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Potential risk factors of persistent postural-perceptual dizziness: a pilot study

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Abstract

Background Persistent postural-perceptual dizziness (PPPD) unifies the main characteristics of chronic subjective dizziness, visual vertigo and related diseases, which is a common chronic disease in neurology. At present, the pathology of PPPD is not fully understood.

Objective In this single-center retrospective case series review, we aim to investigate the potential risk factors of PPPD.

Methods Eighty inpatients diagnosed with PPPD were recruited with 81 apparently healthy controls. Patient-specific clinico-radiological data were collected from both groups. Conditions of hypertension, diabetes, smoking, and drinking were derived from medical history. Blood test results were recorded including total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fibrinogen, vitamin B12, folic acid, total cholesterol, triglyceride, and folate level. The subjects were examined by carotid artery CTA and cranial MRI, and the imaging findings of carotid atherosclerosis (CAS), white matter hyperintensities (WMHs) and lacunar infarction (LI) were recorded. Binary logistic regression analysis was used to investigate the difference between the case and control groups. Significance was defined as p value less than 0.05.

Results The prevalence rate of hypertension in the case group was significantly higher than that in the control group, and the detection rates of CAS, WMHs, and LI in the case group were significantly higher than those in the control group ($p < 0.05$ for all).

Conclusion Hypertension, CAS, WMHs, and LI are associated with PPPD, which may be potential risk factors for its development.

Keywords Persistent posture-perceptual dizziness · Vestibular system dysfunction · Potential risk factor · Clinico-radiological characteristics · Binary logistic regression analysis

Introduction

Persistent postural-perceptual dizziness (PPPD) is a common chronic dysfunction of the vestibular system and brain, and the second most common disorder in patients with chronic dizziness. The concept of PPPD was proposed by an expert consensus from an exhaustive review of 30 years of research on chronic subjective dizziness (CSD), visual vertigo (VV), phobic postural vertigo (PPV), and space-motion discomfort [1]. The average course of disease among the PPPD outpatient is about 4.5 years, whereas it can be several decades in some patients, leading to great burden to patients and their families [1]. The burden of PPPD is not only psychological and economic, but also physical. The physical symptoms of PPPD can be disabling. Patients often develop secondary gait disorders, anxiety, avoidance behavior, and severe disability [2].

The main clinical manifestations of PPPD include long-term (often longer than three months) non-rotational dizziness, unsteadiness, and fluctuations of symptoms with stimulus-triggered provocation and/or exacerbation (e.g., visual stimuli), with a distinctive feature of short episodes

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of momentary worsening dizziness [3, 4]. PPPD is characterized by persistent dizziness in which the patient feels unbalanced without falling and moving when still but there is no obvious instability or other abnormal neurological symptoms [5]. Thus, the neurological examination often shows normal results. Currently, the main diagnostic criteria of PPPD include persistent non-vertiginous dizziness, unsteadiness, and non-spinning vertigo that are exacerbated by postural challenges and perceptual sensitivity to space-motion stimuli [1].

Symptoms of rotational vertigo predating fully developed PPPD are often due to a precipitating illness, including peripheral or central vestibular disorder, other medical illnesses, or psychological distress, which is the result of maladjustment to sudden events and constitutes long-term maladaptation to neuro-otology, medical or psychological events that cause vestibular symptoms [2]. In addition, some psychological symptoms are observed in PPPD patients due to neuropsychiatric comorbidities. PPPD can exist alone or coexist with other diseases or disorders such as vestibular migraine or other vestibular diseases, anxiety, depression, and other psychiatric disorders related to balance-related problems [1, 6].

The pathology of PPPD is complex and not fully understood. Multisensory maladjustment involving alterations of sensory response pattern including vestibular, visual and motion stimuli is thought to be a key pathophysiological correlate of this disorder [6]. Riccelli et al. compared the brain response and eye movements during a virtual-reality rollercoaster stimulation between PPPD and control groups, and suggested that pathophysiologic mechanisms of PPPD might include the functional alterations in brain processes that affect balance control and the reweighting of space-motion inputs to favor visual cues [7]. However, it is still unknown whether PPPD is a single disorder with one principal pathophysiologic process or is the common manifestation of multiple conditions that produce similar symptoms from different pathophysiologic mechanisms [1]. As a result, there is a lack of accurate diagnostic methods of PPPD. The objective and specific examination methods resulted in a relatively low reported prevalence rate of PPPD [2]. An in-depth understanding in pathology is essential to improve the quality of diagnosis, treatment, and management of PPPD.

Recent development of brain-imaging technologies, especially the functional magnetic resonance imaging (fMRI) examination, has revealed some radiological characteristics of PPPD that may be related to the pathological changes in the brain structure. Especially, the abnormal integration of visual and vestibular information has been widely observed. In patients with PPPD, the functional connectivity of two brain networks in subclinical agoraphobia (visuospatial-emotional and vestibular-navigational) that integrated visual, vestibular and emotional responses to guide spatial movement is lower than healthy controls [8]. Increased visual cortical activity is associated with the severity of dizziness in patients with PPPD [7]. The amplitude of low-frequency fluctuation and regional homogeneity values in the right precuneus and cuneus were significantly lower in PPPD patients, indicating that the change in spontaneous functional activity of the cuneate lobe and anterior cuneate lobe may lead to the abnormal integration of visual and vestibular information [9]. The weakening of the functional connection between the precuneate lobe and the precentral gyrus can lead to the aggravation of symptoms during upright posture, active or passive movement [9]. It was also observed that, in patients with PPPD, areas involved in multisensory vestibular processing showed decrease in gray matter volume. The longer the course of disease, the more obvious the changes in gray matter [6].

The radiological observations indicated that microcirculatory changes may play an important role in the development of PPPD. On microvascular level, patients with PPPD often have reduced blood flow to cortical areas with altered structural and functional connections especially in the visual-vestibular network [10]. The blood-oxygen-level-dependent (BOLD) signal in fMRI and photon emission patterns of single-photon emission computed tomography (SPECT) identify changes in cerebral blood flow (CBF), but those are thought due to metabolic demand of brain tissue [11]. Brain metabolism depends on the neural activity, and is associated with brain perfusion as observed in different pathological and physiological changes [12–14]. Thus, the perfusion (i.e., microcirculatory hemodynamics) observed on clinical imaging data could be used as an alternation to indirectly evaluate brain metabolism. Before the definition of PPPD was proposed, a study of 122 patients with unexplained vertigo (mainly manifested as dizziness, vague instability, and imbalance) found that the severity of white matter hyperintensities (WMHs) were higher in patients with unspecified dizziness which might be associated with PPPD [15]. In patients with cerebral small vascular disease (CSVD), the magnetic resonance imaging (MRI) results show that WMHs are associated with dizziness [16]. In addition, as a biomarker of CSVD, lacunar infarction (LI) indicates the ischemic changes in brain and is closely associated with WMHs [17, 18]. Thus, WMHs and LI may be associated with the PPPD-related hemodynamic (i.e., metabolism at microvascular level) changes. It was also found that some symptoms of PPPD including dizziness, instability, poor visual spatial perception, and the destruction of the brain functional connectivity might be related with the carotid atherosclerosis (CAS), possibly via the hemodynamic changes in microcirculation, while the details of underlying mechanisms are still unknown [19–21].

Therefore, the pathology of PPPD might be associated with the changes of brain structure and hemodynamics.

These observable changes might be potential risk factors for the development of PPPD. As far as we know, there is a lack of research on the relationship between PPPD and the factors above, which deserves further investigation.

By comparing the clinic-radiological characteristics of patients with PPPD with those of healthy controls, this study aims to explore the potential risk factors of PPPD patients, which could provide reference for evidence-based diagnosis and early intervention of PPPD.

Materials and methods

General information

This study was approved by the Ethics Committee of Zhoushan Hospital. Due to the retrospective nature of this study, the requirement of informed consent was waived. A total of 80 patients with PPPD treated in Zhoushan Hospital from March 2018 to February 2021 were selected as the case group. Inclusion criteria were: 1. patients who met the diagnostic criteria of PPPD according to the International Classification of Vestibular Diseases (ICVD) and were diagnosed with PPPD by two experienced chief neurologists in our department who arrived at a consistent conclusion of the disease; 2. no contraindication between MRI and CTA examinations. Exclusion criteria were: 1. with vestibular diseases such as vestibular neuritis, vestibular migraine, Meniere's disease, BPPV, landing syndrome, etc.; 2. complicated by heart, kidney, liver, blood, autoimmune diseases, malignant tumors, autonomic nervous dysfunction, anxiety, depression and other chronic diseases; 3. complicated by cerebrovascular diseases, neurodegenerative diseases or other diseases that may affect the structure and function of the brain; 4. the clinical data were incomplete. In addition, 81 apparently healthy people were selected as the control group. There was no significant difference in sex, age, smoking, drinking and other basic conditions between the two groups (Table 1).

Collection of clinico-radiological data

Medical history and blood test

Patient-specific clinical data were collected from both groups: conditions of hypertension, diabetes, smoking and drinking history. Venous blood samples were collected on the second day after admission. A full set of blood lipids were detected by LX-20 (Beckman Coulter, Inc., USA) biochemical instrument. The coagulation function was detected by Sysmex CN-6000 automated coagulation analyser (Sysmex Corporation, Kobe, Japan), and vitamin B12 and folic acid were detected by DXI-800 automatic microparticle chemiluminescence immunoanalyzer (Beckman Coulter, Inc., USA). The reagents used were all provided by the equipment manufacturers. All steps were carried out strictly according to the operating instructions, and the testing process was strictly controlled. The blood test results included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fibrinogen (FIB), vitamin B12 (VB12), folic acid (FOL), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density

Table 1 Baseline data characteristics of the two groups of subjects $(\bar{x} \pm s)$

Variables	Study group ($n=80$)	Control group ($n=81$)	$t/\chi^2/Z$ value	p value
Gender Male [case (%)]	32 (40.0)	36 (44.4)	0.326	0.568
Age	64.78 ± 10.58	61.27 ± 9.44	1.827	0.070
Smoking [cases (%)]	15 (18.8)	12 (14.8)	0.447	0.504
Drinking [example (%)]	11 (13.8)	12 (14.8)	0.037	0.847
Hypertension [cases (%)]	51 (63.8)	17 (21.0)	30.167	0.000
Diabetes [cases (%)]	21 (26.2)	7 (9.0)	8.686	0.003
TG [M (P25, P75), mmol/L]	1.15 (0.82,1.46)	1.07 (0.81,1.50)	−0.972	0.331
TC [M (P25, P75), mmol/L]	4.02 (3.45,5.05)	4.42 (3.54,4.89)	−0.257	0.797
LDL-C (mmol/L)	2.41 ± 0.83	2.58 ± 0.84	−1.218	0.225
HDL-C [M (P25, P75), mmol/L]	1.14 (1.03,1.35)	1.10 (0.96,1.33)	−1.239	0.215
FIB [M (P25, P75), g/L]	3.54 (3.21,4.16)	3.54 (3.10,3.72)	−1.964	0.049
FOL [M (P25, P75), nmol/l]	18.65 (12.76,26.60)	17.97 (11.49,27.11)	−0.431	0.666
VB12 [M (P25, P75), pmol/L]	294.0 (198.7,392.3)	333.0 (241.5,458.0)	−1.944	0.052
CAS [example (%)]	58 (72.5)	27 (33.3)	24.774	0.000
WMHs [example (%)]	32 (40.0)	5 (6.0)	26.020	0.000
LI [example (%)]	48 (60.0)	17 (21.0)	25.446	0.000

lipoprotein cholesterol (LDL-C), fibrinogen (FIB), vitamin B12 (VB12), and folate (FOL) level.

Radiological tests

Carotid artery CTA was performed with Siemens 64-row spiral CT angiography system (Siemens, Germany). Skull MRI scan was performed with 1.5 T MRI system (Siemens, Germany). On the CTA axial images of carotid arteries, CAS was considered if the plain scan indicated calcification in the carotid wall (hard plaque) or the enhancement scan indicated low-density filling defects (soft plaque). As to the MRI images, WMHs were considered present if hyperintense existed on T2-weighted and fluid attenuated inversion recovery (FLAIR) images. LI was considered present if T1-weighted signals were low, T2-weighted and FLAIR signals were high, and the diameter of abnormal signal was less than 15 mm. The imaging data were obtained and first analyzed by an Associate Radiologist-in-Chief with more than 10 years of experience in interpreting CT and MRI images. Another neuroradiologist with 20 years of experience in interpreting carotid CT and brain MRI images then reviewed the results and finalized the report. The analysis results were finally confirmed by our Radiologist-in-Chief with more than 20 years of experience. The radiologists were blinded to participant groups, i.e., patients vs. controls.

Summary of clinico-radiological characteristics

(1) Hypertension, diabetes, smoking, drinking; (2) venous blood test indicators: TC, TG, HDL-C, LDL-C, FIB, VB12, FOL; (3) CAS, WMHs, and LI.

Statistical analysis

The data were analyzed using SPSS 22.0 software (IBM, USA). The quantitative data with normal distribution were expressed as mean ± standard deviation, with independent sample *t*-test used for inter-group comparison. The quantitative data of skew distribution were expressed by M (P25, P75), where the comparison between groups was carried out using nonparametric test. The count data were expressed by [*n* (%)], and χ^2 test was used for the comparison. In the blood test, the proportion of subjects with testing result outside the laboratory normal range was compared between two groups using χ^2 test. Binary Logistic regression analysis was used to analyze the potential risk factors of patients with PPPD. Significant difference was defined as $p < 0.05$. The analysis results were presented by a four-grid table, and the consistency between regression analysis model and clinical diagnosis was evaluated using Cohen's Kappa.

Results

Radiological observation

On CTA images, we observed that CAS was more prevalent in the PPPD group compared with the control group. Patients in the PPPD group often had multiple soft and hard plaques with vascular wall thickening and lumen stenosis, as shown in Figs. 1 and 2.

WMHs were also more prevalent in the PPPD group. On the MRI images, most of the WMHs were mainly around the ventricle with unclear boundaries, as shown in Figs. 3 and 4.

The PPPD group also had a higher ratio of LI, and LI was mainly multiple, as shown in Figs. 5, 6, and 7. In addition, we found that many patients with PPPD showed two or more radiological characteristics (CAS, WMHs and LI)

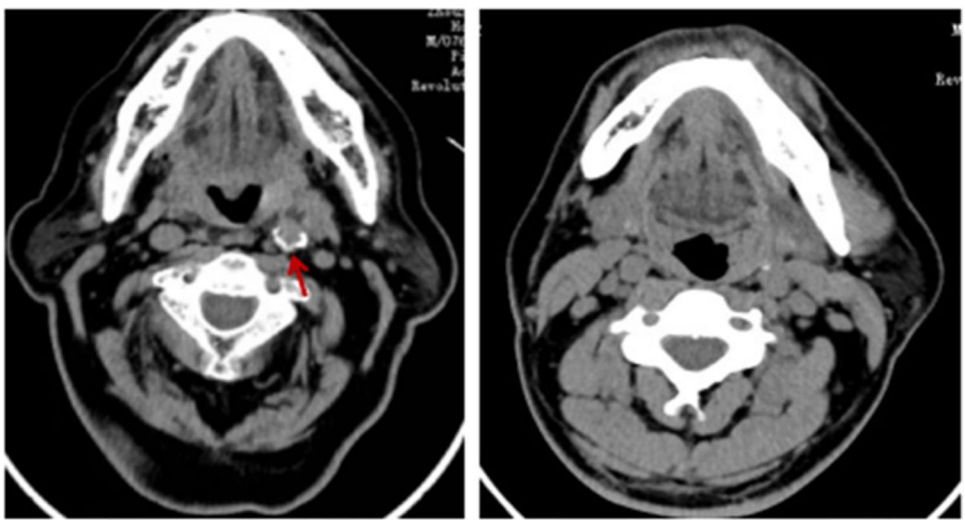

Fig. 1 Axial CTA images of the carotid artery: the initial wall of the left internal carotid artery is thickened with a hard plaque (marked by red arrow, left); image at a similar level from a subject in the control group (right)

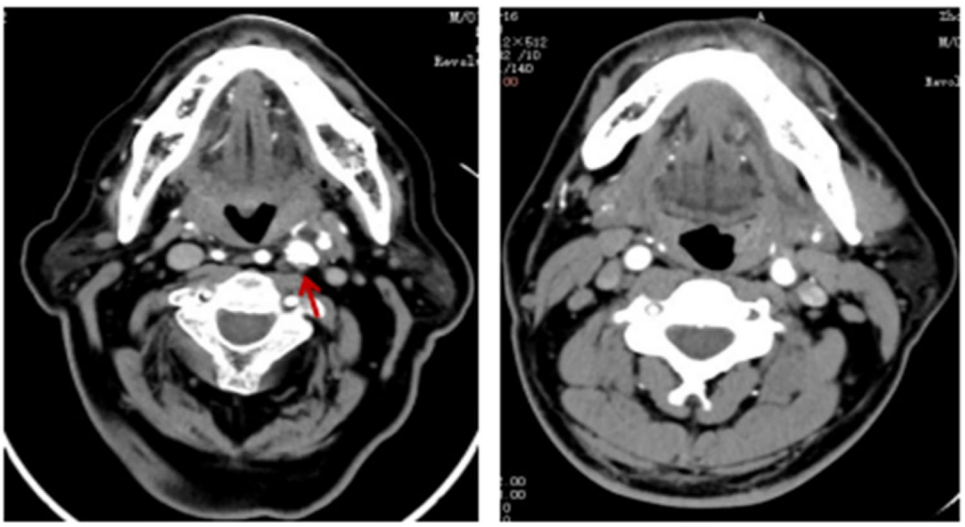

Fig. 2 Axial-enhanced CTA images of the carotid artery: a lateral soft plaque (marked by red arrow) locates at the beginning of the left internal carotid artery (left); image at a similar level from a subject in the control group (right)

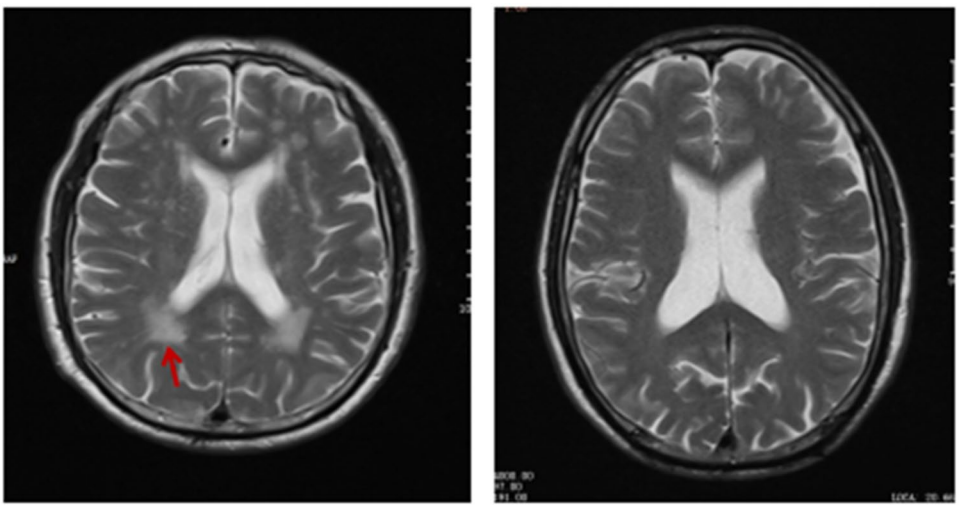

Fig. 3 Axial T2-weighted brain MRI images: numerous white matter hyperintensities (WMHs) (marked by red arrow, left); image at a similar level from a subject in the control group (right)

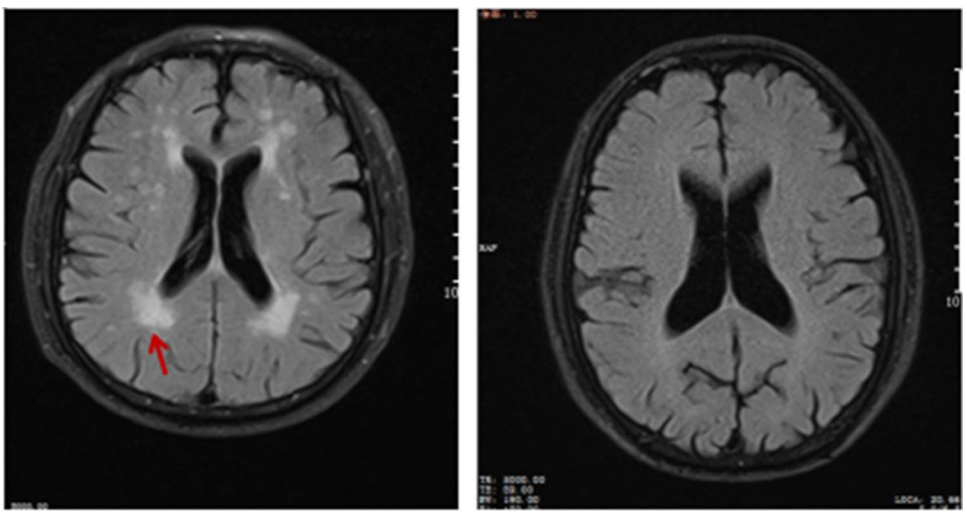

Fig. 4 Axial FLAIR brain MRI images: extensive WMHs predominating in periventricular region (marked by red arrow, left); image at a similar level from a subject in the control group (right)

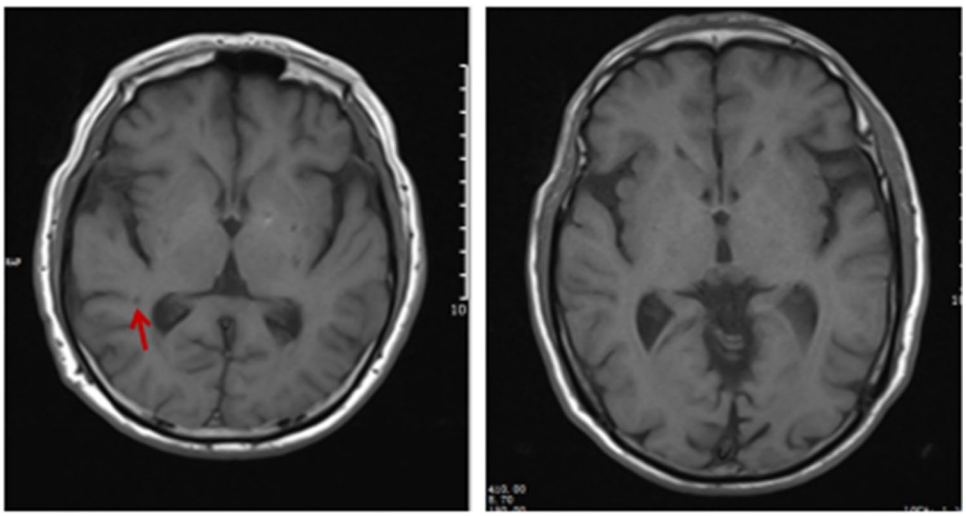

Fig. 5 T1-weighted brain MRI images: isocortical hyposignal (marked by red arrow, left); image at a similar level from a subject in the control group (right)

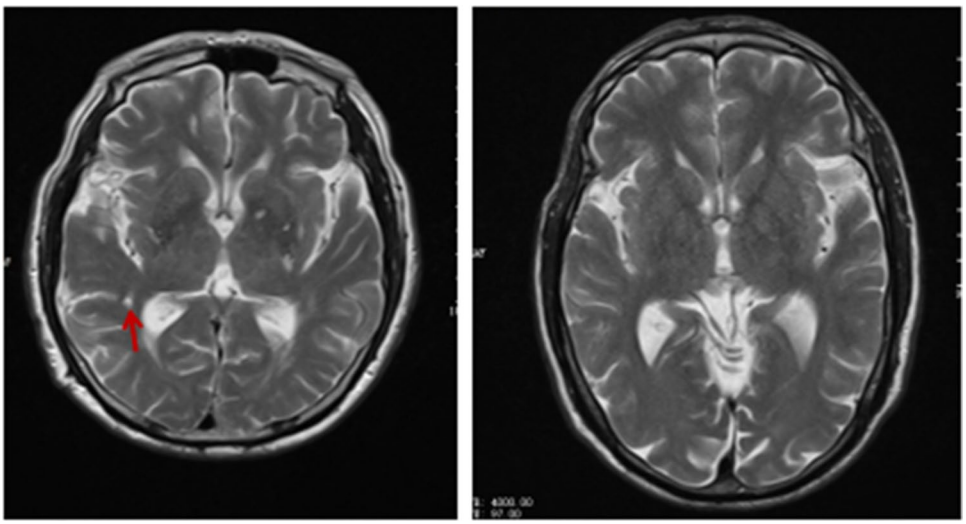

Fig. 6 T2-weighted MRI images: hyperintensity (marked by red arrow, left); image at a similar level from a subject in the control group (right)

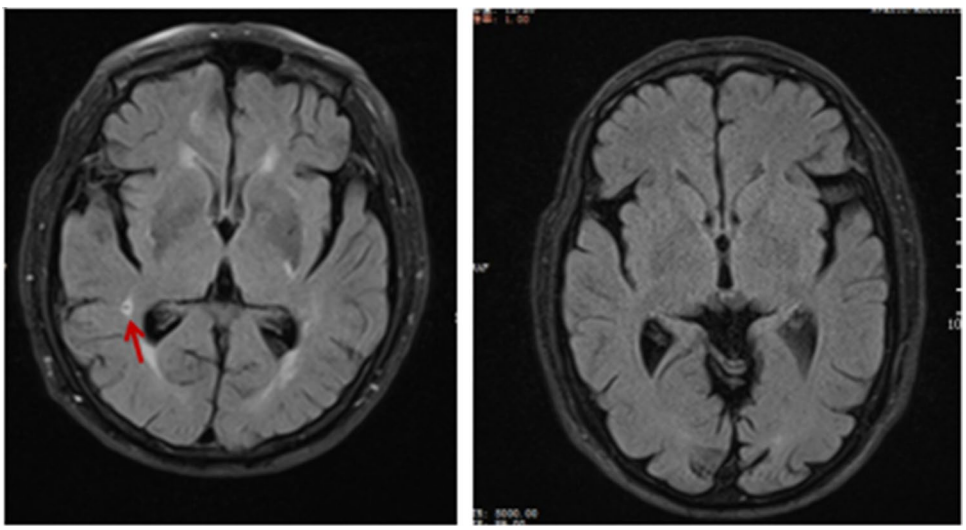

Fig. 7 Axial fluid attenuated inversion recovery (FLAIR) brain MRI images: hyperintensities (marked by red arrow, left); image at a similar level from a subject in the control group (right)

Table 2 Potential risk factors for PPPD

Variables	*B*	Wald	*p* value	OR	95% CI
Hypertension	1.534	14.817	< 0.001	4.639	2.124–10.132
CAS	0.840	3.996	0.046	2.315	1.017–5.273
WMHs	1.223	4.327	0.038	3.397	1.073–10,751
LI	0.903	4.142	0.042	2.466	1.034–5.881

The accuracy of binary logistic multivariate regressor was 74.5%. See Table 3. Cohen's Kappa value is 0.49

Table 3 Classification of PPPD and non-PPPD patients

Observed	Predicted		
	Non-PPPD	PPPD	Percentage correct
Non-PPPD	64	17	79.0
PPPD	24	56	70.0
Overall percentage			74.5

The cutoff value is 0.500

on CT and MRI images (e.g., the left subfigures of Figs. 3, 4, 5, 6, and 7 are from the same PPPD patient who had both WMHs and LI). Out of the total 80 patients with PPPD, 45 patients (56.3%) had different radiological characteristics, among which 21 patients had all the three characteristics simultaneously.

Characteristics of baseline data of two groups

The results of univariate analysis showed that compared with the control group, the study group had higher rates of hypertension and diabetes, higher FIB, lower VB12, and higher rates of CAS, WMHs, and LI. There was no significant difference in sex, age, smoking, drinking, TG, TC, LDL-C, HDL-C, or FOL between the two groups (see Table 1).

The proportion of subjects with FIB exceeding the laboratory normal range was significantly higher ($p < 0.05$) in the study group (32.50%; 26/80) than in the control group (13.58%; 11/81). There was no significant difference between two groups in TC, TG, LDL-C, HDL-C, FOL, or VB12 regarding the proportion of subjects that are outside the laboratory normal range ($p > 0.05$ for all).

Potential risk factors for PPPD

With the statistically significant variables in univariate analysis as independent variables, binary Logistic regression analysis was conducted. The results showed that hypertension, CAS, WMHs and LI were potential risk factors for PPPD, as shown in Table 2. The binary Logistic regression model fitted well with the original data ($p = 0.710$ in Hosmer–Lemeshow test).

Discussion

Pathology of PPPD: an unsolved problem

PPPD is a highly heterogeneous disease with a variety of different triggering factors and comorbidities and its pathological mechanism is complex [22]. Trinidade and Goebel comprehensively analyzed a number of selected case–control studies, suggesting that PPPD is likely to be a maladaptive state for various injuries [23]. Powell et al. noted that PPPD is a complex neurological disease that includes a wide range of perceptual factors and may indicate some brain predisposition to generalized cross-channel sensory overload [24]. In addition, some genetic polymorphisms and molecular mechanisms may be associated with the susceptibility of PPPD, while some genotypes showed potential protective effect on PPPD [25]. Patients with PPPD and controls differ in metabolic parameters and personality traits. The anxiety-related factors play an important role in the development of PPPD. Neuroticism, state anxiety, body vigilance and aberrant illness perceptions have been proposed as the risk factors and contributors of PPPD [26–28]. PPPD affects more women who are postmenopausal with high association with metabolic disorder and migraine [29]. Overall, the pathophysiology of PPPD remains relatively poorly understood. The key pathophysiological mechanisms of PPPD, as well as the related biomarkers derived from neuroimaging and other observational data, are important issues that need to be addressed.

As far as we know, the associations between PPPD and potential clinic-radiological factors have not been comprehensively evaluated. In this study, we found that hypertension, CAS, WMHs and LI showed statistically significant differences between the PPPD and control groups. We hypothesized that these factors are associated with PPPD and might be potential risk factors of PPPD. Here, we explored the possible pathophysiological mechanisms underlying these associations.

Hypertension

We found the most significant association between hypertension and PPPD ($p < 0.001$). We speculate that there might be some pathological interactions between PPPD and hypertension. It is also possible that there may be comorbidity with PPPD in some hypertensive patients, or it may be a confounding signal of some comorbidity, such as anxiety or depression.

On the one hand, PPPD may influence the development of hypertension via different mechanisms such as long-term stress induced by dizziness and the changes in vestibular-autonomic interactions. First, the long-term stress induced by persistent dizziness (not only physical but also psychological) could lead to the sustained increase in sympathetic activity, inducing an increase in blood pressure [30]. Second, PPPD was often secondary to a peripheral or central vestibular disorder. When suffering from the trigger events of dizziness, people would adopt the corresponding adaptations, such as high-risk postural control strategy [31]. The head movements and changes in posture that are detected by the peripheral vestibular system exert widespread effects on homeostatic regulatory physiology, which may adjust the change of vestibular-autonomic interactions and send direct projections to caudal brainstem sites involved in the central regulation of blood pressure [32]. The PPPD patients may persistently keep a high-risk postural control strategy with an excessive vigilance about balance sensations, which may lead to the maladaptation and high risk of hypertension [31].

On the other hand, hypertension may increase the risk of PPPD through cerebral autoregulatory dysfunction and decreased gray matter volume in the brain. Autoregulation of regional cerebral blood flow (rCBF) is a highly regulated mechanism that largely offsets the fluctuations in systemic blood pressure. Hypertension can induce cerebral autoregulatory dysfunction, which is associated with reduced rCBF in many brain regions especially in frontal and subcortical areas [33–36]. Na et al. examined rCBF in 25 patients with PPPD and 25 healthy controls using SPECT and found that rCBF was significantly reduced in the insula and frontal lobe regions of the PPPD patients, predominantly in the left posterior insula, bilateral superior frontal gyrus, right inferior frontal gyrus, right precentral gyrus, and left medial orbital gyrus [14]. Hypertension is associated with decreased gray matter, particularly in the prefrontal, medial frontal, inferior temporal and cerebellar areas [36]. Wurthmann et al. compared the gray matter volume between 42 patients with PPPD and 42 matched controls [6]. They found that the PPPD patients showed gray matter volume decrease in the temporal cortex, cingulate cortex, precentral gyrus, hippocampus, dorsolateral prefrontal cortex, caudate nucleus and the cerebellum, which was correlated with the duration of PPPD. Therefore, we hypothesized that hypertension might influence the development of PPPD by reducing blood flow and causing gray matter volume decrease in PPPD-related brain regions.

However, hypertension is also associated with some comorbidities of PPPD such as depression. In the presence of hypertension, depression is associated with lower volumes of the anterior and middle cingulate cortex which could also be PPPD-related areas [37]. In a diagnostic validation study on CSD (a precursor of PPPD), 45% of patients with CSD had clinically significant depressive symptoms [38, 39]. Therefore, hypertension might be a confounding signal of PPPD.

CAS

The blood supply territory of internal carotid artery includes frontal lobe, temporal lobe, parietal lobe and basal ganglia in the first 3/5 parts of the cerebral hemisphere [40]. CAS could directly reduce CBF and might damage the microcirculatory hemodynamics in these areas. It was observed that, in patients with PPPD, the CBF of the insula and frontal lobe was obviously reduced [14]. We speculate that CAS may promote the development of PPPD by damaging cerebral microcirculation hemodynamics (especially in the frontal lobe).

As aforementioned, with the decrease of perfusion and alteration of morphology in cortical areas, the decrease in the volume of brain regions (mainly gray matter) involved in multisensory vestibular processing is a significant event in the development of PPPD [6, 10]. CAS is independently associated with CSVD and the reduction in gray matter volume especially in cortical areas [41, 42]. This might be due to the high metabolic requirements of gray matter and its susceptibility to factors that affect the regulation of CBF [42]. Therefore, we hypothesized that CAS might induce the reduction of gray matter volume in PPPD-related areas via hemodynamic and metabolic mechanisms. Although our patient and control groups are age-matched, it must be pointed out that, considering the prevalence of CAS in aged patients, the relationship between CAS and PPPD might be due to the comorbidities in the aging process.

WMHs

The white matter lesions that cause dizziness could be cortical–subcortical disconnection syndrome secondary to the destruction of white matter tracts involved in gait and balance control [15, 43]. Pollak et al. found that patients with VV of more than 3 months, which can be a precursor of PPPD, had more unspecific white matter brain changes than controls [44]. This might be due to the multiple white matter changes in subcortical areas that are responsible for feedback inhibition, which could leads to an exaggerated vestibular response to visual stimuli in form of VV [44]. Therefore, a possible link between WHMs and PPPD is that multiple white matter lesions might contribute to the occurrence of VV in the development of PPPD.

However, VV is not a specific symptom of PPPD. The patients with peripheral and central vestibular diseases who do not meet the diagnostic criteria of PPPD may also have VV. In addition, WMHs is nonspecific and may be related to other diseases which can be confounding factors

of PPPD, such as migraine and hypertension [45, 46]. At present, there is no conclusive evidence on the relationship between WMHs and PPPD [31]. The pathological association between PPPD, VV, and WMHs deserves more in-depth investigation.

LI

In the MRI head scan, we observed LI among PPPD patients in basal ganglia region (including caudate nucleus), thalamus, internal capsule, corona radiate, brainstem, and partially located in temporal lobe, frontal lobe, cerebellum and insula. These areas might be associated with the development of PPPD. As aforementioned, in PPPD patients, the rCBF decreases in insula and frontal lobe, with reduce of brain volume in the areas involved in multisensory vestibule treatment [6, 14].

The pathological association between LI and PPPD is unclear. LI is related to the decrease in brain perfusion [47], which may induce hemodynamic changes in PPPD-related areas. In addition, the progression of LI is associated with a greater decrease of total brain and cortical gray matter volumes [48], which may be associated with the structural changes in PPPD-related areas. We hypothesize that LI may reflect the PPPD-related hemodynamic and structural changes of the brain. Meanwhile, it is noteworthy that the occurrence of LI is strongly associated with age [49]. Thus, as hypertension and CAS, LI may also be a confounding signal of PPPD due to the comorbidities in the aging process.

Possible interaction among different potential risk factors

From the discussion above, we hypothesize that hypertension, CAS, LI and WMHs might be associated with hemodynamic and microstructural changes in the PPPD-related brain areas. On one hand, hypertension, CAS, WMHs, and LI may have independent effects on PPPD by specific chronic mechanisms. On the other hand, these potential risk factors of PPPD (hypertension, CAS, WMHs and LI) may be interactive during some pathological processes, including blood–brain barrier dysfunction and endothelial dysfunction during the occurrence and development of PPPD [50–52]. It was observed that CAS was positively related to the occurrence and severity of WMHs [42]. The possible interaction among different potential risk factors in the development of PPPD deserves further investigation.

Significance for clinical study and application

The results of this study may be helpful to the early intervention and treatment of patients with PPPD. In clinical practice, these potential risk factors could be formulated into a risk profile to improve the early detection of PPPD in high-risk groups. In addition, based on the risk assessment, the evidence-based early intervention and supplementary treatment strategies including vestibular rehabilitation, cognitive behavioral therapy, non-invasive vagus nerve stimulation, and lifestyle improvement may delay the course of PPPD development and reduce the burdens for the patients and their families [10].

Limitations and future directions

There are some limitations in this preliminary study. First, in this pilot study, the sample size is relatively small with a lack of long-term follow-up. The potential patient selection bias cannot rule out the possibility of inaccurate or incomplete case identification. Second, this is a cross-sectional study which was not aimed for disclosing the causal relationship between PPPD and the potential risk factors. It is difficult to infer whether these factors are the precursors, results, or just confounding signals of PPPD. We must admit that we could not determine the specific causes of PPPD in some cases due to the lack of complete medical history about vestibular/non-vestibular trigger events. In addition, existing studies on pathophysiologic mechanisms of cerebrovascular disease, in general, and research involving patients with other causes of chronic dizziness may not be applicable to PPPD. Finally, anxiety and/or depression is another significant confounder in this patient population, which was not included in this study. In the future, in-depth investigations in pathology and prospective multicenter studies with more patients can be performed to validate our findings and further elucidate the pathophysiological mechanism of PPPD.

Conclusions

Hypertension, CAS, WMHs, and LI are associated with PPPD, which may be potential risk factors for its development through various pathological mechanisms.

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Data availability statement The data are available from the corresponding author.

Declarations

Conflicts of interest Corresponding authors declare on behalf of all the authors that there is no conflict of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Zhoushan Hospital (Date 27 May 2021/ No.20210013).

Informed consent The clinical and radiological data were retrospectively retrieved from existing datasets. The data were anonymized before analysis. Informed consent form was waived by local ethics committee.

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