Relationship between right-to-left shunt detected by c-TCD and clinical characteristics in migraine patients

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ABSTRACT

الأهداف: التحقق من العلاقة بين وجود أو معاملات التحويل من اليمين إلى اليسار (RLS) التي تم الكشف عنها بواسطة c-TCD و السمات السريرية في مرضى الصداع النصفي المصحوب بهالة (MA^+) أو بدون هالة (MA^-).

المنهجية: اشتملت الدراسة على مرضى الصداع النصفي المصحوب بهالة ومرضى الصداع النصفي بدون هالة (MA^-) على التوالي. تم تقييم RLS من خلال فحص c-TCD.

النتائج: ادرجنا مجموعه من 528 مريضاً بالصداع النصفي و 71 من الأصحاء. كان انتشار التحويل من اليمين إلى اليسار (RLS) خاصةً في التحويلات الخفيفة أعلى في المرضى الذين يعانون من الصداع النصفي. أصيب مرضى MA^+ بالصداع النصفي في وقت سابق وعانوا من ألم أكثر حدة، ورهاب ضوئي أكثر تكرارًا، ورهاب صوتي، على الرغم من أن التكرار السنوي، ومدته، ودرجة الألم أو نوع التحويلة وحجمها كانت متشابهة. علاوة على ذلك ، فإن المرضى الذين يعانون منMA^+ وRLS^+ عانوا أيضًا من رهاب الضوء ورهاب الصوت أكثر من ذلك بدون RLS^-. كانت النتيجة مماثلة في مجموعة MA^-RLS^+. يعاني المرضى الذين يعانون من متلازمة RLS المتوسطة أو الشديدة من الألم لمدة أطول في كلتا المجموعتين MA^-RLS^+ وMA^+RLS^+. كان توزيع الجنس مختلفًا بشكل كبير فقط في مجموعة MA^+RLS^+، حيث كانت النساء أكثر عرضة للمعاناة من RLS وخاصة التحويلة الخفيفة.

الخلاصة: اظهرت الدراسة انتشار وشدة أعلى لRLS في مرضى الصداع النصفي، وخاصة أولئك الذين يعانون من الهالة. يتطور مرضى MA^+ في وقت مبكر ويعانون من ألم أكثر حدة. كانت المدة متوافقة مع حجم التحويل في كلتا المجموعتين MA^+RLS^+ و MA^-RLS^+.

Objectives: To explore the relationship between the presence or parameters of right-to-left shunt (RLS) detected by c-TCD and attack clinical features in migraine patients with aura (MA^+) or without aura (MA^-).

Methods: Migraine patients with aura and migraine patients without aura (MA^-) were recruited consecutively. The RLS was assessed by a c-TCD examination.

Results: A total of 528 migraine patients and 71 healthy were included. The prevalence of RLS especially of mild shunts was higher in patients with migraine. Patients of MA^+ developed migraine earlier and experienced more severe pain, more frequent photophobia and phonophobia, although the yearly frequency, duration and degree of pain or type and size of shunt was similar. Moreover, patients with MA^+ and RLS (MA^+RLS^+) also experienced more photophobia and phonophobia than that without RLS (MA^+RLS^-). The result was similar in MA^-RLS^+ group. Patients with moderate or massive of RLS experience longer duration of pain in both MA^+RLS^+ and MA^-RLS^+ groups. The sex distribution was only significantly different in MA^+RLS^+ group, in which women were more likely to suffer from RLS especially mild shunt.

Conclusion: A higher prevalence and severity of RLS was found in the migraine patients, especially those with aura. MA^+ patients develop earlier and experience more severe pain. The duration was consistent with the shunt size in both MA^+RLS^+ and MA^-RLS^+ groups.

Neurosciences 2022; Vol. 27 (3): 143-149
doi: 10.17712/nsj.2022.3.20210109

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Received 27th August 2021. Accepted 28th October 2021.

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Migraine is a common chronic disease in adults, and migraineurs are at a higher risk of stroke than nonmigraineurs, partly due to the high incidence of right-to-left shunt (RLS) of them.[1-3] The relevance between the clinical aspects of pain and features of RLS in migraine patients is still controversial. On the one hand, studies have reported that migraine patients have a larger RLS, mainly resulting from PFO.[4,5] Increasing studies have shown that migraines and PFO-related RLS were highly correlated.[6-8] The morbidity of RLS is 2.5 or 1.4-fold higher in migraine patients with aura (MA^+) and migraine patients without aura (MA^-) than that in healthy population, respectively.[9] These results supported the notion regarding the important effect of RLS on migraine and may shed light on PFO closure trials.[10] The pain could be significantly relieved by the transcatheter PFO closure in migraine patients.[11] On the other hand, no relevance was found between migraine characteristics and existence or degree of RLS in some studies.[12,13] The causative role of RLS and its relationship with migraine still need further exploration due to the negative results from the a large-scale clinical trials[14] and the contradictory results of the relationship between RLS and clinical features of migraine.[15]

With the development of technology and the improvement in related methods, the test of contrast enhancement transcranial Doppler (c-TCD) is considered to be effective at detecting RLS in the migraine population, especially under Valsalva maneuver (VM),[16] and it improves the possible of the related research. This study aims to explore the relationship between the presence or parameters of RLS detected by c-TCD and attack clinical features in migraine patients with aura (MA^+) or without aura (MA^-).

Methods.

Study population. The procedure of this study was reviewed and approved by the Medical Ethics Committee of Aviation General Hospital. The written informed consent had been provided by every patient prior to participating. We enrolled a total of 533 patients diagnosed with migraine consecutively at the outpatient clinic of the Aviation General Hospital from January 2019 to March 2020. Five patients of them were excluded: three were excluded because they did not have an adequate acoustic window, and two were excluded because they were unable to perform an effective Valsalva maneuver (VM). In addition, 71 healthy volunteers (mean age 38.65±12.19 years, 24 men and 47 women) were recruited in the health group. Ultimately, 527 patients (age 36.73±12.50 years, male: female, 156: 371) were recruited in this study. MA^+ and MA^- were diagnosed according to the diagnostic criteria in the guidelines.[17] When a patient has been attacked by both MA^+ and MA^-, he/she would be excluded. We obtained clinical information by questionnaire, including onset age and family history of migraine; photophobia; phonophobia; sensitivity to smell; and triggers of migraine attacks (including stress, sleep disorders, changing weather, specific foods, hormonal factors, certain circumstances, strenuous exercise and so on). The judgment of sleep quality of the previous night based on the mental and physical status of the patients on the next day. If the patients on the second day show drowsiness, lack of energy, difficulty in thinking, emotional instability, and difficulty in concentrating, they are usually judged to have sleep disorders. Stress status was confirmed by 2 scales. The score of self-rating anxiety scale (SAS) >50 points mean there is anxiety. The score of self-rating depression scale (SDS) >53 points mean there is depression. Either of them is positive, the patients were recognized as with stress. Environmental factors include changes in the light, temperature, sound, radiation, and humidity and so on of environment.

RLS detection. The initial screening for the presence of RLS was performed through c-TCD, which could detect RLS effectively.

All patients underwent c-TCD (EMS-9A, Delica, China) by 2 trained neurologists. First, we allowed patients to lie comfortably and placed an 18-gauge catheter in their right antecubital vein. Firstly, we would perform a baseline TCD examination. Then, we mixed air (1 ml) into isotonic saline solution (9 ml). Then a drop of the patient's own blood was added. The mixed liquid was repeatedly pumped and mixed between 2 10-ml syringes through a 3-way stopcock and injected these microbubbles (MBs) created by mixing medium back-and-forth 30 times rapidly to the patients. The procedure was carried out three times successively: the first time during quiet breathing and 2 times during the Valsalva maneuver (VM) procedure. The VM was performed 5 s after starting the injection of mixed liquid and lasted for 10 s. Each interval of VM lasted at least 5 min from the last observed MBs. The occurrence frequency of microbubbles in the 20 s of all the 3 times was recorded, of which the highest value was taken as the final result. We quantified the RLS by the number of MBs. Without RLS=0 MBs, mild of RLS=1 to 10 MBs, moderate of RLS=11 to 20 MBs, massive of RLS≥ 20 MBs. If an RLS can only be detected after the VM, it is termed latent RLS, and if it is detected during calm breathing, it is termed permanent RLS.

Statistical analysis. Enumeration data were described as proportions (%). Means (± standard deviation) was used to describe the measurement data of normal

Table 1 - The type and size of RLS and other clinical features of pain in migraine patients with or without aura.

Variables	MA⁺(n=134)	MA⁻(n=394)	*P*-value
Age	35.89±13.70	37.05±12.07	0.317
Sex (Male: Female)	43:91	113:280	0.465
Family history of migraine, n (%)	49 (36.57)	142 (36.04)	0.913
Age of onset	25.45±12.99	28.04±11.73	0.032
Yearly frequency of pain	21.75±17.46	22.73±18.11	0.585
Duration of pain (hours)	13.18±6.38	12.11±5.97	0.078
Degree of pain	6.35±1.60	5.89±1.76	0.007
Type of RLS, n (%)			
Without RLS	53 (39.55)	183 (46.4)	0.201
Latent RLS	38 (28.36)	127 (21.3)	
Permanent RLS	43 (32.09)	84 (32.2)	
Size of shunts, n (%)			
Without RLS	53 (39.55)	183 (46.45)	0.324
Mild of RLS	37 (27.61)	113 (28.68)	
Moderate of RLS	14 (10.45)	32 (8.12)	
Massive of RLS	30 (22.39)	66 (16.75)	
Photophobia, n (%)	37 (27.61)	36 (9.14)	<0.001
Phonophobia, n (%)	34 (25.37)	35 (8.88)	<0.001

RLS - right-to-left shunt, MA - migraine patients without aura

Table 2 - The clinical features of pain in MA⁺ patients with or without RLS.

Variables	MA⁺RLS⁺ (n=81)	MA⁺RLS- (n=53)	*P*-value
Age	36.72±12.93	34.40±14.81	0.151
Sex (Male: Female)	21:60	22:31	0.059
Family history of migraine, n (%)	32 (39.51)	17 (32.08)	0.383
Age of onset	24.46±12.44	26.96±13.75	0.169
Yearly frequency of pain	23.32±17.34	19.34±17.52	0.703
Duration of pain (hours)	12.99±6.38	13.47±6.45	0.177
Degree of pain	6.41±1.52	6.26±1.72	0.196
Photophobia, n (%)	14 (17.28)	23 (43.40)	0.001
Phonophobia, n (%)	13 (16.05)	21 (39.62)	0.002

RLS - right-to-left shunt, MA - migraine patients without aura

distribution. All of them were analyzed by SPSS software version 21.0 (SPSS, Inc., Chicago, IL, USA). A t-test was used for measurement data with a normal distribution, Chi-square test was used for comparison of paired categorial variables, and two-tailed Fisher exact tests was used for counting data from three or more groups. All measurement data was normal distributed tested by one sample K-S. If the *p*-value is greater than 0.05, the data is considered to be normally distributed. All data were tested bilaterally, and $p<0.05$ was recognized as different significantly.

Results. ***Incidence of RLS in patients with migraine and control.*** We included a total of 528 patients diagnosed with migraine according to the relative diagnostic criteria and 71 healthy people as control. There were no differences of gender distribution between 2 groups.

Patients with migraine had a higher incidence of RLS than the healthy group. In the migraine group, 55.30% (292/528) of patients had RLS, of whom 122 (23.11%) had latent RLS and 170 (32.19%) had permanent RLS. In the healthy group, only 36.62% (26/71) had RLS, 11 (15.49%) had latent RLS, and 15 (21.13%) had permanent RLS, which was significantly fewer than that in the migraine patients ($p=0.012$).

The incidence of mild shunts in migraine patients was higher than that in control, although a large proportion of normal people had massive shunts ($p=0.022$). In the migraine group, mild of RLS were found in 150

Table 3 - Difference of clinical features in MA^+RLS^+ patients with different shunts size (n=81).

Variables	Size of shunts, n (%)			*P*-value
	Mild of RLS	Moderate of RLS	Massive of RLS	
Gender, n (%)				
Male, 21 (25.93)	8 (9.87)	1 (1.23)	12 (14.81)	0.049
Female, 60 (74.07)	29 (35.80)	13 (16.05)	18 (22.22)	
Location of headache				
Left	9 (11.11)	4 (4.94)	9 (11.11)	0.474
Right	11 (13.58)	7 (8.64)	8 (9.88)	
Bilateral	17 (20.99)	3 (3.70)	13 (16.05)	
Age of onset	26.73±14.27	23.64±11.33	22.03±10.20	0.300
Yearly frequency of pain	27.38±17.35	25.14±17.92	17.47±15.93	0.059
Duration of pain (hours)	11.51±5.49	11.79±4.76	15.37±7.43	0.034
Degree of pain	6.62±1.46	5.64±1.34	6.50±1.61	0.112
Photophobia	7 (18.92)	3(21.43)	4(13.33)	0.754
Phonophobia	7 (18.92)	2(14.29)	4(13.33)	0.809

Table 4 - The clinical features of pain in MA^- patients with or without RLS.

Variables	MA^-RLS^+ (n=211)	MA^-RLS^- (n=183)	*P*-value
Age	36.57±11.91	37.61±12.25	0.739
Gender (Male: Female)	56:155	58:125	0.261
Family history of migraine, n (%)	79 (37.44)	63 (34.43)	0.534
Age of onset	27.24±11.65	28.97±11.79	0.740
Yearly frequency of pain	23.07±17.45	22.34±18.89	0.249
Duration of pain (hours)	11.82±5.70	12.44±6.28	0.143
Degree of pain	5.94±1.77	5.82±1.76	0.694
Photophobia, n (%)	26 (12.32)	10 (5.46)	0.018
Phonophobia, n (%)	26 (12.32)	9 (4.92)	0.010

patients (28.41%), moderate of RLS were found in 46 patients (8.71%), and massive of RLS were found in 96 patients (18.18%). However, in the control group, mild of RLS were found in 16 patients (22.50%), moderate of RLS were found in 4 patients (5.60%), and massive of RLS were found in 6 patients (8.50%).

The type or size of RLS and clinical features of pain in migraine patients with aura. Among the 528 migraine patients, 134 had aura (MA^+), and 394 did not (MA^-). The age of onset in the MA^+ patients was significantly younger than that in the MA^- patients (25.45±12.99 vs 28.04±11.73, p=0.032), although the distribution of sex, family history, yearly frequency and duration of pain had no significant difference (**Table 2**). In addition, the degree of pain in MA^+ group was much higher than that in MA^- group (6.35±1.60 vs 5.89±1.76, p=0.007) (**Table 1**). There were no differences in the shunt types (p=0.201) or shunt sizes (p=0.324) between MA^+ and MA-, although photophobia and phonophobia symptoms occurred more frequently in the MA^+ group (p<0.001 and p<0.001, respectively, **Table 1**).

A total of 134 MA^+ patients were divided into two groups, namely, 81 (60.45%) patients in the RLS (MA^+RLS^+) group and 53 (39.55%) patients in the non-RLS (MA^+RLS^-) group. In the MA^+RLS^+ group, 38 patients (46.91%) had latent RLS (57.89% mild shunt, 13.16% moderate shunt and 28.95% massive shunt), and 43 patients (53.09%) had permanent RLS (34.88% mild shunt, 20.93% moderate shunt and 44.19% massive shunt) (**Table 2**). The sex distribution, family history, onset age, yearly frequency, duration and degree of pain were similar between the MA^+RLS^+ and MA^+RLS^- groups, although photophobia and phonophobia symptoms occurred more frequently in the MA^+RLS^- patients (p=0.001 and p=0.002, respectively, **Table 2**).

There was a significant difference noted in the sex distribution (females vs males: 74.07% vs. 25.93%,

Table 5 - Difference of clinical features in MA$^-$RLS$^+$ patients with different shunts size (n=211).

Variables	Size of shunts, n (%)			*P*-value
	Mild of RLS	Moderate of RLS	Massive of RLS	
Gender, n (%)				
Male, 56 (26.50)	30(14.22)	8 (3.79)	18 (8.53)	0.972
Female, 155 (73.50)	83 (39.34)	24(11.37)	48 (22.75)	
Location of headache				
Left	28 (13.33)	13 (6.19)	18 (8.57)	0.547
Right	22 (10.48)	5 (2.38)	12 (5.71)	
Bilateral	62 (29.52)	14 (6.67)	36 (17.14)	
Age of onset	27.54±12.70	28.56±9.74	26.09±10.62	0.571
Yearly frequency of pain	22.19±17.39	21.22±14.57	25.45±18.79	0.393
Duration of pain (hours)	10.83±5.48	13.16±5.04	12.85±6.10	0.025
Degree of pain	5.80±1.60	6.16±1.66	6.09±2.07	0.426
Photophobia, n (%)	8 (7.08)	6 (18.75)	12 (18.18)	0.045
Phonophobia, n (%)	8 (7.08)	6 (18.75)	12 (18.18)	0.045

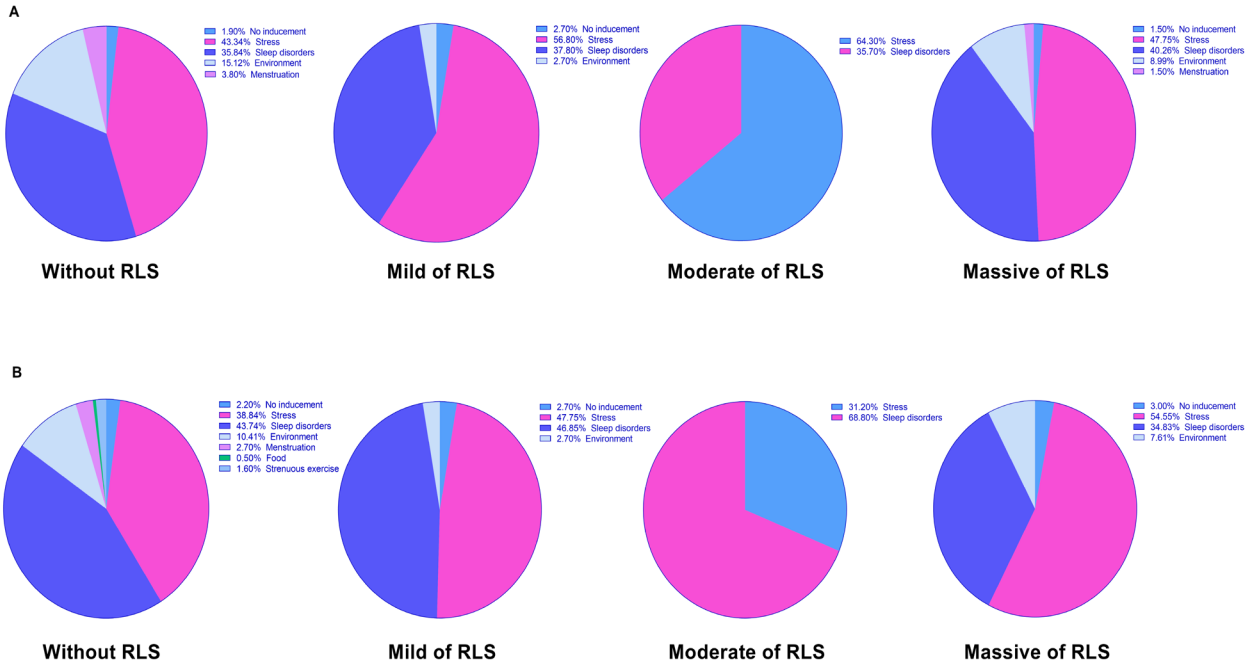

Figure 1 - Crisis triggers in RLS patients with different shunt sizes. **A)** Crisis triggers among MA$^+$ patients with different sizes of shunts. **B)** Crisis triggers among MA$^-$ patients with different sizes of shunts. RLS - right-to-left shunt, MA - migraine patients without aura

p=0.049) of MA$^+$RLS$^+$ patients with different shunt sizes, and female patients with shunts predominantly had mild shunts (35.80%) and massive shunts (22.22%) (**Table 3**). There was no significant difference in the triggers (**Figure 1A**) or location of headache among the MA$^+$RLS$^+$ patients with different shunt sizes (*p*>0.05) (**Table 3**).

The age of onset and yearly frequency of pain in patients with different shunt sizes was similar. The duration of pain in MA$^+$RLS$^+$ patients with different shunt sizes was significantly different (**Table 3**). The duration of pain in MA$^+$RLS$^+$ patients with massive shunts was 15.37±7.43 hours, which was more serious than that in patients with mild shunts (11.51±5.49

hours) (p=0.034). However, the degree of pain was also similar in MA^+RLS^+ patients with different shunt sizes (**Table 3**).

The type or size of RLS and clinical features of pain in migraine patients without aura. In the MA^- group, 53.55% (211/394) of patients had RLS, 127 cases (60.19%) had latent RLS, and 84 cases (39.81%) had permanent RLS. There were no obvious differences in age (36.57±11.91 vs 37.61±12.25, p=0.739), onset age of migraine (27.24±11.65 vs 28.97±11.79, p=0.740), sex (female 73.46% vs 68.31%, p=0.261), family history (37.44% vs 34.43%, p=0.534), yearly frequency (23.07±17.45 vs 22.34±18.89, p=0.249), duration of pain (11.82±5.70 vs 12.44±6.28 hours, p=0.143), or degree of pain (5.94±1.77 vs 5.82±1.76, p=0.694) (**Table 4**).

There were 113 (28.68%) patients who had mild of RLS, 32 (8.12%) patients who had moderate of RLS, and 66 patients (16.75%) who had massive of RLS. There was no significant difference in crisis triggers (**Figure 1B**) or location of headache (p=0.547) among the MA^-RLS^+ patients with different shunt sizes (**Table 5**).

The age of onset and the yearly frequency in patients with different shunt sizes were similar (p=0.571 and p=0.393, respectively). The duration of pain in MA^-RLS^+ patients with different size of shunts was also different. The duration of headache in MA^-RLS^+ patients with massive shunts was 12.85±6.10 hours, which was longer than that in patients with mild shunts (10.83±5.48 hours) (p=0.025). However, the degree of pain was not significantly different in MA-RLS+ patients with different shunt sizes (p=0.426, **Table 5**).

Discussion. Migraine is a major cause of chronic pain in adults, and migraineurs are at a higher risk of stroke than nonmigraineurs, partly resulted from the high incidence of RLS in these patients.[1,2] The deeper mechanism linking migraine, RLS, and stroke may be compromised dynamic cerebral autoregulation.[18] Moreover, the mechanism of RLS-induced migraine mainly involves the following aspects: cerebral endothelial dysfunction,[19] higher breath-holding index,[20] cerebral vasomotor reactivity,[21] local arterial area hypoperfusion,[22,23] microembolism (venous thrombosis, fat emboli or concentration of metabolites), and aerogenic microembolism and its involvement with subclinical cerebral ischemia.[21,24] Therefore, to help doctors clinically select migraine patients especially that with RLS, it is crucial to determine the detailed characteristics and clinical manifestations of migraine for the prediction of RLS, although European consensus does not recommend RLS screening for all migraine sufferers.[2] In addition, it may be beneficial to select PFO closure to alleviate migraine attacks for migraine sufferers with RLS if the relationship is confirmed.

In this study, we studied the incidence and severity of RLS and its relationship to clinical manifestations of attacks in migraine patients and healthy controls. We found a high prevalence of RLS (55.30%), especially in MA^+ patients (60.45%), which is consistent with that results from other studies.[25,26] The frequency of mild shunts in patients with migraine was higher, although a large proportion of normal people have massive shunts.

We also found that the pain in the MA^+ group was much more serious than that in the MA^- group, although some previous studies[9,27] have shown that the degree of headache pain is unrelated to the type. There were no differences in the shunt size or shunt type between the MA^+ and MA^- groups. However, MA^+ patients developed migraine earlier and experienced more severe pain, in which 60.45% of patients had RLS (MA^+RLS^+). In the MA^+RLS^+ group, 74.07% were female, which means that RLS is more common in women. Moreover, shunts in women were predominantly mild shunts or massive shunts. In MA^+RLS^+ patients with massive shunts, the duration of headache was the longest, although the onset age, yearly frequency and the degree of pain were not significantly different in MA^+RLS^+ patients with different shunt sizes. In the MA^-, 53.55% (211/394) of patients had RLS, which was lower than that in the MA^+ group. Interestingly, the yearly frequency, onset age and degree of pain were similar among MA^-RLS^+ patients with different shunt sizes, although the duration was consistent with the shunt size, as in MA^+RLS^+ patients. Patients with RLS experienced more photophobia and phonophobia than that without RLS in both MA^+ and MA^- groups.

In our study, we classified the migraine patients with RLS into the MA^+RLS^+ and MA^- RLS^- group, and the relationship with the cause, duration and degree of pain was further analyzed. Of course, there are some limitations to our study. First, this is only a study based on one center. Second, we detected RLS by using c-TCD examination, with which intracardiac and extracardiac shunts could not be distinguished. In future studies, the underlying mechanism of the correlation between RLS and migraine needs to be explored.

Collectively, a higher incidence of RLS was found for migraine patients, especially that with aura. The

duration was consistent with the shunt size detected by c-TCD. The c-TCD is therefore effective at detecting RLS in migraine patients.

Acknowledgement. *The authors would like to to thank all the participating patients.*

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