Can cervical VEMPs predict recurrence in benign paroxysmal positional vertigo?

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Abstract
Benign paroxysmal positional vertigo (BPPV) is the most frequent form of peripheral vertigo, characterized by a high tendency to relapse. To date, few studies have been published on the possibility that disorders of the maculae can act as a possible predisponing factor for recurrences. We collected cervical vestibular evoked myogenic potentials (C-VEMPS) in 3043 subjects treated for BPPV in two centers between 2014 and 2018. They did not report lifetime vertigo outside BPPV. The mean age in the total population was 63.4±13.3 years. There were 2339 (76.9%) females. In the total sample 763 had pathological VEMPs (25.1%). Recurrent episodes were demonstrated in 2049 subjects (67.3%). In our cohort, patients presenting pathological VEMPs more frequently had bilateral recurrences (72.7%) than patients with normal VEMPs. A Pearson test demonstrated a correlation between bilateral pathological VEMPs and presence of bilateral recurrences ($p \leq 0.001$). In contrast, no correlation was found between pathological VEMPs and the age of patients ($p=0.2$). Our data suggest the hypothesis that bilateral otolithic macular alterations should be considered among the causes of recurrences.

Keywords*: Benign Paroxysmal Positional Vertigo; Cervical VEMPs; Recurrence of BPPV; Episodic Vertigo*

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent form of peripheral vertigo, characterized by an high tendency to relapses. The incidence increases with age, reaching a maximum in subjects over 70 years [Von Brevern M. et al., 2007]. The disorder can be suspected by a medical history of violent but short-lasting vertigo, triggered by the assumption of a position on the side of the bed; therapy relies on physical maneuvers [Von Brevern M. et al., 2015]. The accepted pathophysiological mechanism is detachment of concretions of calcium salts called otoconia, which are present in the utricular macula, and their passage into one of the semicircular canals [Nuti D. et al., 2016; Brandt T. et al., 1993]. Several conditions have been hypothesized to be predisposing factors and causes of frequent relapses, including head trauma, migraine, dysmetabolic disorders, reduced plasma levels of calcium and vitamin D, vascular disorders (diabetes) and autoimmune thyroiditis [Teggi R. et al., 2021; Song P. et al., 2020; Chen J. et al., 2020]. Other authors have postulated that a primary disorder of the macula can be a possible reason for otoconia detachment and relapses of BPPV, which may explain the residual dizziness often reported by many patients after successful repositioning maneuvers [Von Brevern M. et al., 2006; Xu H. et al., 2016; Teggi R. et al., 2013]. VEMPs (vestibular evoked myogenic potentials) represent a diagnostic tool employed in clinical practice with the aim to evaluate both utricular (O-Vemp) and saccular (C-Vemp) function [Murofushi T. et al., 2016].

In this perspective, the purpose of our work is to evaluate whether a macular alterations of the otolithic organs can predispose to a higher frequency of recurrence of BPPV in a large cohort of patients studied with VEMPs.

Materials and Methods

Study Cohort

In this retrospective study we included 3043 subjects treated for BPPV in two centers between 2014 and 2018. Data were retrieved from clinical charts. The work was approved by our Ethics Committee. To be included, patients had to have a diagnosis of BPPV according to the criteria of the Barany Society guidelines [Von Brevern M. et al., 2015] and have performed a cervical VEMPS in one of the two participating hospitals. For patients enrolled before 2015, analysis of data confirmed the diagnosis of BPPV according to Barany Society guidelines. Much of the sample is (2590 of 3042) the same as that of a previous work [Teggi R. et al., 2021].

Patients were not included if they reported a lifetime vertigo other than BPPV and if clinical bedside examination demonstrated a spontaneous nystagmus or a nystagmus provoked by skull vibration test and post-head shaking test, possibly related to a previous vestibular disorder other than BPPV. All enrolled patients with recurrent BPPV underwent a central nervous MRI to rule out other clinical conditions mimicking BPPV.

Clinical Intervention

Diagnostic maneuvers for BPPV were performed at first consultation, Semont or Dix-Hallpike to assess posterior or superior canal BPPV, and supine head roll test for the lateral canal; the final diagnosis was made when we observed a nystagmus presenting latency, duration, and typical features for the stimulated canal. Patients were asked to return on the second – third day until complete recovery was observed. Semont or Epley repositioning maneuvers were performed for the posterior canal, Yacovino for the superior canals, and head shaking, barbecue, or Gufoni for apogeotropic and geotropic variants of the lateral canal. We normally prefer to firstly treat the vertical canals, and lateral canals at a later time. In the following 15 days, patients were asked to perform cervical VEMPS. Since these exams were performed in different centers, we considered pathological VEMPs only when there was an absence or an asimmetry of potential of at least 50% between sides at 90 dB as significative for a macular disorder, with the diseased side being pathological.

We considered recurrent BPPV when patients presented typical signs after at least 2 months from complete recovery. Data on recurrence were also collected by phone interview in patients who were not evaluated in our clinics after the first successful repositioning maneuver for another vestibular disorder. Before being considered non-recurrent, a time of at least 4 years had to have been observed.

Statistical analysis

Continuous variables are reported as mean and standard deviation. Statistics were calculated with a t-test. Categorical variables are presented as total number and percentage and a chi-square test was performed to assess significance. A p value ≤ 0.05 was considered statistically significant. Pearson's test was performed to assess correlation between pathological VEMPs and frequency of recurrence. We used SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA) for statistical analyses.

Results

The mean age in the total population was 63.4±13.3 years. There were 2339 (76.9%) females. The age of the first episode of BPPV was 52.8 ± 14.5 years (range 10-90). Recurrent episodes were demonstrated in 2049 subjects (67.3%). In the total sample, 763 had pathological VEMPs (25.1%). The subgroup of subjects with normal VEMPs

was composed of 2280 subjects. The mean age was 61.5±12.9 years; there were 1777 (77.9%) females, while the age at onset of the first BPPV was 51±14.1 years. Recurrent BPPV was present in 1494 (65.5%) cases. In 1131 cases, recurrence was always on the same side, while in 363 cases (15.9%) recurrences involved both sides.

The subgroup of subjects with pathological cervical VEMPs was composed of 763 subjects. The mean age in this subgroup was 68.8±12.9 years and 562 (73.6%) were females; the age of the first BPPV was 59.1±29.9 years.

In this group, recurrent BPPV was demonstrated in 555 (72.7%) patients. One-hundred and sixty-eight (30%) had recurences on both sides, while in 387 subjects recurence was demonstrated on the same side; 73 (13.1%) patients presented bilateral absent VEMPs, and 72 had recurrences on both sides.

Overall, in the sample of 3043 subjects a Pearson test demonstrated a correlation between pathological VEMPs and frequency of recurrences (p=0.0003)

Pearson's test demonstrated a correlation between bilateral pathological VEMPs and presence of bilateral recurrences (p≤0.001). In contrast, no correlation was found between pathological VEMPs and patient age (p=0.2).

Results and statistical analyses are summarized in Table 1.

	Subjects with normal VEMPs (n=2280)	**Subjects with pathological VEMPs (n=763)**	**Statistics**
Age at inclusion (years)	61.5±12.9	68.8±12.9	t=12.8, p≤0.0001
Age of first BPPV (years)	51±14.1	59.1±29.9	t=9.9 p≤0.0001
Females N (%)	1777 (77.9%)	562 (73.6%)	$\chi 2$=4.9, p=0.02
Recurrences N (%)	1494 (65.5%)	555 (72.7%)	$\chi 2$=13.5, p=0002
Unilateral recurrences N (%)	1131 (49.6%)	387 (50.7%)	n.s
Bilateral recurrences N (%)	363 (15.9%)	168 (22%)	$\chi 2$=14, p=0.0001

Table 1. Age at inclusion, age of the first BPPV, total number and frequences of sex, recurrences (unilateral and bilateral) in the group of subjects with normal VEMPs and pathological VEMPS. For statistical analyses, a t test was performed for continous variables, while frequences were assessed with a chi square test.

Discussion

The present analysis is likely the largest cohort to date on cVEMPs in BPPV ever published. Although with potential limitation and bias, we found a high rate of subjects with pathological cVEMPS, and these abnormalities were correlated with increased risk to develop recurrence.

In our sample, 25.1% of subjects had pathological VEMPs. Recent literature reported controversial data on Cervical and Ocular Vemps abnormalities in patients with BPPV [Nakahara H. et al., 2013]. A recent review [Oya R. et al., 2019] found that alterations of cVEMPS latencies were correlated with the side of BPPV: since latencies are more correlated with retrolabirinthine disorders [Murofushi T. et al., 2001], the authors concluded that a systemic alteration may act as a predisposing factor for the detachment of otoconia. Another group reported that abnormalities in galvanic ocular and cervical VEMPS were higher than skull vibration test anomalies in subjects with BPPV [Chang C. et al., 2021], and concluded that a primary disorder of the maculae may lead to BPPV. Another prospective work found abnormalities of cVEMPS in 30% of subjects with BPPV, which is line with our findings [Xu H. et al., 2016; Lee JD. et al., 2013]. According

to some authors, this condition may explain the phenomenon of the residual dizziness after successful repositioning maneuvers [Teggi R. et al., 2013].

Moreover, we found a correlation between cVEMP abnormalities and recurrences of BPPV; above all, patients presenting pathological VEMPs more frequently presented bilateral recurrences. Of note, of the 73 subjects presenting absent cVEMPs, 72 also had bilateral recurreces. To our knowledge, two other studies have reported data on this aspect. In the first, the authors assessed VEMPs abnormalities in 31.6% of the 16 enrolled subjects with recurrences [Kim E. et al., 2015], while in a retrospective analysis on 102 subjects with BPPV, recurrences were correlated with abnormalities during VEMP examination [Yetiser S. et al., 2014].

We believe that abnormalities of the maculae are not the only predisposing factor leading to recurrences, although it should be considered. Above all, vascular disorders of the maculae may act as a predisposing factor; of note, the sample of subjects with abnormal VEMPs had a higher age than the sample without.

One possible bias of the present analysis may be the different mean age of the 2 groups without and with pathological VEMPs, although it should be underlined that Pearson's test did not find a significant difference in the age of subjects in the entire sample and those with abnormal VEMPs. Other possible bias should be considered; firstly, exams were performed in different centers, with probably different methods and accuracy in the exams, although we always suggested university centers. Finally, only air conducted cVEMPs were performed, studying saccule, while ocular VEMPs, specifically assessing utricle, but are not routinely performed in all centers and were thus not studied.

Our data are not inconsistent with the hypothesis that in same cases a primary otolithic macular disorder may be among the predisposing causes of recurrences of BPPV.

Author Contributions: Conceptualization, R.T. and G.G; methodology, R.T. and G.G.; formal analysis, R.T.; writing—original draft preparation I.C., R.T, R.G; writing—review and editing, R.T. and I.C.; supervision, M.B.; data collecting, M.F, G.G. R.G and O.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: This retrospective study received ethical approval by an internal committee of San Raffaele Scientific Institute (No. 103/INT/2020).

Conflicts of Interest: The authors declare no conflict of interest

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