The Relationship Between Paroxysmal Vertigoes and Right-To-Left Shunt: A Large Observational Study

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Research article

Keywords: Benign recurrent vertigo, Right-to-left shunt, Paroxysmal vertigoes

Posted Date: November 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1087535/v1>

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Abstract

Background

The association between paroxysmal vertigo and right-to-left shunt (RLS) is rarely reported. We investigated the incidence and correlation of RLS in patients with different paroxysmal vertigo diseases.

Methods

This large observational study included patients with paroxysmal vertigo from seven different hospitals in China from 2017 to 2021 (NCT04939922). Migraine patients within the same period were included for comparison. Demographic data and medical history were collected, contrast transthoracic echocardiography (cTTE) was performed, and the clinical features, dizziness handicap inventory, and incidence of RLS in each group were recorded.

Results

This study used a consecutive sampling of 4536 patients from seven centres, and a total of 2751 patients were enrolled. The proportion of RLS in patients with migraine with aura (MA), migraine without aura (MoA), vestibular migraine (VM) with headache, VM without headache, and benign recurrent vertigo (BRV) was significantly higher than that in patients with benign paroxysmal positional vertigo (BPPV), Meniere's disease (MD), and vestibular paroxysmia (VP) ($P < 0.05$). There was no statistical difference between the frequency of RLS in patients with BRV and those with MoA ($P = 0.931$), MA ($P = 0.997$), VM with migrainous headache ($P = 0.787$), and VM without migrainous headache ($P = 0.754$). There was a positive correlation between the RLS grade and the dizziness handicap inventory scores of VM and BRV patients ($P < 0.01$).

Conclusions

RLS was significantly associated with BRV and VM. RLS may be involved in the pathogeneses of BRV and VM and may serve as a reference index for the differential diagnosis of central and peripheral vertigo.

Trial registration:

CHRS, NCT04939922, registered 14 June 2021- retrospectively registered, <https://register.clinicaltrials.gov>

Background

Paroxysmal vertigo resulting from different diseases has distinct clinical symptoms and signs. However, significant overlaps exist in the clinical symptoms of different vestibular diseases, such as vestibular migraine (VM), which may have manifestations similar to Meniere's Disease (MD) or benign paroxysmal positional vertigo (BPPV) [1]. Furthermore, some VM patients may have no headache, while MD may be accompanied by migraine, photophobia, phonophobia, and other symptoms. This increases the difficulty in distinguishing these diseases from each other [2, 3]. Benign recurrent vertigo (BRV) was first described by Slater and is defined as a group of clinical syndromes with recurrent vertigo without nervous system and cochlear symptoms [4]. At present, there are no recognised diagnostic criteria for paroxysmal vertigo; thus, diagnosis by exclusion is often used [5]. Follow-up studies have shown that BRV is closely associated with migraine as 51–87% of BRV cases are comorbid with migraine [6, 7]. This proportion of BRV meets the description of definite VM or possible VM. BRV and VM differ in terms of the definition and diagnostic criteria. BRV can have no headache and migraine, while VM requires at least a history of migraine or migraine-like symptoms [8]. Given that BRV and VM have no specific physical or auxiliary examination findings, clinical diagnosis is often a challenge. Therefore, identifying anatomic features related to certain forms of paroxysmal vertigo that may aid in establishing diagnosis may be helpful. This may also help in determining the pathogenesis of diseases with similar clinical symptoms.

Many studies have found that the incidence of patent foramen ovale (PFO) in migraine patients is significantly higher than that in normal people [9, 10]. The relationship between PFO and migraine has been studied and is a major concern [11]. Vestibular migraine is considered to be related to vestibular symptoms caused by migraine mechanisms, and its pathogenesis may be related to ion channel defects, enhanced cortical excitability, and central sensitisation, which are caused by genetic susceptibility [12, 13]. PFO is the most common cause of right-to-left shunt (RLS). RLS refers to the potentially abnormal channels between the left and right atrium and ventricle, or systemic circulation and

pulmonary circulation. Based on its location, RLS can be categorised as intracardiac shunt and extracardiac shunt. The former includes PFO, while the latter includes pulmonary arteriovenous malformation and patent ductus arteriosus, among others. Current research rarely focuses on the relationship between RLS and paroxysmal vertigo. Diagnostic tests used for detecting RLS mainly include contrast transcranial Doppler, contrast transthoracic echocardiography (cTTE), and contrast transoesophageal echocardiography. Given that cTTE is easy to operate and has high sensitivity and specificity [14], we chose this method to investigate the incidence of paroxysmal vertigo (VM with headache, VM without headache, BRV, MD, BPPV, and VP) in adults with RLS compared to migraine patients, thus evaluating the correlation between RLS and different types of paroxysmal vertigo diseases.

Methods

Study design and patient population

The patients included in the study were mainly from the headache and vertigo clinics of seven different hospitals in China from July 2017 to July 2021 (ClinicalTrial.gov ID: NCT04939922). The study used a consecutive sampling of patients (n=4536) with migraine or paroxysmal vertigo aged over 18 years. Patients were screened for VM, pure BRV, definite MD (dMD), BPPV, vestibular paroxysmia (VP), migraine with aura (MA), and migraine without aura (MoA) and, if positive, were included in the study. Patients who were diagnosed with probable migraine, psychiatric vestibular disorder, probable MD, probable VP, functional vestibular disorder, vertebral basilar transient ischemic attack (TIA), migraine with brain stem aura, episodic ataxia, cerebellopontine angle tumour, vestibular epilepsy, superior canal dehiscence/perilymphatic fistula, and other paroxysmal vertigo patients who did not meet the diagnostic criteria of all other vertigo diseases were excluded. A flowchart of patient inclusion and exclusion is depicted in Figure 1.

The inclusion criteria for VM patients met the definite and probable diagnostic criteria for VM established by the International Barany Society and the International Headache Society [8].

The inclusion criteria for BRV in this study were based on the exclusive diagnostic method proposed in the literature [15], and a personal history of no migraine headache, visual aura, photophobia, and phonophobia (to distinguish and exclude definite VM and probable VM), which we defined as pure BRV here (Table 1).

Table 1
Inclusion criteria for pure benign recurrent vertigo

More than 2 attacks of spontaneous rotational vertigo that does not occur during the head movements or positional changes
No associated migrainous headaches or auditory symptoms during or between the attacks
No associated photophobia and phonophobia
No associated visual aura
No associated focal neurologic symptom during the attack or afterward suggesting episodic ataxia, transient ischemic attack, or vestibular epilepsy
No evidence of peripheral vestibulopathy on head-impulse, caloric, and rotatory tests
No asymmetric hearing impairment documented in pure-tone audiometry
No lesions on brain MRIs responsible for the benign recurrent vertigo
No history of disorders that may explain the recurrent vertigo
Not better accounted for by another vestibular disorder, including compensated vestibular neuritis, vestibular migraine, Meniere’s disease, benign paroxysmal positional vertigo, and vestibular paroxysmia

The selection criteria for dMD, BPPV, and VP patients were in accordance with the diagnostic criteria established by the Barany Association, and the selection criteria for migraines were consistent with the diagnostic criteria of The International Classification of Headache Disorders, 3rd edition [16–19]. As RLS is strongly related to migraines with auras, migraines were further divided into MA and MoA, and VM was further divided into VM with and without headache. All VP patients selected in this study were responsive to carbamazepine treatment. All patients were diagnosed by two experienced neurologists to reduce bias.

The patients included underwent cTTE and were assigned into eight groups based on diagnosis: VM with migrainous headache, VM without migrainous headache, pure BRV, dMD, BPPV, VP, MA, and MoA. This study was approved by the ethics committees of the participating centres, and all patients signed informed consent forms.

Contrast transthoracic echocardiography inspection method

While the patients were in the supine position, venous access was established by conventional elbow venipuncture, and a three-way tube was connected to the puncture site. The contrast medium was formulated after 8 mL saline, 1 mL venous blood, and 1 mL air was fully injected and concussed through the tee tube. The contrast was quickly injected while the patient was at rest and while doing Valsalva manoeuvre. The apical four-chamber section was selected, and the number of microbubble signals in the left cardiac system was observed within 10 cardiac cycles after the right cardiac system was filled with microbubble signals. RLS of the heart was considered when there was more than one microbubble in the left cardiac cavity.

The RLS was graded quantitatively according to the number of microbubbles in the left ventricular cavity after the Valsalva manoeuvre. The grading standard are as follows: grade 0 - no microbubbles in the left cardiac cavity and no RLS; grade I - 1 to 10 microbubbles/frame were seen in the left ventricular cavity and a small amount of RLS; grade II - 10 to 30 microbubbles/frame were seen in the left cardiac cavity and a medium amount of RLS; grade III - more than 30 microbubbles/frame were seen in the left ventricular cavity, or the left ventricular cavity was almost full of microbubbles [20].

RLS from PFO was considered when microbubbles were found within 3–5 cardiac cycles, while RLS from pulmonary arteriovenous malformations was considered when microbubbles were found in more than five cardiac cycles during the cTTE examination [21].

Dizziness Handicap Inventory

The quality of life measure for vestibular disorders was assessed using the 25-item Dizziness Handicap Inventory (DHI), which has three response categories: the functional, emotional, and physical aspects of life [22]. The total score ranges from 0 (not handicapped) to 100 (severely handicapped).

Statistical analysis

Data measurements assumed a normal distribution and are expressed as $\bar{x} \pm s$. We used the χ^2 test and t-test (or Mann–Whitney U-test) to compare categorical and continuous variables. Differences between more than two groups were analysed using one-way ANOVA. Spearman's correlation coefficient was used to analyse the correlation between the DHI and RLS grades. The level of statistical significance was set at $P < 0.05$. All analyses were performed using the SPSS version 20.

Results

Patient demographic and clinical characteristics at baseline

Within the time frame, a total of 2751 patients completed cTTE at the outpatient departments of seven participating centres. The mean age was 43.16 ± 14.58 years, and 65.18% were female. The demographics and clinical characteristics of the patients are summarised in Table 2.

Table 2
Demographic and clinical characteristics of patients at baseline

	MoA without vertigo (n=1399)	MA without vertigo (n= 216)	VM with migrainous headache (n=410)	VM without migrainous headache (n=119)	MD (n=148)	BPPV (n=331)	VP (n=57)	BRV (n=71)
Sex (female, %)	73.27	75.46	76.83	72.27	57.43	64.65	59.65	71.83
Age (mean±SD)	39.85±15.47	37.7±15.41	42.67±12.56	36.67±14.99	52.35±7.28	56.13±10.48	53.74±6.15	50.7±18.93
Duration of attacks								
< 1 min			45	17	0	331	47	7
< 5 min	NA	NA	94	15	0	0	10	13
< 1 h			128	29	85	0	0	26
< 24 h			118	41	63	0	0	18
> 24 h			25	17	0	0	0	7
Migrainous headache	1399	216	410	0	0	0	0	0
Aura	0	216	53	16	0	0	0	0
Photophobia	992	156	386	107	0	2	1	3
Phonophobia	984	167	389	110	1	0	0	1
Photophobia & phonophobia	961	144	372	101	0	0	0	0
Abbreviations: BPPV, benign paroxysmal positional vertigo; BRV, benign recurrent vertigo; MA, migraine with aura; MD, Meniere's disease; MoA, migraine without aura; NA, not available; VM, vestibular migraine; SD, standard deviation; VP, vestibular paroxysmia.								

Right-to-left shunt in patients from different groups

A total of 61.98% of RLS-positive patients were detected by cTTE after the Valsalva manoeuvre. The proportion of RLS in patients with BRV and VM with and without migrainous headache was significantly higher than that in patients with MD, BPPV, and VP ($P<0.05$). There was no statistical difference between the frequency of RLS in patients with BRV and those with MoA ($P=0.931$), MA ($P=0.997$), VM with migrainous headache ($P=0.787$), and VM without migrainous headache ($P=0.754$) (Table 3 and Figure 2).

Table 3
Right-to-left shunt and Dizziness Handicap Inventory in patients from different groups

	MoA without vertigo (n=1399)	MA without vertigo (n= 216)	VM with migrainous headache (n=410)	VM without migrainous headache (n=119)	MD (n=148)	BPPV (n=331)	VP (n=57)	BRV (n=71)
RLS (%)	65.33	81.01	77.07	76.47	27.03	25.38	26.31	73.24
PFO	828	153	292	79	35	73	14	46
PAVM	57	12	19	9	2	8	1	4
PFO & PAVM	29	10	5	3	3	3	0	2
Grading of RLS								
0	485	41	94	28	108	247	42	19
I	263	33	68	17	17	40	7	12
II	257	54	106	34	14	30	3	18
III	394	88	142	40	9	14	5	22
DHI	NA	NA	46.33±10.61	47.46±9.40	51.26±9.48	47.37±13.42	50.69±6.87	46.87±10.37
Abbreviations: BPPV, benign paroxysmal positional vertigo; BRV, benign recurrent vertigo; DHI, Dizziness Handicap Inventory; MA, migraine with aura; MD, Meniere's disease; MoA, migraine without aura; PAVM, pulmonary arteriovenous malformation; PFO, patent foramen ovale; RLS, right-to-left shunt; VM, vestibular migraine; VP, vestibular paroxysmia.								

Right-to-left shunt in benign recurrent vertigo patients

The proportion of patients with RLS in seven patients with BRV lasting less than one minute was similar to those lasting for more than one minute (71.43% vs 73.44%). This was significantly higher than in VP (26.31%) and BPPV (25.38%). The proportion of RLS in BRV patients aged <50 years and those ages ≥50 years was similar (73.08% vs 73.68%), and the difference was not statistically significant (Figure 3).

Association between right-to-left shunt grade and dizziness handicap index scores

Based on the semi-quantitative classification of RLS, the DHI scores of grades 0, I, II, and III of patients from different groups are shown in Table 3. The RLS grade and DHI scores in patients with VM with ($r=0.361$, 95% CI 0.27–0.44), without headache ($r=0.528$, 95% CI 0.38–0.65) and BRV ($r=0.565$, 95% CI 0.38–0.71) are shown in Figures 4A–C, respectively. The DHI score and RLS grade of all patients with VM or BRV ($r=0.412$, 95% CI 0.34–0.48) are presented in Figure 4D. In VM and BRV patients, DHI scores increased with increasing RLS grade, and there was a positive correlation between them.

Discussion

VM is a separate disease entity with a genetic predisposition to recurrent dizziness or vertigo, with or without headache [23]. When presented with positional vertigo, VM and BPPV are difficult to distinguish. The difference lies in the atypical nystagmus of VM, which is usually not aligned with a single semicircular canal, while the nystagmus of BPPV induced by positional testing is synchronised with the symptoms and has a characteristic short duration, brief latency, and fatigability [2, 24]. VM and BRV may also show spontaneous vertigo, similar to MD. The auditory symptoms of VM and BRV are mild, whereas the hearing loss of MD patients is gradually aggravated with disease progression [16]. When the duration of spontaneous vertigo in VM or BRV is less than one minute, it can be similar to VP. VP is caused by vascular compression of the vestibular nerve, with attacks ranging from 30 times a day to several times a year, without headache. Carbamazepine is an effective treatment for VP [18]. However, the selected VM patients in this study were effectively treated with flunarizine, which increased the reliability of VM diagnosis. Since the subjects were all older than 18 years, the possibility of BPV in children was excluded.

Common paroxysmal vertigo can be categorised based on aetiology: central and peripheral aetiologies. The most common central causes are VM and transient ischemic attack, and the common peripheral causes are BPPV, MD, and VP. However, the classification of these four diseases does not cover all paroxysmal vertigo. Those with unknown causes of recurrent vertigo are classified as BRV, with a high incidence

in the clinic. The BRV selected in previous clinical studies did not rule out a history of migraine and migraine-related symptoms, so a considerable number of BRV may have met the diagnostic criteria for VM [6, 7]. To avoid confusion, the selected BRV in this study only showed paroxysmal vertigo, that is, pure BRV. The selected VM patients without headache could be differentiated from pure BRV by its migraine characteristics, such as photophobia, phonophobia, or visual aura. A recent study reported for the first time a group of patients with paroxysmal vertigo with interictal headshaking nystagmus (HSN) [15]. The authors believe central lesions lead to a prolonged time constant, strong HSN, and perverted nystagmus through activated and asymmetric central velocity storage mechanisms. Our results demonstrated that BRV had a significantly higher proportion of RLS than peripheral vertigo diseases such as MD, BPPV, and VP. Although there were no central symptoms of photophobia, phonophobia, or visual aura, we speculate that pure BRV may be central vertigo without these central symptoms and is worthy of further study and discussion.

There is a dose-effect relationship between PFO and migraine. Larger PFO, permanent PFO, and anatomical variation of PFO can aggravate RLS, which is associated with migraine attacks [11]. Meanwhile, PFO is more associated with MA than MoA. The correlation between RLS and migraines does not imply causality, and the mechanism between the two is not clear. The possible mechanism is that vasoactive substances and microemboli from the venous system directly enter systemic circulation without passing through the pulmonary circulation, causing transient hypoperfusion in the area supplied by the cerebral arteries or cortical spreading depression, activating the trigeminal neurovascular system, and causing migraine attacks [25, 26]. The initiating mechanism of VM is considered to be similar to migraine because RLS not only induces migraine but also causes vertigo by inducing plasma extravasation in the inner ear [27]. Microemboli or vasoactive substances may induce CSD and activate the caudal parabrachial nucleus, which receives both trigeminal receptors and vestibular nerve afferents, resulting in simultaneous vestibular symptoms and migraine symptoms [1, 28]. Therefore, we speculate that RLS may be involved in the pathogenesis of VM.

Many studies have found that BRV is highly correlated with migraine or VM and may have similar pathogenesis [6, 29, 30]. However, some studies have suggested otherwise [31]. Whether BRV is a separate entity is still controversial, but a considerable number of BRVs are free from inner ear dysfunction and migraine and therefore do not develop into MD and VM, suggesting that there may be different mechanisms in this aspect of BRV [7]. This study showed that the proportion of RLS in patients with BRV, VM, and migraine was significantly higher than those with peripheral vertigo disease, suggesting that RLS might play an important role in the pathogenesis of BRV, VM, and migraine. The current literature remains discordant as to whether a linkage exists between RLS grade and the degree of vertigo. We found that the DHI score increased with an increase in the RLS shunt, suggesting that RLS plays an important role in the degree of vertigo and quality of life of vestibular disorders. The proportions of RLS in patients with BRV and VM were similar to those of migraine, suggesting that the above-mentioned mechanisms may share some features in the pathogenesis of migraine. When the related mechanism of migraine only involves the vestibular system, it can manifest as pure BRV, whereas when the vestibular system and trigeminal neurovascular system are simultaneously involved, it can manifest as VM. When only the trigeminal neurovascular system is involved, the symptoms may include migraine, suggesting that BRV and VM may be subtypes or equivalents of migraine. VM and pure BRV can be unified in the migraine category. In this study, the RLS of patients with BPPV and VP was significantly lower than that of patients with migraine, suggesting that RLS was not involved in the pathogenesis of these peripheral vertigo diseases. RLS can play a role in the differential diagnosis of paroxysmal vertigo. In the future, for refractory VM and BRV patients, the evaluation of RLS and the intervention and treatment of RLS are worthy of further exploration.

Previous literature has predominantly defined the duration of BRV as more than 1 min or even more than 5 min, mainly distinguishing it from BPPV and VP, which are less than 1 min. There are few reports of a BRV of less than 1 min. A previous study found six cases of BRV with migraine that were less than 1 min, and only one case of BRV without migraine was less than 1 minute [6]. In clinical practice, there are truly spontaneous recurrent vertigoes lasting less than 1 min. These patients do not meet the diagnostic criteria for BPPV and VP, and they do not meet the diagnostic criteria for VM. The duration of BRV was not specifically limited in this study. The proportion of RLS between the patients with BRV lasting less and more than 1 minute was similar, and significantly higher than that of VP and BPPV. Thus, strictly defining the duration for diagnosis of BRV may be debatable, and the evaluation of RLS might help to provide a reference for BRV diagnosis.

Due to the low probability of migraine onset after 50 years of age, patients with headache-free BRV after the age of 50 have a very low probability of developing VM, while patients with BRV before the age of 50 still have the possibility of progressing to VM. Therefore, we regarded age 50 as the threshold for the intragroup (subgroup) analysis of BRV. The results showed that the proportion of RLS in patients with BRV before and after 50 years of age was not significantly different and was similar to that of migraine. This may be related to the fact that BRV rarely evolves into VM [32].

With the insight into VM and the gradual clarification of its concept, there is an overlap between the classical concepts of BRV and VM, leading to ambiguity in the concept of BRV; thus, its effective use in clinics is difficult. In this study, pure BRV was proposed for the first time, and it can be effectively distinguished from VM in the absence of migraine-related characteristics. Pure BRV can also be effectively

distinguished from peripheral vertigo, such as MD. Therefore, the concept of pure BRV is helpful for clinicians to further study the mechanism, clinical characteristics, and prognosis of the disease. The concept and classification of VM and BRV in the future are worthy of further discussion.

There are several limitations to our study. First, because TIA, persistent postural-perceptual dizziness, epileptic vertigo, and paroxysmal ataxia were excluded from the selection criteria of BRV in this study, these paroxysmal vertigoes were not compared with RLS. Second, BRV with HSN has been reported to originate from the central nervous system, and in this study, BRV was not subdivided according to whether it was associated with HSN.

Conclusions

In conclusion, this is a large multicentre study and the findings suggest that RLS differs in different types of paroxysmal vertigo. The incidence of RLS in pure BRV and VM was similar but significantly higher than that in MD, BPPV, and VP. There was a positive correlation between RLS grading and DHI among patients with BRV and VM. The existence of RLS is valuable in the etiological diagnosis of paroxysmal vertigo and may be used as a reference for the differential diagnosis of paroxysmal vertigo.

List Of Abbreviations

BPPV	Benign paroxysmal positional vertigo
BRV	Benign recurrent vertigo
cTTE	Contrast transthoracic echocardiography
DHI	Dizziness Handicap Inventory
dMD	Definite Meniere’s disease
HSN	Headshaking nystagmus
MA	Migraine with aura
MD	Meniere’s disease
MoA	Migraine without aura
PAVM	Pulmonary arteriovenous malformation
PFO	Patent foramen ovale
RLS	Right-to-left shunt
TIA	Transient ischemic attack
VM	Vestibular migraine
VP	Vestibular paroxysmia

Declarations

Ethics approval and consent to participate

The study procedure was approved by the ethics committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University. All patients signed informed consent forms.

Consent for publication

Not applicable

Availability of data and materials

All the data supporting our findings is contained within the manuscript

Competing interests

None

Funding

We acknowledge funding support from the Zhejiang Provincial Natural Science Foundation of China (Grant No. LY19H090025, Grant No. LQ15H090003), National Natural Science Foundation of China (Grant No. 82171561, Grant No. 82174132). The funders had no role in the design of this study or in the interpretation or presentation of its results.

Authors' contributions

KL conducted the design and conceptualization of the study, interpretation of the data, and revising the manuscript. XZ wrote and designed the manuscript. XT analyzed and interpreted the data. WH, YX, JC, HJ, XX, TZ, LZ, and MP collected and organized the data.

Acknowledgements

None

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Figures

Figure 1

Flowchart of the inclusion and exclusion of patients

Figure 2

The frequency of RLS in patients with different diseases There is a statistical difference between the frequency of RLS in BRV patients and that in MD, BPPV and VP patients. The proportion of RLS in BRV patients is significantly higher than that in patients of MD, BPPV and VP ($P<0.05$). The proportion of RLS in VM patients without migrainous headaches is also significantly higher than that in MD, BPPV and VP patients ($P<0.05$). However, there is no statistical difference between the frequency of RLS in BRV patients and that in MoA patients ($P=0.931$), MA ($P=0.997$), VM with migrainous headache ($P=0.787$), and VM without migrainous headache ($P=0.754$). Abbreviations: BPPV, benign paroxysmal positional vertigo; BRV, benign recurrent vertigo; MA, migraine with aura; MD, Meniere's disease; MoA, migraine without aura; RLS, right-to-left shunt; VM, vestibular migraine; VP, vestibular paroxysmia

Figure 3

The frequency of RLS grouping by age in patients with BRV The proportion of RLS in BRV patients aged <50 years and those aged ≥50 years was similar, and there was no statistical difference. Abbreviations: BRV, benign recurrent vertigo; RLS, right-to-left shunt

Figure 4

The DHI scores of RLS grade in patients with VM and BRV (A) In patients with VM with migrainous headache, DHI score increased with increasing RLS grade, and there was a positive correlation between them. (B) In patients with VM without migrainous headache, DHI score increased with increasing RLS grade, and there was a positive correlation between them. (C) In BRV patients, DHI score increased with increasing RLS grade, and there was a positive correlation between them. (D) In all patients with VM or BRV, the DHI score increased with increasing RLS grade, and there was a positive correlation between them. Abbreviations: DHI, Dizziness Handicap Inventory; RLS, right-to-left shunt; VM, vestibular migraine; BRV, benign recurrent vertigo