

VESTIBOLOGY

Recurrence of benign paroxysmal positional vertigo: experience in 3042 patients

Le recidive della vertigine parossistica posizionale benigna: dati su un campione di 3042 soggetti

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SUMMARY

Objectives. Benign paroxysmal positional vertigo (BPPV) is a disorder of the inner ear with a high rate of recurrence. Vascular disorders, migraine and autoimmune disorders have been considered facilitating factors for relapsing episodes. Our aim was to assess the role of vascular disorders, migraine and anti-thyroid antibodies in patients with recurrences.

Methods. We retrospectively analysed records of 3042 patients treated for BPPV without other lifetime vertigo. Clinical data included previous vascular disorders of the central nervous system, heart disorders, migraine and recent head trauma. The presence of anti-thyroid autoantibodies was assessed in all patients.

Results. Mean age of the first BPPV was 52.8 ± 14.5 years; there were 2339 females (76.9%), while 2048 (67.3%) of patients presented recurrences within two years of follow-up. Previous disorders of the central nervous system, presence of anti-thyroid antibodies, head trauma and migraine showed an association with recurrences. Above all, in subjects having the first BPPV while aged between 40 and 60 years, anti-thyroid antibodies were predictive for recurrences.

Conclusions. Our data are consistent with the hypothesis that anti-thyroid autoantibodies may play a role in recurrences in subjects with initial manifestations between 40 and 60 years.

KEY WORDS: benign paroxysmal positional vertigo, bppv, anti-thyroids autoantibodies, migraine, vascular disorders of the central nervous system

RIASSUNTO

Obiettivi. La vertigine parossistica posizionale benigna (VPPB) è una patologia con numerose recidive. Disturbi vascolari, emicrania, traumi cranici e patologie autoimmuni sono stati considerati come fattori facilitanti. Scopo del nostro lavoro è stato stabilire il ruolo di tali fattori e la presenza di anticorpi anti tiroide come facilitanti le recidive.

Metodi. Retrospectivamente abbiamo analizzato i dati di 3042 soggetti trattati per VPPB con storia negativa per altri tipi di vertigine. I dati clinici includevano la presenza di disturbi vascolari del sistema nervoso centrale, del miocardio, emicrania, traumi cranici recenti. Era inoltre stato chiesto di effettuare un dosaggio degli anticorpi anti tiroide.

Risultati. L'età media del primo episodio era di 52,8; i soggetti di sesso femminile erano 2339 (76,9%), mentre 2048 (67,3%) hanno presentato una ricorrenza nei 2 anni successivi. Precedenti vascolari del sistema nervoso centrale, positività per anticorpi anti tiroide (soprattutto nel soggetti tra 40 e 60 anni), traumi cranici ed emicrania erano correlati con recidive.

Conclusioni. I nostri dati sono compatibili con l'ipotesi che gli anticorpi anti tiroide possano giocare un ruolo favorente le recidive nei soggetti la cui prima manifestazione sia avvenuta tra i 40 e 60 anni.

PAROLE CHIAVE: vertigine parossistica posizionale benigna, vppb, anticorpi anti tiroide, emicrania, disturbi vascolari del sistema nervoso centrale

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Conflict of interest

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Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder, and its lifetime incidence in the general population has been estimated at around 10%¹. Its prevalence normally increases with age and presents a female-to-male ratio of 2:1 or 3:1². The commonly accepted pathophysiological mechanism is displacement of otoconial debris from the utricular macula, floating freely in the semicircular canals or attached to the cupola; gravity acting on the debris during head movements leads to an abnormal stimulation of the cupola thus provokes short lasting paroxysmal vertigo mainly when lying in bed in a specific head position³. In most cases BPPV can be suspected by collecting clinical history and is easily diagnosed by performing positional provocative manoeuvres; it can be treated with repositioning manoeuvres which are specific for each single canal and the positions of the debris. Recently, the Barany Society published diagnostic criteria for BPPV based on the onset of a short-lasting canal-specific nystagmus⁴. BPPV has been classified in primary and secondary (to head trauma, Menière's Disease, otologic surgery, prolonged bed rest)⁵. Recurrence of BPPV is far from being rare and according to previous authors about 50% of BPPV subjects present new episodes after successful repositioning manoeuvres⁶. Different clinical conditions have been proposed as facilitating factors for recurrence, including diabetes, osteoporosis and vascular disorders^{7,8}. Other authors have focused on a possible role of low levels of vitamin D as a predisposing factor for recurrent BPPV⁹ or high plasma levels of anti-thyroid autoantibodies¹⁰.

The aim of this work was to assess the clinical conditions and anti-thyroid autoantibody positivity possibly associated with an increased rate of recurrences in a large sample of patients with BPPV.

Materials and methods

Study cohort

In this retrospective study we included 3042 patients treated for BPPV from 2014 and 2018; clinical data were obtained from our records. All patients found in our clinical records were included if they fulfilled criteria for single or multiple canal BPPV according to the Barany Society guidelines⁴ and performed an analysis for thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase autoantibodies) and if positive for hormone dosage; since data were collected from different centres, we were able only to assess if they had normal or elevated thyroid hormone values. A retrospective analysis of data confirmed the diagnosis of BPPV according to these recent guidelines.

Clinical history was collected by a senior neurotologist and subjects were included if they did not refer previous long lasting (more than 5 minute) episodes of vertigo possibly related to Menière's disease, vestibular migraine or unilateral vestibular loss. Regarding clinical history, we collected the following data:

- Migraine: subjects were considered migraineurs if reporting typical headaches according to IHS criteria¹¹ and cautiously if they had a confirmatory neurological consultation.
- Vascular disorders of the central nervous system: we considered mainly previous ischaemic or haemorrhagic episodes or transitory ischaemic attacks.
- Heart disorders including ischaemic episodes, previous myocardial infarction or atrial fibrillation.
- Recent (in the previous month) head trauma; we also included mild traumatic brain injuries not provoking loss of consciousness.

Clinical intervention

All subjects underwent a bedside examination including head impulse test, head shaking and stepping test. All clinical tests were performed with the aid of video Frenzel (Interacoustics – Assens – Denmark).

In a second moment, we performed diagnostic manoeuvres for BPPV, Semont or Dix-Hallpike to assess posterior or superior canal BPPV, supine head roll test for the lateral canal; final diagnosis of BPPV was made when patients referred vertigo in the diagnostic position and we observed a nystagmus presenting latency, duration and typical characteristics for the stimulated canal. Semont or Epley repositioning manoeuvres 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 vertical canals and lateral canals at a later time. Patients were evaluated after 2 days; complete recovery was considered when all diagnostic manoeuvres were negative and patients referred no vertigo during triggering manoeuvres. Patients were considered to have a history of previous BPPV only if this was explicitly documented¹³⁻¹⁵.

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

These patients were excluded if reporting clinical history

or presenting any sign possibly related to a vestibular dysfunction different from BPPV. A few cases with intractable BPPV were not included.

In order to exclude cerebellar disorders leading to positional vertigo, all relapsing episodes underwent an MRI or CT scan of the central nervous system and subjects were included only if they had negative imaging.

Since previous works reported an overlap with autoimmune thyroiditis, we routinely suggested that anti-thyroglobulin and peroxidase antibodies be assessed in all patients and, when positive, blood hormonal values were assessed; in the present sample we included only subjects completing all diagnostic pathways.

Statistical analysis

Continuous variables are reports as mean and standard deviation. Categorical variables are presented as total number and percentage. A p value ≤ 0.05 was considered statistically significant. A linear regression model was calculated to assess the independent role of migraine, head trauma, vascular disorders of the central nervous system, heart disorders and positivity for thyroid antibodies on recurrence of BPPV. An identical analysis was performed in the subgroups of subjects aged below 40, between 40 and 60 and over 60. Finally, a Pearson test was performed to correlate age of onset of BPPV and recurrence. We used SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA) for statistical analyses.

Results

The sample was composed of 3042 subjects; there were 2339 females (76.9%). Age at inclusion was 63.3 ± 13.3 years. The age of the first episode of BPPV was 52.8 ± 14.5 years (range 10-90). Recurrent episodes were demonstrated in 2048 subjects (67.3%). A strong correlation was found between age and recurrences (r = -0.14, 95% CI -0.17 -0.10, p < 0.0001), with the elderly having more frequent recurrences. In order of frequency, thyroid autoantibodies were demonstrated in 801 subjects (26.3%), vascular disorders of the central nervous system in 382 subjects (12.5%), 324

were migraineurs (10.6%), heart disorders were present in 269 subjects (8.8%) and a recent head trauma was reported by 212 subjects (6.9%). Only 442 subjects with positivity for thyroid autoantibodies (55.2%) presented increased thyroid hormonal levels. Among patients with recurrent BPPV, positivity for thyroid autoantibody was present in 599 subjects (29.2%), central nervous system vascular disorders in 306 (14.9%), migraine in 234 (11.4%), heart disorders in 181 (8.8%) and head trauma in 158 subjects (7.7%). A linear regression model demonstrated that all these factors with the exclusion of cardiological disorders were predictive of recurrence of BPPV (Tab. I).

In the sample of 703 males, 439 (62.5%) reported recurrent BPPV, 72 (10.2%) had anti-thyroid antibodies, 41 (5.8%) were migraineurs, heart disorders were reported in 118 (16.8%) subjects, while 130 (18.5%) had CNS vascular disorders and 78 (11.1%) had head trauma. Among 2339 females, recurrent BPPV was found in 1609 (68.8%) of cases. Thyroid antibodies were present in 731 (31.2%), 284 (12.2%) were migraineurs, heart disease was found in 152 (6.5%) cases and CNS vascular disorders in 253 (10.8%) subjects; finally, a head trauma was reported by 134 (5.8%) cases.

Moreover, we studied the frequency of migraine, thyroid antibodies positivity, heart disorders, CNS vascular disorders and head trauma separately in the subgroups of patients with onset of the first BPPV below 40, between 40 and 60 and over 60 years. In Tables II-IV the results of a linear model considering migraine, thyroid antibodies positivity, heart disorders, CNS vascular disorders and head trauma as independent variables and recurrences as dependent variable are reported. Recent head trauma was the main causal factor for recurrence, while positivity for thyroid autoantibodies was correlated with relapsing episodes only in the subgroup of subjects aged between 40 and 60 years.

In order to assess anti-thyroid autoantibodies as a causal factor for recurrence, we selected 1981 subjects not presenting migraine, head trauma or a clinical history of vascular disorders of the heart/CNS. Among them, 683 had positive while 1298 negative autoantibodies. No difference

Table I. Linear regression model in the total sample considering the recurrence of BPPV as dependent variable and the presence of thyroid autoantibody, migraine, heart disorders, CNS disorders and head trauma as independent variables.

	Coefficient	95% CI	SE	t statistic	p
Thyroid antibody	0.03656	0.02119 to 0.05194	0.007842	4.66	< 0.0001
Migraine	0.05663	0.00265 to 0.11061	0.027531	2.06	0.04
Heart disorder	-0.005523	-0.064358 to 0.053311	0.0300064	-0.18	0.85
CNS vascular disorders	0.07905	0.05387 to 0.10423	0.012842	6.16	< 0.0001
Head trauma	0.1907	0.1280 to 0.2534	0.03199	5.96	< 0.0001

Table II. Linear regression model in the sample with BPPV onset below 40, considering the recurrence of BPPV as dependent variable and the presence of thyroid autoantibody, migraine, heart disorders, CNS disorders and head trauma as independent variables.

	Coefficient	95% CI	SE	t statistic	p
Thyroid antibody	0.02165	-0.01041 to 0.05370	0.016316	1.33	0.18
Migraine	0.04502	-0.03940 to 0.12945	0.042975	1.05	0.29
Heart disorders	-0.05833	-0.32045 to 0.20379	0.133435	-0.44	0.66
CNS vascular disorders	0.03717	-0.06881 to 0.14314	0.053946	0.69	0.49
Head trauma	0.2396	0.0961 to 0.3832	0.07306	3.28	0.001

Table III. Linear regression model in the sample with BPPV onset between 40 and 60 considering the recurrence of BPPV as dependent variable and the presence of thyroid autoantibody, migraine, heart disorders, CNS disorders and head trauma as independent variables.

	Coefficient	95% CI	SE	t statistic	p
Thyroid antibody	0.04569	0.02459 to 0.06678	0.010753	4.25	< 0.0001
Migraine	0.008642	-0.068450 to 0.085733	0.0393008	0.22	0.82
Heart disorders	0.121	0.017 to 0.225	0.0530	2.28	0.02
CNS vascular disorders	0.1161	0.0748 to 0.1573	0.02102	5.52	< 0.0001
Head trauma	-0.267	-0.369 to -0.165	0.0522	-5.11	< 0.0001

Table IV. Linear regression model in the sample with BPPV onset over 60 considering the recurrence of BPPV as dependent variable and the presence of thyroid autoantibody, migraine, heart disorders, CNS disorders and head trauma as independent variables.

	Coefficient	95% CI	SE	t statistic	p
Thyroid antibody	0.02741	-0.00179 to 0.05661	0.014882	1.84	0.06
Migraine	-0.03125	-0.17399 to 0.11148	0.072739	-0.43	0.66
Heart disorders	0.02074	-0.05859 to 0.10007	0.040428	0.51	0.61
CNS vascular disorders	0.09822	0.06246 to 0.13397	0.018220	5.39	< 0.0001
Head trauma	-0.09042	-0.18561 to 0.00477	0.048508	1.86	0.06

was detected for the age of the first vertigo between the 2 groups (51.1 ± 12.8 and 51.3 ± 13.4 respectively). Among 683 subjects with positive autoantibodies 511 (74.8%) had more than one episode of BPPV, while 810 (62.4%) patients with negative autoantibodies had relapsing episodes (chi-square statistic with Yates correction 30.4827, p-value < 0.00001). In the group of 683 subjects with positive autoantibodies, 287 (42%) presented elevated hormonal values and 396 (58%) had normal values; 208 (72.5%) out of 287 with hyperthyroidism while 303 (76.5%) of 396 (chi squared, $p = 0.23$) had recurrent episodes.

Finally, in the entire sample, we found a higher rate of recurrences in females, mainly in the subsample of younger subjects; moreover, in females we found a higher rate of thyroid autoantibodies in the entire sample and subsamples. In Table V, the rates and statistical significance are summarised.

Table V. Total number, percentages (between parentheses), and statistical significance of BPPV recurrency and thyroid autoantibodies in the entire sample and in subsamples of males (M) and females (F) with onset of the first BPPV below 40, between 40 and 60 and over 60.

	Recurrent BPPV	Autoantibodies
M _{tot} (n = 703)	439 (62.5%)	72 (10.2%)
F _{tot} (n = 2339)	1609 (68.8%)	731 (31.2%)
p	0.001	< 0.00001
M _{<40} (n = 98)	67 (68.4%)	8 (8.1%)
F _{<40} (n = 443)	346 (78.1%)	135 (30.5%)
p	0.04	< 0.00001
M ₄₀₋₆₀ (n = 306)	205 (67%)	49 (16%)
F ₄₀₋₆₀ (n = 1172)	823 (70.2%)	386 (32.9%)
p	ns	< 0.00001
M _{≥60} (n = 299)	167 (55.8%)	49 (16%)
F _{≥60} (n = 724)	440 (60.8%)	210 (29%)
p	ns	0.00002

Discussion

Some of our results are mainly confirmatory; for example, we found a female to male ratio that was increased three-fold, which is in the range of previously published studies^{1,5,16}.

Moreover, BPPV presents a high rate of recurrences, which were present in our study in 67.3% of subjects, and especially in females. Previous authors estimated the value at a lower range between 35 and 50%^{17,18}; this difference might in our opinion be justified with our longer period of observation of these patients (up to five years); on the other hand, it should be considered the probability that a bias in our work may result from the fact that we excluded subjects that we were unable to contact by phone, possibly without recurrences, leading to an overestimation of the value.

On the whole, even if small differences can be noted, our results are in line with previous works regarding head trauma as an important causal factor predisposing to recurrent episodes¹⁹. Since some authors found an increased rate of VEMP dysfunction in BPPV patients occurring after head trauma compared to idiopathic BPPV, they proposed that the trauma may provoke a macular disorder leading to otoconia detachment.

Migraine per se has a strong association with different vertigo, including BPPV; a recent survey study reported a correlation between BPPV and migraine that was two times more frequent in migraineurs²⁰, and, more recently, a meta-analysis of literature data included migraine among the factors predisposing to recurrences of BPPV²¹.

Risk factors for vascular disorders have been widely studied in BPPV and its recurrences, and a general consensus has been reached on the fact that hyperlipidaemia, hypertension, low vitamin D plasma levels and diabetes may play a role in predisposing to BPPV^{8,21,22}. In a previous work, BPPV was correlated with an increased risk of ischaemic stroke during 9-year follow-up; however, controversial results have been published on CNS vascular disorders as a predisposing factor for recurrences²¹. The different inclusion criteria may justify the different results.

Probably the most interesting finding of our work regards the high rate of subjects with positivity for anti-thyroid autoantibodies (26.3% in the entire sample and 29.2% in recurrent BPPV with a female preponderance in both cohorts), which strongly correlates with recurrences above all in subjects presenting the first episode of BPPV while aged between 40 and 60 years. A possible overlapping between autoimmune disorders and BPPV has already been postulated by previous papers^{23,24}.

It could be speculated that other factors may play a major role in patients aged below 40 (head trauma) and over 60 (vascular disorders of the central nervous system) years.

The prevalence of positive anti-thyroid autoantibodies in the general population has been estimated to range between 3% and 17%, and differences may be due to genetic, environmental factors or methods applied for antibody measurement²⁵. Anti-thyroid antibodies have been correlated with different inner ear disorders, including autoimmune inner ear disorders and Ménière's disease²⁶. As far as we know, the present study reports on the largest sample of BPPV subjects tested for anti-thyroid autoantibodies to date, although two previous investigations have been published on the topic^{10,27}. Although not all authors reported an overlapping between anti-thyroid autoantibodies and BPPV²⁸, regarding the overlap between anti thyroid antibodies and BPPV, several hypotheses can be made. Some authors postulated a cross reaction mechanism; according to this theory, the inner ear would share common antigens with potentially harmful organisms such as viruses or bacteria. Other authors have postulated mechanical stimulation by immune complexes and the possible co-existence of a micro-angiitis in the inner ear in the context of an autoimmune multi-organ disease. In both cases a primary vascular disorder of the macula could be the triggering factor leading to the detachment of otoconia^{26,27}. Moreover, our data support the possibility that recurrence may be linked to autoantibodies per se rather than increased plasma levels of hormones; our data are not different with those of previous works reporting that in the recurrence the hormonal situation is less important than the hormonal status^{27,29}, while, on the opposite, a recent work based on data obtained by the Korean public register demonstrated an association between hormonal status and BPPV³⁰.

Some limitations of our work should be underlined. Firstly, in our sample we were unable to retrieve complete data on other variables possibly related to relapsing episodes, such as diabetes, hypertension, hypercholesterolaemia and hyperlipidaemia. Moreover, the strict diagnostic criteria we applied possibly led to an underestimated proportion of patients with migraine or vascular disorders. Finally, in subjects with negative anti-thyroid autoantibodies, the plasma levels of thyroid hormone were not assessed, and thus a role of plasma thyroid hormonal levels in recurrences of VPPB cannot be excluded.

Conclusions

We believe that our data are not inconsistent with the hypothesis that among others, positivity for anti-thyroid autoantibodies may play a role as predisposing factor for recurrence of BPPV. If confirmed, our data support the possibility that they should be routinely evaluated above all in middle-aged subjects with frequent recurrences.

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