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A study on the relationship between patent foramen ovale and white matter lesions in
migraine patients

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Declarations

Contributors: J.Y. Huo and Y. Fu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D.S. Fan conceived of the research and guided the process, and NL was responsible for the data acquisition and analysis. W.M. Wan and J.Y. Huo acquired the data and analysed the results. J. Wang and X. Cai performed the TCD. J.Y. Huo wrote the paper, and Y. Fu reviewed and edited the manuscript. All authors read and approved the manuscript.

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Abstract

Background Migraine is a common clinical primary headache with unclear aetiology. In recent years, studies have shown that migraine is related to patent foramen ovale, and some patients with migraine have white matter lesions. However, the relationship among the three is unclear.

Objective To explore the characteristics of white matter lesions (WMLs) in migraine patients with patent foramen ovale and to predict the occurrence of patent foramen ovale through magnetic resonance imaging (MRI) characteristics in patients with migraine.

Methods Seventy-seven patients clinically diagnosed with migraine were examined by transcranial Doppler ultrasound (cTCD) and MRI. The patients were grouped according to the presence of WMLs, with matching by age, sex, hypertension, diabetes, PFO and other characteristic data. We observed the MRI fluid attenuation inversion recovery sequence (FLAIR) image and compared and analysed the difference in WMLs between the PFO-positive group and the PFO-negative group.

Results There were 42 cases and 35 cases of migraine with and without WMLs, respectively. A statistically significant difference in near-cortical WMLs with PFO in migraine patients was observed ($P=0.001$). Logistic regression analysis adjusted by age, sex, hypertension and diabetes identified PFO status as the sole determinant for the presence of near-cortical WMLs (OR = 0.14; 95%CI 0.045–0.421; $p < 0.001$)

Conclusion Near-cortical white matter lesions in migraine patients are related to PFO. Transcranial Doppler ultrasonography may reveal more PFO in patients with migraine and near-cortical WMLs.

Key word: migraine; white matter lesions; patent foramen ovale

Introduction

Migraine is a chronic neurological disease that is characterized by moderate or severe headache. Typical symptoms include photophobia, phonophobia, skin allodynia and gastrointestinal symptoms, such as nausea and vomiting¹. The prevalence of migraine in the Chinese adult population diagnosed with primary headache is approximately 9.3%, and it is listed as one of the seven major causes of disability by the World Health Organization². In the past, it was believed that no imaging manifestations could be detected in migraine patients. However, with the development of imaging technology, white matter lesions (WMLs) have been found in an increasing number of migraine patients, though the mechanism of WMLs has not been fully elucidated. Recent studies have found that some patients with migraine have patent foramen ovale (PFO)³, and the headache can disappear or be relieved after foramen ovale closure surgery⁴. In patients with PFO, blood shunting from right to left occurs, which is one of the causes of cryptogenic embolism. Thus, it is possible that the abnormality of white matter in patients with migraine caused is by PFO and that abnormal white matter changes in a special area of those with migraine can predict the presence of PFO. This article explores the effect of PFO on WMLs in migraine patients through retrospective research, clarifies whether PFO increases the risk of WMLs in migraine patients, and provides a reference for future clinical diagnosis and treatment.

Material and methods

Study population

In this study, 77 migraine patients who were admitted to the Neurology Clinic of Peking University Third Hospital from January 2019 to May 2020, were enrolled. The inclusion criteria were as follows: ① migraine patients meeting the diagnostic criteria of ICHD-3; ② aged 18-60 years; ③ received contrast transcranial Doppler ultrasound (cTCD) and magnetic resonance imaging (MRI) examination. The exclusion criteria were as follows: ① other types of primary headaches; ② history of cardiovascular and cerebrovascular diseases; ③ intracranial organic diseases; ④ idiopathic WMLs (multiple sclerosis, leukodystrophy); ⑤ tumour; and ⑥ contraindications on MRI examination. This research was approved by the Ethics Committee of Peking university third Hospital. Informed consent was obtained. All methods were performed in accordance with the relevant guidelines and regulations.

Clinical data collection

Data collected included age, sex, disease history, duration of headache (months), attack frequency (d/month), and duration (h/d).

PFO assessment

Using a transcranial Doppler ultrasound diagnostic apparatus and a 2 MHz probe, the subject was placed in a supine position, and the neurologist in the M function mode is a single channel multi-depth mixture of mL normal saline, 1 mL air and 1 mL autologous venous blood. The saline solution was activated and injected quickly into the median vein of the right elbow, and changes in the blood flow spectrum signal of the bilateral middle cerebral arteries in the resting state and after the Valsalva manoeuvre were detected. Microbubbles (MBs) in the resting state or after the Valsalva manoeuvre indicate positivity for PFO; negativity for PFO is indicated if MBs are not detected. The cTCD test positive standard is as follows: MBs appearing within 10 s are defined as positive and are classified according to the number of MBs, as Class 0 (no MBs), Class I (1-10 MBs), Class II (more than 10 MBs but no rain curtain), or Class III (forming a rain curtain).

MRI examination

Using a 3.0 T superconducting magnetic resonance scanner, the subjects were asked to lie on their backs, relax, close their eyes, and stay awake during data collection. T1WI, T2WI and fluid-attenuated

inversion recovery (FLAIR) images were collected, with a layer thickness of 5 mm and a layer spacing of 6 mm.

Image post-processing analysis and WML evaluation

WMLs were evaluated by 2 experienced neurologists who used the image processing workstation to assess the WMLs of T2 FLAIR images in the population eligible for inclusion. Data with imaging artefacts were not included in this study. The signal characteristics of WMLs were defined as follows: high signal on T2WI and T2 FLAIR sequences and equal or low signal on T1WI sequences. To ensure good consistency in this study, when the two evaluators disagreed, a consensus was reached through discussion.

Statistical analysis

SPSS 24 was used for data processing. Count data are expressed by the rate, and comparison between groups is expressed by the chi-square test. For measurement data, those with normal distribution after inspection are expressed by the mean \pm standard deviation ($\bar{x} \pm s$), and comparison between groups is expressed by two Independent sample t-test. If the measurement data did not conform to the normal distribution, the data are represented by the median and quartile [M(Q25, Q75)], and comparison between groups was carried out using two independent sample nonparametric tests. The presence of a linear trend between groups was assessed through linear association; multivariate logistic regression was used for analysis of independent influencing factors of WMLs in migraine patients. A P value <0.05 indicates a statistically significant difference.

Results

According to the inclusion and exclusion criteria, a total of 77 migraine patients were enrolled in this study. As shown in Table 1, 42 patients (54.5%) had WMLs, and 35 patients (45.4%) did not have WMLs; 19 patients in the WML group had PFO (45.2%), and 11 patients (31.4%) in the group without WMLs had PFO. The prevalence of PFO in the WML-positive group was higher than that in the WML-negative group (PFO, 45.2% vs 31.4%, $P = 0.012$). With the exception of PFO and age, there were no differences in characteristics between the WML-positive and -negative groups. Moreover, the prevalence of PFO in the near-cortical WML-positive group was significantly higher than that in the near-cortical WML-negative group (PFO, 66.7% vs 24.0%, $P = 0.001$), and there was a linear correlation trend between near-cortical WMLs and RLS grade.

Table 2 shows that there was a statistically significant difference in the distribution of WMLs in the anterior cerebral artery between the PFO-positive and sPFO-negative group ($P=0.003$). Near-cortical WMLs are related to PFO, but deep WMLs are related to non-PFO.

As shown in Table 3, multivariate analysis was conducted to adjust for age, hypertension, and diabetes, which may influence WML prevalence. The results indicated the presence of PFO and age to be associated with the presence of WMLs. According to multivariate logistic regression analysis, the presence of PFO was independently associated with the presence of near-cortical WMLs ($P < 0.001$; OR = 0.14; 95%CI 0.045–0.421).

Discussion

Migraine is a chronic neurological disease that is more common in women than in men, with a male to female ratio of 1:3. The onset of migraine usually starts in late childhood or early adolescence, and the incidence peaks in middle age⁵. Decades of headaches recur during the active cycle and may become chronic or more difficult to treat in some patients⁶. Migraine has been identified by the World Health Organization as one of the main causes of global disability, especially for individuals under 50 years of age⁷. The aetiology of migraine is unclear. Some people exhibit WMLs on MRI. Furthermore, the

mechanism has not been fully elucidated.

Table 1 Comparison of characteristics between the WML-positive and WML-negative groups and near-cortical WML-positive and WML-negative groups

Clinical data	WMLs(+) (n=42)	WMLs(-) (n=35)	p	Near-cortical WMLs(+) (n=27)	Near-cortical WMLs(-) (n=50)	P-value
Age (y)	42.23±14.54	34.83±11.27	0.031	41.59±14.05	36.36±12.64	0.492
Female, n (%)	21 (50.0)	22 (62.8)	0.503	18 (66.7)	25 (50.0)	0.16
Diabetes, n (%)	1 (2.3)	1 (2.8)	0.706 ^a	1 (3.7)	1 (2.0)	0.581 ^a
Hypertension, n (%)	4 (9.3)	2 (5.7)	0.402 ^a	4 (14.8)	2 (4.0)	0.176 ^a
PFO	19 (45.2)	11 (31.4)	0.012	18 (66.7)	12 (24.0)	0.001
PFO Grades						
0	16 (38.1)	31 (88.6)	0.035	9 (33.3)	38 (76.0)	<0.001
I	9 (21.4)	5 (14.3)		7 (25.9)	7 (14.0)	
II	5 (11.9)	3 (8.5)		5 (18.5)	3 (6.0)	
III	5 (11.9)	3 (8.5)		6 (22.2)	2 (4.0)	

^aFisher's test; ^bLinear by linear association; PFO: Patent Foramen Ovale; WMLs: White matter lesions

Table 2. Comparison of white matter lesions between the PFO-positive group and the PFO-negative group

Lesion location	PFO(+)	PFO(-)	P-value
Near-cortical, n (%)	18 (60)	9 (19.1)	0.001
Paraventricular, n (%)	7 (23.3)	14 (29.8)	0.17
Deep brain, n (%)	1 (3.3)	8 (17.0)	0.02 ^a
ACA blood supply area, n (%)	15(50.0)	7 (14.9)	0.003
MCA blood supply area, n (%)	15 (50.0)	14 (29.8)	0.269
PCA blood supply area, n (%)	1 (3.3)	8 (17.0)	0.082

^aFisher's test; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; PFO: patient foramen ovale

Table 3 Multivariate logistic regression analysis of white matter lesions and near-cortical white matter lesions

	WMLs				Near-cortical WMLs			
	crude OR (95%CI)	P-value	adjusted OR(95%)	P-value	crude OR (95%CI)	P-value	adjusted OR(95%)	P-value
age	0.96(0.920,0.993)	0.019	0.95(0.910,0.995)	0.03	0.97(0.937,1.006)	0.104	0.98(0.938, 1.028)	0.438
sex	0.73(0.296,1.818)	0.503	1.22(0.428,3.484)	0.709	0.50(0.189, 1.323)	0.163	0.66(0.210, 2.090)	0.482
HBP	0.39(0.067,2.255)	0.291	0.89(0.111,6.999)	0.904	0.24(0.041,1.405)	0.113	0.25(0.031, 2.020)	0.194
diabetes	0.83(0.050,13.758)	0.896	3.98(0.195,81.32)	0.369	0.53(0.032, 8.834)	0.659	1.77(0.086, 36.07)	0.712
PFO	0.30(0.115,0.778)	0.013	0.26(0.090,0.729)	0.011	0.16(0.056, 0.442)	<0.001	0.14(0.045, 0.421)	<0.001

WMLs: White matter lesions; PFO: Patent foramen ovale

The main feature of WMLs is a high signal on T2-weighted or FLAIR images⁸. Although the aetiology of WMLs is unknown, recent studies have shown that WMLs may originate from ischaemia. In addition, haemodynamic changes may be related to white matter ischaemia^{9 10}, and impaired cerebral blood flow autoregulation is the most common type of haemodynamic change. WMLs in patients with migraine may be caused by ischaemia due to paradoxical embolism, which in turn causes high white matter signals.

PFO is the main cause of paradoxical embolism. The foramen ovale is the physiological passage of the heart chamber during the foetal period. It is usually closed by the time an individual reaches the age of 2 years old. PFO is caused by failure of the fusion of the primary septum and the atrial septum. In the general population, the rate of PFO is approximately 15%-35%¹¹. PFO is the most common right-to-left shunt disease, accounting for approximately 95% of all right-to-left shunt diseases. When a patient has PFO, there will be a permanent shunt of blood from the right atrium to the left atrium or only when the right atrium pressure increases further, such as with the Valsalva manoeuvre.

Although transoesophageal echocardiography is still considered to be the gold standard for diagnosing PFO, transcranial Doppler echocardiography is more sensitive than transthoracic or transoesophageal echocardiography, and it is the preferred screening method for PFO¹². Studies have shown that transcranial Doppler ultrasound contrast-enhanced ultrasound has a sensitivity of 96.8% and a specificity of 78.4% for detecting PFO¹³. Therefore, the use of cTCD to detect PFO, as applied in this study, is a reliable approach.

Our findings based on retrospective observation suggest a significant relationship between PFO and near-cortical WMLs in Chinese patients with migraine. The results showed that WMLs were significantly different between the PFO-positive group and the PFO-negative group. In migraine patients with PFO, WMLs are mostly distributed in the frontal and parietal lobes. In the blood supply area of the anterior cerebral artery. However, no difference in age, sex, hypertension, or diabetes in patients with or without PFO was found for these near-cortical WMLs. This study is consistent with previous studies in South Korea and Japan showing that the presence of WMLs is related to PFO in migraine patients. For instance, Park's study in Korea showed that 89 of 242 migraine patients had right-to-left shunts, demonstrating that deep WMLs with small nuclear magnetic fields were independently related to the right-to-left shunts of migraine patients¹⁴. This is different from our results related to near-cortical WMLs. Additionally, in a study of 98 migraine patients in South Korea, Yoon found that among migraine patients with right-to-left shunts, FLAIR images often showed WMLs near the cortex and proposed that these lesions are related to cerebral ischaemia caused by abnormal embolism. Emboli block microcirculation and cause local blood flow hypoperfusion¹⁵. In 2017, Farzianpour's study of 107 Japanese migraine patients reported that right to left shunt is an independent risk factor for WMLs in migraine patients¹⁶, though further analysis of the WMLs was not carried out.

Some studies have had the opposite results. In 2018, a multicentre study involving 334 migraine patients in China found that right-to-left shunts were not associated with WMLs in migraine patients¹⁷. Another study conducted in 139 children and adolescents with migraine in the United States in 2013 showed that WMLs in migraine patients did not correlate to the existence of right-to-left shunts, the degree of right-to-left shunts, or the subtype of migraine¹⁸. Overall, the differences in these research results may not only be related to different races but also differences in the definition and classification of WMLs in different studies, the age of the research subjects, and the difference in magnetic resonance equipment, setting parameters, and research methods.

The migraine patients included in this study were matched for intergroup age, sex, previous cerebrovascular disease and other interfering factors, and it was preliminarily concluded that PFO is

related to WMLs and to near-cortical WMLs of the anterior cerebral artery supplying areas. At present, there is controversy regarding the treatment of migraine with PFO closure surgery, but the preventive effect of PFO closure surgery on cryptogenic embolism has been confirmed by large-scale experiments¹⁹⁻²¹. Therefore, for migraine patients with anterior cerebral artery subcortical WMLs, cTCD can detect PFO, and occlusion treatment in advance can prevent the occurrence or recurrence of stroke in the future. Although this study obtained some preliminary conclusions, there are still some shortcomings. First, the sample size was small, which may lead to bias. In future work, the sample size will be further expanded for subgroup analysis to analyse the impact of different PFO splits on WMLs.

This study found that PFO is associated with near-cortical WMLs in migraine patients and that the lesions are mostly located in the blood supply area of the anterior cerebral artery. Therefore, cTCD for migraine patients who present clinically with near-cortical WMLs will help to identify the cause and provide a basis for future treatment decisions.

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