Subclinical Brain Lesion in MRI is a Potential Indicative of PFO-Related Migraine in Younger Patients

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Abstract

Background: The causal relationship of migraine with PFO remains controversial and a major question unresolved is how to define the PFO-attributable migraine.

Objective: In this study, we evaluated diffusion-weighted-imaging (DWI) presentation in brain MRI and its association with PFO in patients with migraine. We aimed to define if brain lesion could be a potential indicative of PFO-related migraine.

Methods: Consecutive migraine patients <60 years with or without aura from 2017 to 2019 who underwent transthoracic echocardiography (TTE) or transcranial Doppler (TCD) examination with agitated saline contrast (ASC) injection were assessed for right-to-left shunt (RLS). We then assessed brain DWI findings in the patients and tested the association of brain lesion with PFO.

Results: A total of 424 patients with mean age 44.39±12.06 years were included in the study. Among them, 244 patients (57.5%) had PFO and 246 patients (58%) had subclinical brain lesion. The brain lesion presented as single or multiple scattered lesion. Although there was no association between PFO prevalence and brain lesion in the total cohort (OR 0.499, 95% CI 0.236-1.052), the association was significant in patients who were aged less than 46 years (OR 3.614 in group of age<34 years, 95% CI 1.128-11.580, and 3.132 in group of 34 years≤age<46 years, 95% CI 1.334-7.350, respectively). DWI lesion in patients with PFO was more coming from anterior or multiple than posterior vascular territory (p=0.033). DWI lesion numbers, location and RLS amounts were not affecting the association between DWI lesion and PFO.

Conclusions: This study demonstrated that subclinical brain lesion are associated with PFO in migraineurs younger than 46 years. The DWI pattern of brain lesions may be used as a potential predictor of PFO-related migraine in patients who are aged less than 46 years and aids in selection of appropriate candidates for PFO closure.

Introduction

Migraine is a disease with high prevalence and a high disability rate [1, 2]. Despite intensive investigations in the past decades, its fundamental pathophysiology hasn't been fully understood and the current therapies are often unsatisfactory [3, 4].

PFO was initially linked to migraine by the findings that the incidence of PFO was significantly higher in migraine patients than that in the healthy controls, and in turn, patients with PFO suffer from migraine more frequently than the general population [5–8]. Subsequently, some observational studies reported that the migraine patients responded well to PFO closure, which further strengthened the link between PFO and migraine [9–13]. However, all randomized controlled studies by far to evaluate the benefits of PFO closure for migraine failed to reach the primary efficacy endpoint [14–16]. Therefore, PFO may be incidental and the presence of PFO alone does not fully account for migraine attack and guide the

therapy of PFO closure in migraine. How to differentiate migraine-related from incidental PFO is the major challenge for future trials and clinical practice.

The characteristics of migraine patients who are more likely to be associated with PFO have been investigated. Several studied have shown a closer relationship between PFO and migraine with aura, especially atypical aura, than that without aura [17–19]. The higher attack frequency, HIT-6 and MIDAS scores may also provide more evidences suggesting the relationship of PFO with migraine [20]. In turn, permanent PFO and PFO with large RLS may increase the incidence of migraine [21, 22]. Although these clues, more objective and reliable predictors are required to help in the diagnosis of “true” PFO-related migraine.

Paradoxical tiny embolism is the most probable underlying mechanism on how PFO can cause migraine attack, which may lead to tiny brain infarctions at the same time [23]. The effectiveness of antiplatelet and anticoagulation therapy in treating migraine provide evidences supporting this hypothesis [24, 25]. Thus, in this study, the DWI features of migraine patients and their association with RLS amounts were investigated. We aimed to evaluate if the DWI pattern could be used to define the group of patients with probable “true” PFO-related migraine.

Methods

Study population

Consecutive migraine patients <60 years old with or without aura who were referred to Tongji Hospital (Wuhan, China) and underwent either a transthoracic echocardiography (TTE) or a transcranial Doppler (TCD) examination with agitated saline contrast (ASC) injection for assessment of PFO, from 2017 to 2019, were retrospectively screened. Among this cohort, we excluded the patients fulfilling the following criteria: 1) had a history of stroke; 2) had no brain MRI data; 3) with cardiac diseases including atrial fibrillation, congenital heart disease except PFO, heart failure and significant valvular heart disease. Finally, a total of 424 patients were included in this study. The study was approved by the Institutional Review Board.

Brain MRI study

Brain MRI diffusion-weighted image (DWI) study was conducted for all enrolled patients and the results were analyzed by two independent neurologists who were blinded to patient’s clinical information. A consensus was achieved in case of discrepancies. We evaluated the DWI lesion numbers, involved vascular territories and DWI lesion locations. We firstly classified DWI lesions into three categories according to the lesion numbers: 1) no lesion; 2) single lesion; and 3) multiple lesions. We then assessed DWI lesions based on their vascular territory involvements and their locations. The vascular territories were: 1) posterior territory; 2) anterior or multiple territories. DWI lesion locations were: 1) non-cortical lesion; 2) cortical lesion. The patients with cortical lesion were define as patients who had cortical lesion only or had both cortical and non-cortical lesion.

Transthoracic echocardiography (TTE) or Transcranial Doppler study (TCD) with agitated saline contrast (ASC) injection

All patients were screened for the presence of R to L shunt (RLS) by undertaking either a TTE or a TCD study following intravenous ASC bolus injection during rest and Valsalva maneuver. For ASC bolus injection, a mixture of 8ml saline with 1ml of air and 1 ml of blood was agitated between two 10 ml syringes connected by a 3-way stopcock and then quickly injected into the brachial vein. Valsalva maneuver was completed by forced expiration against a manometer to 40mmHg [26].

TTE was performed using a Vivid E9 apparatus (GE Vingmed; Horten, Norway) and the apical four-chamber view was used for visualization of microbubbles. At least one movie of the apical four-chamber view for resting and two movies for provocation were recorded. If a patient had a suboptimal TTE image or inconclusive RLS, we additionally injected ASC and acquired movies once more. In order to define the timing of RLS, the number of cardiac cycles when early microbubbles started to be seen the LV after RA opacification were counted. Early appearance (within three cardiac cycles) of microbubbles was defined as a positive RLS. Late appearance (after three cardiac cycle) was defined as an indeterminate shunt. TCD was carried out using a TCD monitoring device. Bilateral middle cerebral arteries were simultaneously monitored through the temporal window to detect microembolic signals (MESs) after ASC injection. MESs were recorded by a computer software and counted by seeking for high-intensity transient signals (HITS). TTE and TCD findings were analyzed by an expert who was blinded to the patient's clinical data.

Definitions for RLS amount

TTE with ASC injection was used as first-line examination to define RLS. TCD with ASC injection was used for patients who didn't perform TTE. We analyzed the amount and diagnosis of RLS using both resting and provocation images. The amount of RLS was semi-quantified according to a 6-level scale modified from a previously described scale method [12]: 0 = absence of shunt (no microbubble or indeterminate shunt on TTE); 1= latent shunt of mild degree (1–20 microbubbles after Valsalva maneuver); 2= latent shunt of moderate degree (21-50 microbubbles after Valsalva maneuver); 3= latent shunt of high degree (>50 microbubbles on TTE or curtain on TCD after Valsalva maneuver); 4= permanent shunt of mild/moderate degree (>10 microbubbles at rest and >50 microbubbles on TTE or curtain on TCD after Valsalva maneuver); 5=(>50 microbubbles on TTE and curtain on TCD at rest). RLS were then classified as 1) no RLS (scale 0), 2); 2) small RLS (scale 1-2); and 3) large RLS (scale 3-5).

Statistics

All analyses were performed using SPSS version 21.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were obtained for all study variables. Categorical variables were expressed as frequencies (percentages), normally distributed continuous data as mean with standard deviation. Categorical variables were analyzed by the Chi-square test or Fisher's exact test, and continuous variables between groups were analyzed by Student t test or Mann-Whitney U test according to their distributions. Multiple

linear regression analysis was used to test the possible associations of PFO presence with DWI lesion, lesion number, location and involved vascular territory, as well as the association between DWI lesion and RLS amounts. Age and sex were introduced as confounders in each model. Binary logistic regression models with an interaction term were then used to confirm if different age groups have the different correlations between DWI lesion and PFO presence. Finally, univariate analyses were performed to confirm the association between DWI lesion and PFO presence and the association between brain lesion and RLS amounts according to different age groups.

Results

Demographic, clinical and brain imaging characteristics between migraine patients with and without PFO

The demographic, clinical and brain imaging characteristics were compared in migraine patients with and without PFO and described in table 1. The study included a total of 424 patients with migraine for analysis, of whom 244 patients (57.5%) had PFO. The mean age was 44.39±12.06 years. There were more females (62.7%) in the patient cohort, but there was no sex difference between patients with and without PFO. The other clinical characteristics, including hypertension, diabetes, dyslipidemia and current smoking, was also not different between patients with and without PFO.

Of 424 patients, 58% had DWI lesion. Among them, 9.4% had single lesion and 48.6% had multiple lesions. They all presented as small scattered lesion, of which 50.9% were cortical lesion (cortical only or both cortical and non-cortical lesion) and 50.2%% were from anterior vascular territory. In the analyses that compared the difference of DWI pattern between patients with and without PFO, the presence or absence of DWI lesion, lesion number and lesion location (cortical or non-cortical) were all not associated with the presence or absence of PFO. However, the proportion of PFO-positive was higher than that of PFO-negative in patients with single DWI lesion (11.9% vs 6.1%). Moreover, DWI lesion was more likely to come from anterior or multiple vascular territory instead of posterior vascular territory in PFO positive patients compared with PFO negative patients (p=0.033).

DWI lesion and its association with PFO presence

Multivariate logistics regression analysis revealed no association between the PFO prevalence and the presence or absence of brain DWI lesion (OR 0.499, 95% CI 0.236-1.052). We then tested the association between DWI lesion and PFO presence in different age groups (table 2). All patients were divided into four age groups: 1) age<34 years; 2) 34 years≤age<46 years; 3) 46 years≤age< 55 years; 4) age≥55 years. DWI lesion was found in 246 patients (58%) and the incidence of DWI lesion increased with age (from 5.4% in group of age<34 years to 24.3% in group of age≥55 years).

In DWI lesion-positive patients, the proportion of PFO presence was significantly higher than that of PFO absence in group of patients who were younger than 46 years (13% vs 4%, p<0.017, in group of age<34 years; and 25.3% vs 11%, p<0.005, in group of 34 years≤age<46 years, respectively). In turn, in group of 46 years≤age< 55 years, the proportion of PFO-negative and PFO-positive patients was not significantly

different (30% vs 28.8%, p=0.835). Interestingly, in group of age≥55 years, the proportion of PFO-positive patients was inversely lower than that of PFO-negative patients (32.9% vs 55%, p<0.0005). Consistently, regression analysis by age found that the odds of PFO presence in patients with DWI lesion were diminished by older age (table 3). The OR value was 3.614 in group of age<34 years, 3.132 in group of 34 years≤age<46 years, 1.071 in 46 years≤age< 55 years and 0.727 in group of age≥55. In comparison, in DWI lesion-negative patients, there was no difference between the proportion of PFO-negative and PFO-positive patients for all four age groups.

These findings suggest that the association of DWI lesion with the presence of PFO in migraine patients is age dependant. The association is significant only in patients younger than 46 years but not in those equal to or older than 46 years.

DWI lesion and its association with RLS amounts

We tested the association between brain DWI lesion and RLS amounts. In 244 patients (57.5%)who had PFO, the RLS amounts were distributed as 1) 47 (19.3 %), small RLS and 2) 197 (80.7%), large RLS. Multivariate logistics regression analysis found the association between different RLS amounts and the single or multiple brain DWI lesion was negative (OR 1.020, 95% CI 0.993-1.047). In addition, the odds of PFO with large RLS amounts in patients with DWI lesion were also age dependant and diminished by older age (table 4). The OR value was 4.000 in group of age<34 years, 2.738 in group of 34 years≤age<46 years, 1.021 in 46 years≤age< 55 years and 0.709 in group of age≥55. To confirm the results, we performed univariate analysis in patients who were aged less than 46 years, there was still no difference for the probability of brain lesion between large-RLS and small-RLS (OR 0.939, 95% CI 0.390-2.260) (table 5). In comparison, OR was 3.049 (95% CI 1.540-6.036) between large-RLS and RLS negative, and 3.248 (95% CI 1.231-8.570) between small-RLS and RLS negative (table 5). The results revealed that the association between the PFO and DWI lesion is probably independent of RLS amounts in migraine patients.

Discussion

This study found that a subgroup of migraineurs showed characteristic DWI patterns, a single or multiple small scattered lesions. The association of DWI lesion with PFO presence is probably age dependent and the prevalence of PFO was much higher in patients with DWI lesion who were younger than 46 years. The findings strongly suggest that PFO presence is one of the underlying etiologies leading to subclinical brain lesion in migraine, particularly in younger migraineurs. Therefore, DWI lesion from the brain MRI could be a supporting evidence of PFO-related migraine in younger migraineurs and could aid clinical decision making and future trial design in the management of migraine.

In migraine patients, a number of studies reported the incidence of PFO was 14.6–66.5% in comparison with 9-27.3% in general population [6, 7, 23, 27]. In this study, PFO was found in 57.5% of migraine patients, which is consistently higher than that in general population and in line with previous studies. Numerous studies also linked migraine with increased risk of stroke [28, 29], and brain lesions were

frequently observed at MRI in patients with migraine according to previous studies [30, 31]. In our study, asymptomatic DWI lesion was found in 58% of migraine patients, which is remarkably higher than 7.2–17.7% in the general population [32, 33]. However, the mechanism behind the migraine-stroke link is currently unknown. Whether PFO is one of the shared causal factors by both migraine and stroke has not been confirmed.

A single infarction or multiple small-scattered lesions in the brain have been reported to be the typical imaging pattern of a PFO-related stroke [34–36], and included in Paradoxical Embolism (RoPE) score to detect PFO-attributable cryptogenic stroke [37]. Considering paradoxical embolism as the common underlying mechanism for PFO-stroke and PFO-migraine, we hypothesized that small brain lesions may also provide supporting evidence for PFO-related migraine. However, in the whole cohort of the study, we didn't reveal the association between the PFO prevalence and the presence of brain lesion. Early studies had proved the importance of age in determining the association between PFO and cryptogenic stroke. And age has been incorporated into the RoPE score to stratify the probability of PFO-attributable cryptogenic stroke [37]. Interestingly, the association between migraine and ischemic stroke is stronger in women younger than 45 years [38]. Therefore, we performed the analysis by incorporating age factor. The results proved the significantly strong correlation between PFO and brain lesion in patients who were aged less than 46 years. The correlation was diminished with older age and even reversed in patients older than 55 years. In older patients, vascular disease and vascular risk factors as hypertension are more likely the major reasons causing the ischemic brain lesions. In younger patients who are less likely to have vascular disease, PFO is probably the major underlying factor for the ischemic lesion by paradoxical embolism. PFO with large RLS may increase the incidence of migraine [21, 22] and PFO with massive RLS has been recognized as high-risk PFO and aids clinical decision in selecting patients with cryogenic stroke for PFO closure [36, 39, 40]. However, RLS amounts didn't correlated with either brain lesion presence or lesion numbers in our study. Further study is needed to evaluate the significance of RLS amounts in PFO-related migraine. Overall, our results proved the importance of age in determining the association of DWI lesion with PFO in migraine, and suggested the potential role of subclinical brain lesion as an indicative of PFO-related migraine in patients who are aged less than 46 years.

We also compared the DWI features in migraine patients with PFO and without PFO in the study, including the lesion location, number and involved vascular territory. The imaging characteristics of the brain lesions in migraine patients with PFO were very similar as that reported in PFO-related stroke [34–36], such as single or small scattered lesions and multiple vascular territory involvement. Brain lesion numbers didn't differ significantly between PFO positive and PFO negative patients. However, the prevalence of single brain lesion was higher in patients with PFO. As to the involved vascular territory, the brain lesion of the patients with PFO in the study was more likely coming from anterior or multiple territories. Predominance of either posterior or anterior circulation involvement in PFO-related stroke has been reported in previous studies [36, 41, 42] and the significance of specific vascular territory involvement in defining PFO-related migraine needs further studies. Brain lesion in PFO-related stroke is more likely superficial or cortical. In contrast, no difference was found between cortical and non-cortical lesion in the study. Cortical lesion in our study was defined as multiple lesions that were both cortical and

non-cortical, which may affect the results. Whether the location of brain lesion is useful in defining PFO-related migraine needs further studies as well.

Limitations

There are several caveats in the study. First, the study was a retrospective single-center study with relatively small size. Thus, patient's selection bias should be considered. For example, some patients were pre-selected in the local hospital and then referred to our program, which will probably cause higher PFO incidence in the study population. Second, the results from the study can only demonstrate the relationship between PFO and migraine with brain lesions but can't confirm the causality. Prospective studies, especially studies testing the efficacy of PFO closure in migraineur with cortical lesions, are needed. Third, the diagnostic method to detect PFO may also affect the study results. This study used TTE as the diagnostic tool and the current gold standard reference for evaluating PFO is TEE. However, the accuracy of TTE with ASC injection in diagnosing PFO has been confirmed in previous studies [43–45] and is recommended by the guidelines [46]. Moreover, adequate Valsalva maneuver that is important to detect PFO was not assessed by objective findings as decreased E velocity in the study, although Valsalva maneuver against a manometer to 40mmHg has been frequently used in clinical practice and its sensitivity to detect RLS has been proved [26]. Finally, other confounding factors contributing to the relationship between PFO and migraine, such as migraine type, migraine attack frequency, PFO size and underlying vascular disease, are not considered in the study and may also bias our results.

Conclusion

The debate about the implication of PFO as an etiology for migraine and the benefit of PFO closure for treating migraine has been around for a few decades. All three RCTs evaluating the benefits of PFO closure for migraine by far failed to obtain the positive results, and patient selection remains the major challenge for designing future trials and clinical decision making. Although it is very difficult to find the direct evidence in PFO-related migraineurs, our study demonstrated that the presence of brain lesion and younger age are consistently associated with increasing prevalence of PFO. We proposed that the presence of subclinical brain lesion is probably valuable in determining the probability of PFO-related migraine but the value is age-dependent. The subgroup of migraine patients with PFO who are aged less than 46 years and at same time have subclinical brain lesion by MRI could be true PFO-related migraineurs and the appropriate candidates of PFO closure.

Abbreviations

ASC: agitated saline contrast; DWI: diffusion-weighted-imaging; HITS: high-intensity transient signal; MESs: microembolic signals; MRI: Magnetic Resonance Imaging; PFO: patent foramen ovale; RLS: right-to-left shunt; RoPE score: Paradoxical Embolism score; TCD: Transcranial Doppler; TTE: Transthoracic Echocardiography

Declarations

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Authors' contributions

Author contributions: F.M., H.W., and D.W.W. were responsible for the study design. F.L. and X.L. did the statistical analysis of the test data and generated tables. F.M., R.L., Q.Z. and Hs.Z. were responsible for collecting and preprocessing the datasets.

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Availability of data and materials

All included references in the present review article are available on the Internet.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Tongji Hospital and conducted in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Competing interests

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Authors' information

Not applicable.

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Tables

Table 1. Different demographic, clinical and brain imaging characteristics between patients with and without PFO.

	Total (n=424)	PFO-negative (n=180)	PFO-positive (n=244)	p-value*
Female, n (%)	266(62.7)	112 (62.2)	154(63.1)	0.851
Age, years (mean ± SD)	44.39±12.06	45.81±13.04	43.34±11.22	0.089
Hypertension, n (%)	117(27.6)	51(28.3)	66(27.0)	0.771
Diabetes, n (%)	48(11.3)	19(10.6)	29(11.9)	0.670
Dyslipidemia, n (%)	127(30.0)	56(31.1)	71(29.1)	0.656
Current of smoking, n (%)	61(14.4)	27(15.0)	34(13.9)	0.758
MRI brain lesion, n (%)				0.379
Negative	178(42.0)	80(44.4)	98(40.2)	
Positive	246(58.0)	100 (55.6)	146(59.8)	
MRI brain lesion number, n (%)				0.065
Single	40(9.4)	11(6.1)	29(11.9)	
Multiple	206(48.6)	89(49.4)	117(47.9)	
Involved vascular territory of brain lesion, n (%)				0.033*
Anterior or multiple	213(50.2)	81(45.0)	132(54.1)	
Posterior	33(7.8)	19(10.6)	14(5.7)	
Brain lesion location, n (%)				0.476
Non-cortical lesion	30(7.1)	14(7.8)	16(6.6)	
Cortical lesion	216(50.9)	86(47.8)	130(53.2)	

Data are mean (SD) for continuous variables or frequencies (%) for categorized variables; *p-value calculated for PFO-positive vs PFO-negative; the group of patients with cortical lesion included patients who had cortical lesion only and patients who had both cortical and non-cortical lesion.

Table 2. PFO prevalence in patients with or without brain lesions according to different age groups.

	Total (n=424)	PFO-negative (n=180)	PFO-positive (n=244)	p-value*
DWI lesion-negative, n (%)	178(42.0)	80 (44.9)	98(55.1)	0.379
age<34	81(19.1)	35(43.2)	46(56.8)	0.673
34≤age< 46	56(13.2)	27(33.8)	29(29.6)	0.555
46≤age< 55	30(7.1)	13(16.2)	17(17.3)	0.713
age≥55	11(2.6)	5(6.2)	6(6.1)	0.972
DWI lesion-positive, n (%)	246(58.0)	100(55.6)	146(59.8)	0.379
age<34	23(5.4)	4(4.0)	19(13.0)	0.017
34≤age< 46	48(11.3)	11(11.0)	37(25.3)	0.005*
46≤age< 55	72(17.0)	30(30.0)	42(28.8)	0.835
age≥55	103(24.3)	55(55.0)	48(32.9)	0.0005*

Data are frequencies (%) for categorized variables; *p-value calculated for PFO-positive vs PFO-negative;

Table 3. Probability of PFO presence in patients with brain lesion compared with those without brain lesion in different age groups.

	OR (95% CI)			
Age (years)	age≤34	34≤age≤46	46≤age≤55	age≥55
PFO probability	3.614* (1.128-11.580)	3.132* (1.334-7.350)	1.071 (0.453-2.532)	0.727 (0.209-2.534)

* p≤0.05

Table 4. Probability of PFO with L-RLS amounts in patients with brain lesion compared with those without in different age groups.

	OR (95% CI)			
Age (years)	age≤34	34≤age≤46	46≤age≤55	age≥55
Probability of L-RLS	4.000* (1.215-13.170)	2.738* (1.137-6.590)	1.021 (0.414-2.518)	0.709 (0.192-2.617)

* p≤0.05

L-RLS, large-RLS

Table 5. The probability of brain lesion in patients younger than 46 years according to different RLS amounts.

	OR (95% CI)		
RLS amounts	L-RLS vs S-RLS	L-RLS vs RLS (-)	S-RLS vs RLS (-)
Probability of brain lesion	0.939 (0.390-2.260)	3.049# (1.540-6.036)	3.248* (1.231-8.570)

* p<0.05 # p<0.005

L-RLS, large-RLS; S-RLS, small-RLS; RLS (-), RLS-negative