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ARE THE PERSISTENT POSTURAL-PERCEPTUAL DIZZINESS (PPPD) PATIENTS MORE ANXIOUS THAN THE PATIENTS WITH OTHER DIZZINESS?

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SUMMARY

Background: *The Behavioral Subcommittee of the Bárány Society Committee for Classification of Vestibular Disorders recently established the diagnostic criteria for a persistent postural-perceptive dizziness (PPPD).*

Objectives: *This study aims to determine how significant the degree of anxiety and depression of PPPD patients is, compared to the patients with other dizziness.*

Subjects and methods: *The study was conducted on 78 patients, 39 (50%) of whom suffer from PPPD, and of a control group consisting of the same number of patients with other types of dizziness. All the patients filled out the DHI and HADS questionnaire and were subjected to a VNG and VEMP examination.*

Results: *The DHI showed significant disability in the majority of patients, slightly more in the control group. The HADS showed an equal degree of anxiety in both groups of patients, but significantly higher pathological anxiety in the PPPD group (49%:31%).*

Conclusions: *Majority of the patients in both groups experienced mild anxiety, while those with the pathological degree were more represented in the PPPD group. Depression was more expressed in the group of other dizziness. We can consider only the patients with a pathological degree of anxiety as predisposed to the emergence of PPPD.*

Key words: *persistent postural-perceptual dizziness – anxiety – depression - handicap*

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INTRODUCTION

Among all the causes of dizziness, functional dizziness stand out with their representation and signify the second most common cause of vertigo in general population, right behind benign paroxysmal positional vertigo (BPPV), and in some age groups, such as adolescents (Jahn 2011) and those from 30-50 years of age even the most common cause (Strupp et al. 2011). The prevalence of functional dizziness as a primary cause of vestibular symptoms is about 10% in neurotological centres. The rate of psychiatrical comorbidity in patients with structural vestibular disorders are much higher, about 50%, and most of it happens to patients with vestibular migraine, vestibular paroxysmia, and Meniere's disease (Best et al. 2009, Dietrich & Staab 2017). To safely move through space, we need a constant monitoring of our movements and good spatial orientation, as well as the evaluation of danger. This monitoring is done by a close correlation between the brain's neural projections responsible for danger and fear with those responsible for movement control and the position of a body in space (Staab et al. 2013). Over the last years, numerous connections have been established between visual, somatosensory, and vestibular centres with those dedicated to fear, danger, and emotions. The studies on animals have shown feedback connections between vestibular and parabrachial nuclei, as well as parabrachial and central amygdala nuclei (Balaban 2004). Similarly, a feedback link has been established between amygdala nuclei and superior colliculi and thalamus, mainly receiving visual and somatosensory information (Tamietto & Gelder 2010). The recent functional magnetic resonance imaging (MRI) scans confirm such connections on healthy people (Indovina et al. 2014, Riccelli et al. 2017). In a newly published study, Holle D and associates have shown an indubitable connection between the sense of pain and functional balance disorders and have confirmed a hypothesis about their multisensory dimension, as a result of a much broader disturbed adaptation, not just of visual/vestibular and movement sensations (Holle et al. 2015). One of the most novel studies, done by voxel-based morphometry MRI, has shown a decline of the grey matter in Persistent Postural-Perceptual Dizziness (PPPD) patients, for specific regions of the brain included in the multisensory system for balance maintenance (Wurthmann et al. 2017). Subsequent to the exposure to precipitating factors such as the acute or episodic vertigo, a pathophysiological mechanism of the occurrence of functional vertigo in the predisposed

people with a high level of anxiety and a low degree of extroversion, instead of a readaptation of the disturbed balance system the patients maintain or renew the high-risk postural patterns by keeping in mind the head position and body movements, as well as a contraction of leg muscles. At the same time, the brain, acting as corrupted Bayesian estimator, sends top-down information, where previous beliefs dominate over current incoming information (Edwards et al. 2012, Popkirov et al. 2018, Seemungal & Passamonti 2018). Some authors believe that for the occurrence of functional vestibular disorder, with anxiety as a predisposing factor, the most significant is the strength of initial vertigo (Heinrichs et al. 2007). In the last few decades, there has been a dramatic improvement of vestibular diagnostics, so we are nowadays able to go to the most hidden parts of the labyrinth while performing the tests in a broad spectre of speeds and frequencies on which vestibular system functions. Regardless of that, a large share of patients shows no specific deviations in vestibular tests, so we have wrongly concluded that we are dealing with psychogenic or somatoform disorders until recently. Nowadays, for these occurrences, we use a new term, functional vertigo, which describes them better, because they are made of a combination of vestibular, structural, and psychiatric disorders, which by acting together lead to the disorder of balance keeping function. The clinical traits of PPPD are as follows: a constant vertigo manifesting itself as dizziness, loss of spatial orientation and/or instability (without any perception of circular movement), lasting at least for three months, followed by hypersensitivity to movements, whether in one's own body, visual surroundings, as well as hardships during the act of precise visual tasks (e.g., reading, personal computer work, smartphones, etc). The symptoms are present during most days of the week, and also get worse as time goes by, but they can also weaken in some cases. The disease can appear spontaneously or under the influence of sudden movements. Patients feel worse when sitting upright, exposed to complex or movable visual stimuli, as well as during active or passive head movements. The pathophysiological mechanism of PPPD occurrence is unknown, but the illness typically follows an acute or recurring balance disorder (in 25% of the BPPV cases and 29% in neuronitis, even if they are well compensated) (Staab 2016). The most recent concepts claim that the illness is a result of a bad readaptation of the postural system on the experienced vestibular disorder. In the beginning, the symptoms usually appear spontaneously, then consolidate, while a gradual evolution of the disease is quite rare. Previously, the continuation of symptoms after an acute or episodic vestibular disease would be described as chronic vestibulopathy or psychogenic vertigo, which can be considered wrong and outdated today, with adequately defined criteria for a diagnosis of PPPD. Considering that there are no significant deviations in the lab tests or the clinical patient tests, the diagnosis is set exclusively by the medical history, with targeted questions related to the cardinal disorder symptoms (Godemann et al. 2005, Staab et al. 2017). A correct and early diagnosis is important so that the further chronification of the disease is stopped and adequate treatment can be prescribed. If done continually, a treatment that encompasses the education of patients, vestibular rehabilitation (VR), cognitive-behavioural therapy (CBT) and pharmacotherapy significantly reduces the symptoms of the disease and offers a possibility for a long-term remission (Edelman et al. 2012, Holmber et al. 2007, Horii et al. 2004, Meli et al. 2007, Spiegel et al. 2017). As a new entity, PPPD is still quite unexplored, so we have found only a few clinical studies in the available medical literature, and one of those deals with basic clinical traits of illness (Yan et al. 2017), while the other deals with the traits of the posturographic result (Söhsten et al. 2016). The third deals with the results of vestibular rehabilitation in PPPD patients (Thompson et al. 2015), and there are also three pathophysiological studies made by observing the results of functional MRI and a connection between cortical projections for fear, insecurity, and pain with the projections of a balance-keeping system (Holle et al. 2015, Riccelli et al. 2016, Wurthmann et al. 2017). One of the main traits of patients with phobic postural vertigo (PPV), one of the predecessors of PPPD is their obsessive-compulsive personality structure (Brandt & Dietrich 1986). The syndrome of chronical subjective vertigo (CSD) has taken important determinants of PPV, accentuating their connection to anxiety and introverts (Chiarella et al. 2016, Staab et al. 2002, Staab et al. 2013, Staab & Ruckenstein 2003, Staab & Ruckenstein 2007). The beginning of PPPD is a period of strengthened anxiety and oversensitivity to the balance disorder, which leads to the occurrence of illness, eventually leading to the secondary anxiety, functional disorders of walking, creation of the new spare strategies and avoidance in behaviour. Some authors believe that, in the core of the PPPD occurrence, there is an increased use of visual cues in the balance-keeping process (Cousins et al. 2014). Our study aimed to check the rate of anxiety and depression in PPPD patients related to the patients with different vertigo causes. Our secondary goal was to determine whether PPPD has any measurable influence on the vestibular senses.

SUBJECTS AND METHODS

Subjects

A retrospective review of 78 patients, 39 of whom suffer from PPPD, and the same number of other types of vertigo (control group). The inclusive criterium for the PPPD group was filling out all of the diagnostical criteria (A-E) according to the Barany society working group (Bisdorf et al. 2015, Staab et al. 2017). The

triggering factor for the disease in PPPD group was most commonly: vestibular migraine at 16 (31%), vestibular neuronitis at 10 (26%) and BPPV in 2 (5%) patients. The precipitating factor remained unrecognised in 3 (7.7%) of patients. A significant number of patients reported generalised anxiety at 7 (18%) as the trigger, while structural disorders were much less familiar with representation at 1 (2.6%).

In the control group, 19 (49%) patients had a benign paroxysmal positional vertigo, 16 (42%) suffered from unilateral vestibular hypofunction, 3 (8%) had a vestibular migraine, and one patient (1%) has bilateral vestibular hypofunction. All the patients were checked and diagnostically processed in the ENT Polyclinic of General County and Veterans Hospital Vukovar, in a period from April 2017 to March 2018.

Procedure

At the first check-up, before the clinical examination, all patients have taken the Dizziness Handicap Inventory (DHI) (Jacobson & Newman 1990) and Hospital Anxiety and Depression Scale (HADS) questionnaire (Bjelland et al. 2002, Zigmond & Snaith 1983), individually, in a peaceful and quiet room. We studied the DHI and HADS to analyse data about the distribution of the patients by the degree of anxiety, depression and handicap. In the analysis of the results of the HADS questionnaire, we divided the patients into three groups according to the degree of anxiety and depression: those with no signs (0-7 points), slight (8-10 points) and pathological (11-21 points). Similarly, according to the DHI results, we divided the patients into groups with mild (16-34 points), moderate (35-53 points) and severe (≥54) handicap. We also analyse data about the distribution of the patients by Median (interquartile range) of anxiety, depression and handicap in both groups of patients. The qualitative patient testing consisted of a neuro-otological clinical investigation which encompassed the following: nystagmus tests, Dix-Hallpike (Dix & Hallpike 1952) and Pagnini-McClure (McClure 1985, Pagnini et al. 1989) positioning test, Head Impulse Test (Halmagyi & Curthoys 1988), Alternate Cover Test (Rainey et al. 1998), Dynamic Visual Acuity test (Demer et al. 1994), Romberg test on a soft surface (Shumway-Cook & Horak 1986), and the test of vibration sensitivity (Dyck et al. 1987). Quantitative testing of patients consisted of a full videonystagmography (VNG) battery test, as well as cervical and ocular Vestibular Evoked Myogenic Potential (VEMP) (Colebatch & Halmagyi 1992, Todd et al. 2007). The VNG device used in the study was VN-15, made by Interacoustics, Denmark. In the VNG test, we have done the following procedures: spontaneous nystagmus test, oculomotor tests, Dix-Hallpike test, positional tests and caloric test by Fitzgerald-Hallpike. These tests confirmed or excluded the presence of peripheral or central vestibular disorder. The values which we have compared were as follows: unilateral weakness (UW) and directional preponderance (DP), in both groups of patients, calculated according to Jongkees' formula (Jongkees et al. 1962), as well as a relation of these parameters between the tested groups. The device used during oVEMP and cVEMP tests were Eclipse Platform by Interacoustics, Denmark, Commercial electromyographic (EMG) System Otoaccess™, EP15 and EP25, software version 3.03., Assens, Denmark. The sound was applied monoaurally through Insert earphones ABR 3A from Interacoustics, Assens, Denmark, with earplugs (3M Auditory Systems, Indianapolis, IN, USA). For the auditory stimulus, we have used Tone burst of negative polarity with a linear envelope (2 ms rise/fall time, 1 ms plateau), as recommended by the manufacturer, but also according to our previous experience and studies (Ashford et al. 2016, Özgür et al. 2015, Mendeš et al. 2017). We have compared the values of the interaural asymmetry ratio of peak-to-peak amplitudes (AR) in both groups of patients, as well as with the tested groups. The criterium for the inclusion in the study was also a sufficient intellectual level as well as a sufficient level of patients' literacy, sufficient for the cognition of research nature and individual filling out of the questionnaires. The excluding criteria were as follows: the absence of any A-E clinical diagnostic criteria, as well as the presence of any comorbidity. Unclear and incomplete cases were also excluded from the study and were left for later evaluation. While establishing the E criterium, we have relied on the results of the clinical and laboratory tests.

The Ethics Committee of the respective institution approved this study under protocol number EP-16/2018 (510-05/18) according to the ethical standards of the institutional and national research committees, 1964 Helsinki Declaration and its later amendments. All included patients were adequately informed about the methods and objectives of this study. They have voluntarily accepted to participate in the survey an informed consent was obtained from all participants included in the study.

Statistical analysis

Descriptive statistical methods were used for the frequency distribution of the observed variables. Differences in categorical variables were tested by Chi-squared test and, if necessary, by Fisher's exact test. The normality of the distribution of numerical variables was tested by Shapiro - Wilk test. Differences in not normally distributed, numerical variables between the two groups were tested by Mann-Whitney U test, and according to the diagnoses by Kruskal-Wallis test (Marušić et al. 2008). All P values were two-sided. The significance level was set at Alpha=0.05. Statistical analysis was performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

RESULTS

The study was conducted on 78 patients, of whom 39 (50%) suffer from PPPD, while the same number suffers from other types of vertigo (control group). The women are represented more than the men in both groups. The age median of patients is 54 years of age, whereby the significantly younger patients are in the group with PPPD (Mann Whitney U test, P=0.006) (Table 1). According to the HADS results, pathological anxiety is significantly represented (40%) much more in the PPPD group (49%:31%). A depression of pathological degree is manifested in 18 (23%) patients, equally in both groups of patients (23%:23%). Most patients show a level of mild, borderline depression, 41 of them (53%), which is a bit more represented in patients with other types of vertigo (62%), but without significant differences compared to PPPD patients. There were no significant gender differences about anxiety and depression in both groups according to Mann Whitney U test (Table 1). The DHI test shows an equal level of illness handicaps in both groups, which is mostly manifested as a substantial handicap, in 48 of them (62%), and somewhat more in patients with other types of vertigo (72%), but without a significant difference compared to PPPD group (Table 2). There were no significant differences between observed groups in the area of anxiety, depression and handicap level according to Mann Whitney U test (Table 3). The results of Fitzgerald-Hallpike caloric test performed within the VNG testing show that the patients with other types of vertigo have significantly higher values of UW more than

Table1. Patients by gender and age

	PPPD	Control	p
Gender (n(%))			0.110*
Men	9 (23)	13 (33)	
Women	30 (77)	26 (67)	
Age (Median (interquartile range))	47 (39-60)	59 (48-64)	0.006**

* χ^2 test; **Mann Whitney U test

Table 2. Distribution of patients by the degree of anxiety, depression and handicap

	Number (%) patients			P*
	PPPD	Control	Total	
Anxiety (HADS)				0.18
Without signs	5 (13)	4 (10)	9 (11)	
Slight (Borderline)	15 (39)	23 (59)	38 (49)	
Pathological	19 (49)	12 (31)	31 (40)	
Depression (HADS)				0.15
Without signs	13 (33)	6 (15)	19 (24)	
Slight (Borderline)	17 (44)	24 (62)	41(53)	
Pathological	9 (23)	9 (23)	18 (23)	
Disability (DHI)				0.07
Mild handicap (16-34)	6 (15)	3 (8)	9 (12)	
Moderate handicap (35-53)	13 (33)	8 (21)	21 (27)	
Severe handicap (≥54)	20 (51.3)	28 (72)	48 (62)	
Total	39 (100)	39 (100)	78 (100)	

* χ^2 test

Table 3. Median (interquartile range) of anxiety, depression and handicap in both groups of patients

	Number of patients	Median (interquartile range)	Minimum-maximum	Difference (Hodges – Lehman)	95% confidence interval		P*
					From	To	
Anxiety (HADS)							
PPPD	39	11 (10–13)	2–18	-1	-2	0	0.06
Control	39	10 (9–12)	7–13				
Depression (HADS)							
PPPD	39	9 (8–11)	4–13			2	0.08
Control	39	9 (9–11)	6–15				
Handicap (DHI)							
PPPD	39	56 (42–68)	14–88		-2	14	0.15
Control	39	62 (51–70)	22–88				

*Mann Whitney U test

Table 4. Indicators of laboratory tests for both groups of patients

	Number (%) patients			P*
	PPPD	Control	Total	
Unilateral Weakness				<0.001
≤25%	35 (100)	18 (47)	53 (73)	
<25%	0	20 (53)	20 (27)	
Total	35 (100)	38 (100)	73 (100)	
Directional Preponderance				0.68
≤35%	33 (94)	34 (90)	67 (92)	
<35%	2 (6)	4 (11)	6 (8)	
Total	35 (100)	38 (100)	73 (100)	
Oculomotor tests				0.80
Patological	27 (69)	29 (74)	56 (72)	
Normal	12 (31)	10 (26)	22 (28)	
Total	39 (100)	39 (100)	78 (100)	
Dix- Halpike positioning test				<0.001
Positive	1 (3)	19 (49)	20 (26)	
Negative	38 (97)	20 (51)	58 (74)	
Total	39 (100)	39 (100)	78 (100)	

*Fisher's exact test

25%, related to the patients with PPPD (Fisher's exact test, P<0.001), as well as a positive Dix-Hallpike positioning test (Fisher's exact test, P<0.001). (Table 4). VEMP amplitude was considered pathological when its mean value was for ≥50% (AR≥37%) less than the amplitude detected after contralateral stimulation, regardless of the absolute amplitude value. The findings of VEMP tests show high values of AR for oVEMP and cVEMP, without a significant difference related to the groups, with a median (interquartile range) for cVEMP of 47 (29–58) for the PPPD group, and 56 (36–63) for the control group. The median (interquartile range) values of AR for oVEMP was 38 (19–47) for the PPPD group and 35 (25–46) for control.

DISCUSSION

When talking about representation by gender, in both groups there are more women, in a ratio of 2:1 and more. It can be said that it is expected and corresponds to the gender representation in earlier-published studies well (Bittar & Lins 2015, Staab 2016, Yan et al. 2017). The age of patients in both groups ranges from 39 to 64 years of age, which corresponds to the age structure in most studies that deal with vertigo (Dietrich & Staab 2016, Strupp et al. 2011). Interestingly, patients of our PPPD group are statistically significantly younger than the patients in the control group, with the median of 47:59. It can be explained by the fact that in the adult population, PPPD has the greatest representation particularly in the age group of 30-50 years of age (Strupp et al. 2011). If we look at the part of each vertiginous entities in the control group, we could say that it corresponds to the longevity statistics of our patients, with minor discrepancies being a result of taking a smaller sample, concerning time and numbers. According to the DHI test, most patients in both groups have shown a clinically significant and equal level of handicap, but it is, after all, somewhat smaller than the PPPD group related to the control group (84%:93%). Even though the medium level of handicap in both groups has affected slightly less than a third of the patients (27%), being somewhat more pronounced in the PPPD group, the hard disability handicap had been noted in 48 (62%) of patients, slightly more in the control group (72%), but without a statistically significant difference related to the PPPD group. When looking at the results obtained by the Mann Whitney U test, the average handicap is on the hard level, equal in both groups, somewhat less in PPPD group when related to the control one (55:62). These results show a high level of handicap during usual activities and functions in both groups, which significantly negatively affects the health-related quality of life and implies an important public health problem due to the absence from work or school. The results of the HADS test show that a small and equal share of patients in both groups has no signs of anxiety (11%). The remaining 9/10 of patients manifest smaller or greater symptoms of clinical anxiety, equally represented in both groups, with the one in a moderate form being more represented in the control group (59%:39%), and with a stronger form in the PPPD group (49%:31%). A similar level of anxiety has been described in patients affected by CSD (Staab et al. 2002, Staab et al. 2014, Staab & Ruckenstein 2003, Staab & Ruckenstein 2005). It should be noted that this state of anxiety has been recorded during the arrival of the patients when the disease had already developed. It is hard to say whether it is an old, primary anxiety which was the trigger for the disease, a secondary, new anxiety as a result of the functional disorder, or the old anxiety provoked by the new illness (Staab & Ruckenstein 2003). Related to the state of depression, the patients in both groups have shown a mild, borderline level (53%),

somewhat more in the control group, but without any statistically significant differences related to the PPPD group. The pathological level of depression is represented greatly, and it is shown in 23% of patients, equal in both groups. There was a similar representation (24%) of patients who showed no signs of depression, but this time a lot more in the PPPD than in the control group. The results of the HADS questionnaire, according to Mann Whitney U test, showed anxiety with the median of 10 and depression with the median of 9, without significant differences between the groups. This result shows a mild level of anxiety and depression, which is certainly no cause for an alarm, but it should not be ignored either. The patients should be directed to the additional psychiatric-psychological evaluation. In a recent study, the results of the Generalized Anxiety Disorder 7 Item Scale (GAD-7) have shown a higher level of anxiety in CSD patients when compared to the control group, which consists of patients with exclusively peripheral vertigo (Chiarella et al. 2016). In the lab tests, the results of Fitzgerald-Hallpike caloric test, done within a complete VNG battery tests have shown a significantly higher values of UW in patients with other types of vertigo related to the PPPD group, while the values of DP in less than 90% of patients in both groups less or equal 35%, without a significant difference between the groups. The tested patients with other vertigo types have a significantly greater value of UW greater or equal of 25, related to the patients with PPPD, as well as a positive Dix-Hallpike positioning test. These results are completely understandable, considering that (in the groups of patients with other types of vertigo) we have a significant part of those whose disorder is defined by the weakness of one or both labyrinths or their complete dysfunctionality, as well as the patients suffering from BPPV, for whose a diagnosis setting a positive Dix-Hallpike test is conditio sine qua non. The results of the AR obtained by oVEMP and cVEMP tests are at the levels greater than 35% and for the PPPD median amounted to 47 while for the control group the median amounted to 56, which shows that in both groups there was the greater disorder of the function of otolithic senses. Unfortunately, even this information cannot help us in the differentiation of a PPPD related to other vertigo, because there is statistically no significant difference related to the group, but it points to a possible chronical presence of some of the precipitating factors for the occurrence of PPPD.

The limits of the study were as follow: the number of patients is sufficient for statistical processing, but the results would be much more relevant to a more significant sample. The control group was not homogenous, because it incorporates different vestibular entities, peripheral and central, with a different level of anxiety/depression and incapacitation, so its results are incoherent and reflect the group average, while the results of individual entities about each other, related to PPPD were entirely different.

CONCLUSION

Our study has shown that the greater share of patients in both groups has a certain level of anxiety. However, on the pathological level, it is more represented in the PPPD group, which suggests that these patients should be taken as predisposed for the occurrence of PPPD, and in the prophylactic activity, we should pay particular attention to them. The results of all the laboratory tests do not provide for one parameter that is pathognomonic for the PPPD diagnosis, so we will have to rely exclusively on the new, consensus-made diagnostical-clinical criteria while setting the diagnosis for this disease. A significant AR asymmetry in the VEMP points to the lesion of one of the otolithic senses – it cannot help us establish the diagnosis, but it leads to a possible comorbidity or a permanent presence of some of the precipitating factors and helps to the setting of the diagnostical E criterium.

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Contribution of individual authors:

Sinisa Maslovara & Anamarija Sestak: study design, literature search, data collection, statistical analysis, first draft, manuscript revisions, approval of the final version;

Drazen Begic: study design, literature search, first draft, manuscript revisions, approval of the final version;

Silva Butkovic-Soldo: study design, literature search, data collection, first draft, manuscript revisions, approval of the final version;

Andrijana Vceva: literature search, data collection, first draft, approval of the final version;

Ivana Pajic-Matic: literature search, data collection, first draft, manuscript revisions, approval of the final version.

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