular complaints [2].

BPPV is a mechanical disorder of the posterior labyrinth in which one or more semicircular canals are inappropriately stimulated by loose otoconia upon certain head movements and positions, resulting in brief episodes of vertigo crises [3].

Approximately 94% of BPPV cases involve the Posterior Semicircular Canals (PSC) [4] while the Horizontal Semicircular Canal (HSC) is the next most common [5,6].

Typically clinical features of BPPV are dominated by canal related symptoms in acute condition (brief and intense spells of vertigo after hyperextension or hyperflexion of the head, lying down or standing up from lying position) and macular symptoms after acute condition (prolonged instability which persists even after that patient has recovered from canal related symptomatology) [7,8].

There are two hypotheses to explain the development of BPPV: Schucknect's "Cupulolithiasis" theory and Hall's "Canalolithiasis" theory [9,10]. Although they are both corrected, representing different aspects of the same vestibular disorder [11], they do not explain why the incidence of BPPV progressively increases in the elderly population [12,13].

The elderly tends to have multiple comorbidities which can compromise autonomy and cause a worsening of quality of life [14]. Coincidentally increased age is proportional to the presence of several neurotological disorders associated with deterioration in equilibrium and hearing function (e.g. BPPV, sensory-neural hearing loss, tinnitus, changes in body balance) [15].

Some Authors have demonstrated the negative influence of comorbidities on treatment and prognosis of other diseases, such as laryngeal or breast cancer [16,17]. In neurotological field a relation between psychiatric conditions and vestibular diseases has been underscored [18,19] but how much these problems are involved in BPPV is unknown. In other hands it is well recognized that other common comorbid conditions (e.g. diabetes, hypertension) are related to sudden sensory-neural hearing loss [20] or hearing impairment [21]. On the basis of this knowledge it is right to think about a possible influence of comorbidities also on vestibular system.

Arthrosis, hypertension and diabetes are among the five leading chronic condition in the over 65 year population [22]. Osteoporosis is a frequent but widely underdiagnosed condition [23].

Depression is often present in world elderly community and leads to a worseness of cognitive status, quality of life and powerful co-existent diseases [22,24–27].

Objectives

As primary objective, this study evaluates the relationship between recurrent episodes of BPPV and the most common comorbidities in the elderly population of any country: hypertension, cervical OA, diabetes, osteoporosis and depression. Secondary objective was defining possible "groups of risk" related to the presence of a comorbidity.

2. Methods

2.1. Study design

This is an observational, cross-sectional, multicenter, spontaneous, non-pharmacological study. The data of patients suffering BPPV, evaluated in 11 Institutes referring Centers for BPPV evaluation, were retrospectively collected.

2.2. Statement of ethical approval

This study was carried out in strict accordance with the principles of the Declaration of Helsinki. Study protocol was approved by Ethical Committee of "G.d'Annunzio" University of Chieti-Pescara which represented Study Coordinating Centre and proceeded to coordinate the study and to elaborate data.

2.3. Setting

The Institutes involved in the study were scattered across Europe, Asia and South of America.

Study Centres were invited to share their BPPV patients' data and they reviewed the preliminary results of the statistical analysis. A data collection grid was provided for each subject by Study Coordinating Centre. All appropriate subject data collected during the study were recorded on these forms.

2.4. Participants

We selected all of the medical records from males and females, aged 65 years and above, affected by BPPV and visited in the last 2 years.

We excluded medical records of: individuals aged less than 65 years; individuals affected by other forms of peripheral and central vertigo including secondary BPPV (e.g. Ménière disease); individuals affected by cerebello-pontine angle tumors or other intracranial tumors; individuals who suffered traumatic head injury; individuals who underwent surgery of head and neck district; individuals who received chemotherapy for oncological diseases.

BPPV diagnosis was made on the basis of clinical presentation, by the study of nystagmus (torsional–vertical clockwise or counter-clockwise nystagmus in PC-BPPV; horizontal geotropic or apogeotropic nystagmus in HC-BPPV; nystagmus with a small torsional component in AC-BPPV) during the diagnostic maneuvers (Dix-Hallpike, McClure and Rose tests) under infrared videoscopy.

We did not diagnose comorbidities directly but on the basis of a well-documented clinical history.

Recurrence of BPPV was defined by the relapse of vertigo after a successful treatment. The criteria for diagnosis of BPPV recurrence were the same used in case of first episode.

2.5. Bias

There could be selection, outcome and measurement biases. In order to reduce selection bias we designed a unique data collection form and we provided strict inclusion and exclusion criteria to eliminate all secondary types of vertigo. In addition, in order to make study sample as representative as possible of target population we involved many Centers from different countries and so we obtained a reasonably fair view of the world population.

The outcome bias could be linked to a misclassified outcome: an unknown number of patients, who apparently did not suffer any relapse, may have gone to other Centers or, in consideration of the subjects' mean age, some of them could have died in the meanwhile.

Unfortunately we could do nothing to avoid this bias that remains an intrinsic factor of the study.

Measurement bias should not be present in this study because the diagnosis of BPPV is essentially clinical and it can be further confirmed with diagnostic maneuvers under infrared videoscopy. The diagnostic criteria for BPPV are equal all over the world as well

as treatment based on the use of Canalith Repositioning Maneuvers (CRMs).

Furthermore in case of comorbidity measurement bias was not even evaluated because the diagnosis was not made by the Authors who only collected patient's medical history.

2.6. Study size

Sample size determination was not applicable because of observational nature of the study. The number of 1000 patients was thought to be reasonably adequate.

2.7. Statistical methods

The Chi-square or Fisher's exact test was used to compare proportions. Continuous data were inspected and tested to determine whether distributions are normal and compared using two sample Student's t test and ANOVA for parametric data, or Mann–Whitney rank-sum statistic and Kruskal–Wallis test for non-parametric data. The significance level for all tests was set at 5%. Therefore, the differences between the groups were considered to be statistically significant when p-value was less than 0.05 ($p < 0.05$). All analyses were performed with SPSS 13.0 (SPSS Inc, Chicago, Illinois).

This manuscript was written in accordance with the STROBE statement, giving guidelines for reporting results from observational studies [28].

3. Results

3.1. Participants and descriptive data

1092 subjects were enrolled. The age range was between 65 and 95 years with a mean age of 72.9 years (+6.14). In Table 1 some characteristics of our sample are summarized.

There were no statistically significant differences in sex and age among the continents. Also after stratification by continent, prevalence of involvement of PSC, followed by HSC, was confirmed. In regard to the type of CRM performed during the first episode of vertigo, the most frequently used were the Epley's (57.1%) and the Semont's (19%). After stratification by continent it was noted that the use of the Epley maneuver is clearly predominant in Asia (55.6%) and South America (88.1%); also in Europe this maneuver was proved to be the most widely used (46.3%). Instead Semont maneuver was used in 28.4% of cases in Europe, in 16.5% in Asia and in only 4.4% of subjects from South America.

Table 1
Characteristics of the patients.

Gender [N (%)]	
Female	685 (62.7)
Male	407 (37.3)
Continents [N (%)]	
Asia	541 (49.5)
Europe	390 (35.8)
South America	161 (14.7)
Semicircular Canal [N (%)]	
Posterior	889 (81.4)
Horizontal	153 (14.0)
Anterior	28 (2.6)
Multiple	22 (2.0)
Side [N (%)]	
Right	614 (56.2)
Left	412 (37.8)
Bilateral	66 (6.0)

Table 2
Worldwide distribution of recurrences.

	0 recurrence [N (%)]	1 recurrence [N (%)]	>1 recurrence [N (%)]
Europe	249 (63.7)	85 (21.7)	57 (14.6)
Asia	241 (44.5)	156 (28.8)	144 (26.7)
South America	51 (31.9)	51 (31.9)	58 (36.2)
TOT	541 (49.5)	292 (26.7)	259 (23.8)

3.2. Outcome data and main results

Almost half of sample (49.5%) did not present other episodes of BPPV after the first. On the contrary 50.5% had at least one recurrence: in 26.7% of cases it was only one episode but 23.8% of subjects suffered two or more episodes.

Even in recurrences the most frequently involved semicircular canal was PSC (36.8%). Although women noted to be more affected by BPPV than men, more than half of cases (51.2%) did not show any recurrence. Contrarily 53.3% of men presented recurrence of disease: in 29.5% of them there was one relapse and in 23.8% there were more than two episodes of recurrence. In women relapse rate exceeding two episodes was 23.6%. In view of this it seems like that women suffer a lower relapse rate, but when recurrence occurs they may have more than two episodes as men.

Stratifying by continent the highest rates of recurrence were recorded in South America (67.1%) (Table 2).

Data analysis revealed that in case of relapse Europeans tend to have only one episode (21.7%); for South Americans instead the percentage of recurrence is greater and in 36.2% of cases two or more episodes of vertigo occurred; Asians did not demonstrated any difference in relapse rate. The differences between the continents are all statistically significant ($p = 0.00$).

Relapse of BPPV was not influenced by the semicircular canal involved in the first episode of BPPV.

Regarding evaluated comorbidities, data analysis showed the presence of at least one comorbid disorder in 216 subjects (19.8%) and 2 or more in 408 subjects (37.4%).

More specifically we found out that the prevalence of hypertension was considerably higher (15%) when compared with diabetes (1.5%), OA (1.2%), osteoporosis (1.2%), depression (0.9%).

In a first step we evaluated the relationship between suffering from only one comorbid disease and risk of recurrence and we investigated if this condition influenced also the number of episodes (Table 3). As shown, the prevalence of hypertension, even when associated with the risk of recurrence, was confirmed. In particular it was found that the presence of hypertension or diabetes is associated with a statistically significant increased risk of recurrence. We also noticed that hypertension also influenced the number of relapses in a statistically significant way. In other words, the presence of hypertension seems to determine a number of relapses greater than one. Regards to OA, there was an increased risk of about 3 times but the association became statistically significant when related to the number of recurrences. Osteoporosis and depression did not seem to influence relapses.

Similarly, in a second step we evaluated if the combination of more comorbidities increased the risk of relapses and the number of episodes; so we extrapolated from our sample only the subjects suffering episodes of recurrence: out of 551 subjects who experienced at least one relapse, 123 (22.3%) had one comorbid disorder and 255 subjects (46.3%) suffered from 2 or more comorbidities. Furthermore, the number of associated comorbidities also increased the risk of recurrence: OR = 2.25 in presence of one comorbidity and OR = 2.84 in case of 2 or more diseases.

Table 3
Comorbidities and risk of recurrence.

Comorbidities	Recurrence				1 recurrence				>1 recurrence			
	N	%	OR	*p*	*N*	%	OR	*p*	*N*	%	OR	*p*
Hypertension	100	81.3	2.66	0.000	59	81.9	2.39	0.000	41	80.5	3.20	0.000
Diabetes	10	8.1	2.84	0.038	6	8.4	2.59	n.s.	4	7.8	3.33	0.054
Cervical osteoarthrosis	8	6.5	2.73	n.s.	4	5.5	2.07	n.s.	4	7.8	4.00	0.030
Osteoporosis	1	0.9	0.14	0.030	1	1.4	0.22	n.s.	0	0	/	/
Depression	4	3.2	1.14	n.s.	2	2.8	0.86	n.s.	2	3.9	1.67	n.s.
Total	123	100			72	100			51	100		

n.s., not significant.

We found out that the risk of recurrence (OR) in presence of the only hypertension was 2.66 (Table 2), but it became 4.55 when combined with diabetes and OA and it rises to 6.48 in case of association hypertension-diabetes-OA-osteoporosis.

Moreover there was a statistical significant difference between the number of comorbidities and the number of recurrences.

4. Discussion

4.1. Key results

Thanks to a large number of subjects enrolled (over 1000 persons), this study shows and confirms the association between BPPV and comorbidities.

On the basis of this relationship, we propose the definition of "*Groups of risk*" for BPPV patients based on the presence of comorbidities. Assignment to a specific risk group could be useful to guide the prognosis in BPPV patients.

4.2. Limitations and strength

Cross-sectional studies do not establish the exact temporal sequence between exposure and disease and they do not guarantee a good quality of information on exposure. Actually they include prevalent rather than incident cases and they are susceptible to biases. We could not eliminate all the biases: there could be an underestimation of recurrences because the patients suffering one or more episodes of relapse may have turned to other Centers. At last differences in the treatment of comorbidities there could be among various countries involved in this study.

Nevertheless prevalence is important in Public Health for assessing the burden of a disease in a specified population and in allocating health resources. We planned this study to demonstrate that there could be a association between BPPV and comorbidities, both of them affecting elderly population worldwide. By generating such a hypothesis, we believe we can promote the execution of ad-hoc analytical studies which can confirm the actual association between comorbidity and recurrences of BPPV and possibly shed light on the mechanisms involved.

4.3. Interpretation

We enrolled a total of 1092 patients suffering idiopathic BPPV: almost half of subjects came from Asia. We expected this result because since design phase of the study we planned to collect a sample that could reflect the actual distribution of the human population in the world [29].

In according with Literature, PSC [4] and the right side [30] were the most frequently involved. Moreover PSC records a lower frequency of recurrence (48.1%) and that's probably due to the greater ease of liberation of this semicircular canal, in contrast to the horizontal one (or in case of multiple involvement) which is more difficult to free from debris.

The difference observed in recurrence rates (Table 2) could be explained by differences in lifestyle among involved Countries and by a different accessibility to the National Health Care System. Differences in outcome could also be due to different treatment strategies for comorbid diseases.

Analyzing the recurrence rate, we obtained a sample divided into two nearly equal parts: on the one hand the 50.5% of subjects experienced at least one episode of recurrence, on the other hand the 49.5% of patients remained relapse-free. The characteristic of BPPV of being potentially relapsing is well known for a long time [31] and it was recently confirmed [32].

Brandt in 2006 indicated that relapse rate can be of about 50% in ten years [33] and in addition, most recurrences are observed during the first year after the CRM.

In exclusion of head trauma, surgery and inner ear disease inducing recurrent forms of BPPV [34], many factors appear to be involved in the recurrences, including female gender [34,35].

Given the noteworthy prevalence of BPPV in women, our study also confirms these findings (almost 2:1 ratio), but it could not demonstrate that female gender is an important factor in the genesis of relapse because our results were not statistically significant.

Evaluating association between recurrences and comorbid diseases, it was found that out of 511 patients with recurrences, 378 suffered from at least one of the studied disorders. This finding increased our suspicion that comorbidity could play a decisive role in the recurrence of vertigo.

On the other side, we cannot exclude that the remaining 133 patients with recurrence, but without any of the investigated comorbidities, could present other unknown risk factors (e.g. additional medical conditions) that may increase the relapse rate.

Data analysis revealed that among our patients the absolutely most frequent comorbid disorder was hypertension. With the exception of osteoporosis and depression, all the other comorbidities seem to be related to an increased risk of recurrence; moreover, in the case of hypertension and diabetes this association was statistically significant.

In addition, when present alone, hypertension is able to influence significantly the number of recurrences (Table 3). Similarly patients with diabetes and OA have a statistically significant risk of suffering more than one recurrence which is, respectively, 3.33 and 4.00.

We also wanted to evaluate whether the combination of multiple conditions further increased the risk. The most "dangerous" associations found were: hypertension + diabetes + OA (OR = 4.55) and hypertension + diabetes + OA + osteoporosis (OR = 6.48).

Depression does not seem to represent a risk factor for recurrent BPPV.

It appears evident that the presence of comorbidities exposes the patient to an increased risk of relapse especially if there are more than one comorbid diseases.

The mechanism by which comorbidities can cause this increase is still not known and it is not identifiable by this study. Anyway we may suppose some explanations.

Table 4
HODo risk groups predicting BPPV recurrence.

Risk group	Comorbid disorder	Risk of relapse
Group A	BPPV + 0 comorbidity	Low risk
Group B	BPPV + 1 comorbidity (H, O, D)	Medium risk (>2)
Group C	BPPV + 2 or 3 comorbidities (H ± O ± D)	High risk (>4)
Group D	BPPV + 4 comorbidities (H + O + D + o)	Highest risk (>6)

As recently demonstrated, the semicircular canal function, as well as the otolith one, declines with age [36]. Specifically it is well known that with aging there is a decrease of type I and II sensory hair cells and a degeneration of otoconia (with otoconial body fractures) in the utricular and saccular maculae. This degeneration is a physiological age-related process of demineralization [36], occasionally accelerated by osteoporosis that could cause an instability of otoconia [37]. In our study osteoporosis was related to an increased risk of relapse when it was in combination with other comorbidities. More studies are needed to explain these relations.

Eventually, a vestibular system, altered by age, will get worse with organic changes caused by hypertension or diabetes which promote a diffuse vascular damage resulting in the atherosclerotic disease. In Literature it is well known that occlusion of the anterior vestibular artery causes a sudden vertigo crisis (Lindsay–Hemenway syndrome) that includes otolith disease [38]; besides an inner ear vascular damage caused by atherosclerosis can generate a progressive detachment of otoconia from the otolithic membrane.

In addition to vascular damage, diabetes generates a balance disorder mediated by variations of blood glucose and plasma insulin levels with subsequent cupular deposits and free-floating debris in the semicircular canals [39]. In diabetic patients a vestibular neuropathy is also present. Furthermore diabetic patients present mutations in the BETA2/NeuroD1 gene which is essential for the normal development of the sensory epithelia of cochlea, utricle, saccule and crista ampullaris [40].

It is evident that a vestibular system altered by age and hypertension and/or diabetes could not be able to remain in equilibrium with the addition of other comorbidity such as OA.

The risk of relapsing BPPV in patients with OA increases of 3 times (Table 3) and that's probably due to a mechanical vertebrobasilar alteration of the blood flow with difficult to sprinkle the sensory organs of vestibular system. On the basis of all explained, we propose the definition of "*Groups of risk*" based on the presence of one or more disorders among Hypertension (H), Osteoarthrosis (O), Diabetes (D) and osteoporosis (o). This so-called "HODo Risk Groups" could help to predict BPPV recurrence in patients with one or more comorbidity (Table 4).

Assignment of patients to a specific group might be useful to guide the prognosis after the first episode of BPPV.

4.4. Generalisability

Vestibular system declines with aging. The presence of a systemic disease may worsen the status of the posterior labyrinth causing a more frequent otolith detachment.

The proof that there is a statistically significant association between comorbidity and recurrence allows us to create risk groups useful for evaluating the prognosis of patients with BPPV. However, further studies are needed to investigate the pathophysiology of association comorbidity-vestibular damage and to consider the benefits of an appropriate treatment of comorbidities in reducing the number of vertigo relapses.

Conflict of interest

Disclosure: Each of the Authors has contributed to, read, and approved this manuscript.

None of the Authors has any conflict of interest, financial or otherwise.

This manuscript, or any part of it, has not been previously published, nor is it under consideration elsewhere.

The corresponding Author *(Alessandro De Stefano)* had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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