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Professional paper

PREVALENCE OF MIGRAINE IN PATENT FORAMEN OVALE ASSOCIATED STROKE

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Abstract

Migraine is one of the most common neurological disorders which, despite being benign in nature, can be associated with stroke. The coexistence of migraine with a patent foramen ovale (PFO) - a known risk factor for stroke in young patients, further supports this connection. This paper investigates the prevalence of migraine in patients with cryptogenic stroke or transient ischemic attack associated with PFO. The study hypothesizes that migraine, particularly in younger patients, may be linked to strokes related to PFO through right-to-left shunt (RLS) detected by contrast-enhanced transcranial Doppler ultrasonography (Bubble-cTCD). We conducted a prospective observational study on 86 patients aged 18-60 years, assessing the presence of RLS and migraine history. RLS was detected in 56.6% of patients with cryptogenic stroke or transient ischemic attack and in 18.18% of patients with stroke or transient ischemic attack of known cause. A significant association was found between a history of migraine and cryptogenic stroke or transient ischemic attack with RLS ($p < 0.04$). A history of migraine was reported in 33.33% of patients with RLS and in 8.7% of those without RLS. In conclusion, our results showed a statistically significant association between migraine and cryptogenic stroke patients with RLS, supporting the notion that PFO-related stroke is an important subgroup among younger stroke patients with migraine. This work contributes to the growing body of evidence, strengthening the connection between migraine, PFO, and stroke, and deepening the understanding of the underlying mechanisms that link these conditions

Keywords: migraine, right-to-left shunt, cryptogenic stroke, patent foramen ovale, Bubble- transcranial Doppler ultrasonography

1. Introduction

Migraine is often considered a benign condition that presents episodically, but it is a chronic disorder and one of the most prevalent neurological diseases in the world. Migraine has significant morbidity and high prevalence, especially in young adult. According to the Global Burden of Disease 2019 study, the estimated global prevalence of migraine increased from 721.9 million (95% UI: 624.9–833.4) in 1990 to 1.1 billion (95% UI: 0.98–1.3) in 2019 (Safiri et al., 2022; Amiri et al., 2022). Years of life with disability due to migraine increases from birth, peaks in the 30 to 34 age group, and then gradually declines in both sexes (Safiri et al., 2022). According to the International Headache Society, migraine can also be categorized as a secondary form of head pain when it arises in connection with an underlying medical issue - for example, the presence of a patent foramen ovale (PFO), which itself has been linked to an increased likelihood of brain-related vascular incidents (Mawet et al., 2014).

A PFO represents a birth-related abnormal opening between the atria of the heart, caused by the failure of the foramen ovale to seal entirely following delivery. The persistence of this opening can result in complications, particularly in relation to stroke. In young patients, approximately half of ischemic strokes (IS) are cryptogenic (Amarenco, 2005). Between 40% and 56% of

people younger than 55 who experience unexplained strokes have been identified as having a PFO (Melkumova et al., 2017).
Migraine and PFO are both very common in the general population, but PFO is more commonly seen in people with migraine. One hypothesis is that during a migraine attack, neuroactive and/or vasoactive substances that are usually filtered from the pulmonary circulation can bypass the pulmonary circulation through the right-to-left shunt (RLS) in the PFO and reach the cerebral circulation, causing migraine.
In addition, many meta-analyses and studies have so far shown a clear connection between migraine with aura and IS. Individuals with migraine with aura have a twofold increased risk of IS (Schürks et al., 2009; Lantz et al., 2017). However, the underlying mechanisms of this elevated risk remain unclear and are likely relevant only to a subset of migraineurs (Mawet et al., 2014). PFO may serve as a conduit for arterial microemboli or neuroactive/vasoactive substances, thereby linking migraine and cryptogenic stroke.
The objective of this research was to assess the frequency of migraine among patients with cryptogenic stroke (CS) or transient ischemic attack (TIA) and PFO by identifying RLS using contrast-enhanced transcranial Doppler ultrasonography (Bubble-cTCD). The results aimed to reinforce the link between migraine and stroke related to PFO, while also enhancing comprehension of how migraine is connected to ischemic cerebrovascular events.

2. Materials and methods

A total of 86 sequential individuals, aged between 18 and 60, presenting with either acute cerebral ischemia or TIA, received care at the Neurology Department of the General City Hospital "8th September" in Skopje during the period from February 1, 2023, to February 1, 2024, and were systematically enrolled in the investigation. Participation occurred either during the initial cerebrovascular incident or within 30 days following its identification. Entry requirements encompassed a confirmed diagnosis of TIA or a mild-to-moderate stroke (National Institutes of Health Stroke Scale score above 15), and only individuals suitable for Bubble-cTCD - meaning those without issues related to venous access - were eligible. Exclusion criteria included all patients with quantitatively and qualitatively affected consciousness, patients in a severe life-threatening condition, patients with sensorimotor aphasia, and pregnant women. All patients signed a written informed consent or, in cases where the patient was unable to give consent, the permission was obtained from a legal guardian or relative. We received appropriate permission from the hospital's ethics committee.
Information on baseline characteristics — including age, sex, and contributory factors for cerebral ischemia such as prior tobacco use, elevated blood pressure, high cholesterol levels, and diabetes — was thoroughly documented and analyzed. Specifically, data on previous coronary heart disease and susceptibility to atherosclerosis were gathered through measurement of carotid artery intima-media thickness. Additionally, participants completed a standardized survey to evaluate any prior episodes of migraine. All patients underwent standard diagnostic evaluation, including 12-lead electrocardiography, routine blood tests, neuroimaging methods such as computed tomography and/or magnetic resonance imaging of the brain, duplex ultrasonography of the extracranial cerebral arteries, and computed tomography angiography of the extracranial and intracranial vessels if high-grade Doppler stenosis was detected or patients underwent thrombolysis. Additional cardiovascular evaluations included transthoracic echocardiography and 24-hour electrocardiography Holter monitoring. Further tests were performed as indicated, such as screening for vasculitis, thrombophilia, and genetic disorders. Following completion of routine diagnostic procedures, strokes were categorized etiologically using the TOAST system (Trial of Org 10172 in Acute Stroke Treatment) as defined by Adams et al. (1993), prior to conducting the Bubble-cTCD assessment. Based on this classification,

participants were sorted into two cohorts: those with cerebrovascular events of determined origin, and those with unknown causes — classified as CSs or TIAs. All individuals from both categories underwent Bubble-cTCD, performed by a skilled neurosonology specialist in line with the recommendations of the Venice Consensus Conference (Jauss & Zanette, 2000). The presence and severity of detected RLS were evaluated using the Spencer Logarithmic Scale (Spencer et al., 2004), with a score of grade 3 or above interpreted as a positive indication of RLS.

Statistical Analysis

Categorical variables were presented as absolute frequencies accompanied by their respective percentages. Continuous data were described using means with standard deviations, medians with interquartile ranges, along with minimum and maximum values. Group comparisons for categorical variables were performed using either the Chi-square (χ^2) test or Fisher's exact test, as appropriate. To assess the independent association between CS and PFO, univariate and multivariate logistic regression analyses were carried out, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were executed using SPSS software, version 23.0

3. Results

The participants' ages ranged from 20 to 58 years, with an average age of 42.2 ± 8.3 years. Among the 86 subjects, 26 (49%) were women, and 27 (50.9%) were men. Only 8.14% of the cohort experienced a TIA. Stroke was identified as cryptogenic in 61.63% of cases, while 38.37% were classified as strokes of known origin. Compared to patients with stroke or TIA of established etiology, those with CS/TIA exhibited a notably lower incidence of hypertension, hyperlipidemia, diabetes mellitus, and prior coronary artery disease, with the exception of smoking history, which showed no statistically meaningful difference between groups. RLS was significantly more common among individuals with CS/TIA than in those with stroke/TIA of known cause ($p < 0.0004$). Specifically, RLS was detected in 56.6% of cryptogenic stroke patients and in 18.18% of patients with stroke/TIA of confirmed etiology. (Figure 1)

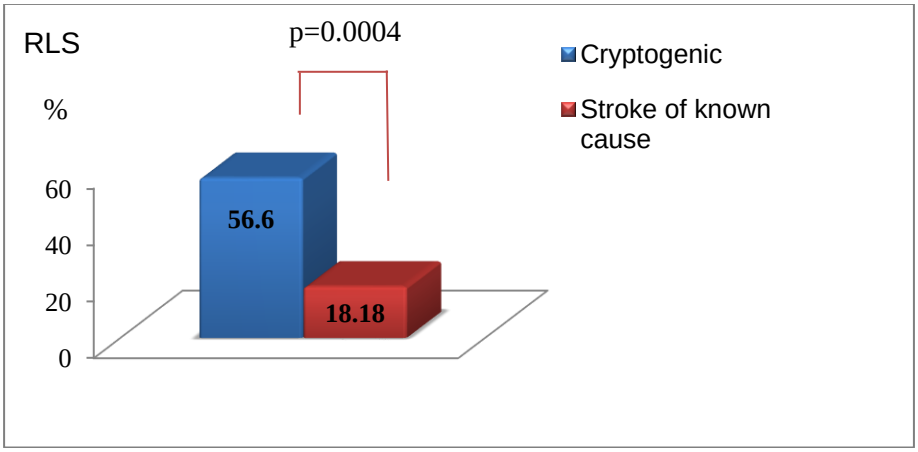

Figure 1. Visual depiction of the occurrence of RLS among patients diagnosed with CS/TIA compared to those with stroke/TIA of established etiology

A significant statistical disparity in smoking status was detected between the two groups ($p = 0.028$). Among patients with CS/TIA, those exhibiting RLS had a significantly lower proportion of smokers compared to patients without RLS (26.67% versus 56.52%). Additionally, hypertension was notably less prevalent in the RLS-positive CS/TIA group compared to their

RLS-negative counterparts (16.67% vs. 52.17%; p = 0.0061). Likewise, hyperlipidemia was notably less common in patients exhibiting both RLS and CS/TIA compared to those without RLS (16.67% versus 56.52%; p = 0.0024). Conversely, no statistically significant difference was found in the prevalence of diabetes mellitus between CS/TIA patients with and without RLS (Table 1).

Table 1. Risk factors for CS in patients with and without RLS

	Cryptogenic stroke/TIA		
	RLS (n=30)	Without RLS (n=23)	p-level
History of smoking	8 (26.67%)	13(56.52%)	P=0.028
Hypertension	5 (16.67%)	12 (52.17%)	p=0.0061
Hyperlipidemia	5 (16.67%)	13 (56.52%)	p=0.0024
Diabetes mellitus	0	3 (13.04%)	p=0.076
X2 (Chi-square test), Fisher's exact test, sig p<0.05.			

Patients with CS/TIA and RLS had significantly lower carotid intima-media thickness (IMT) compared with those without RLS (p = 0.038). The mean IMT was 0.53 ± 0.08 mm in patients with RLS and 0.59 ± 0.10 mm in patients without RLS. (Figure 2)

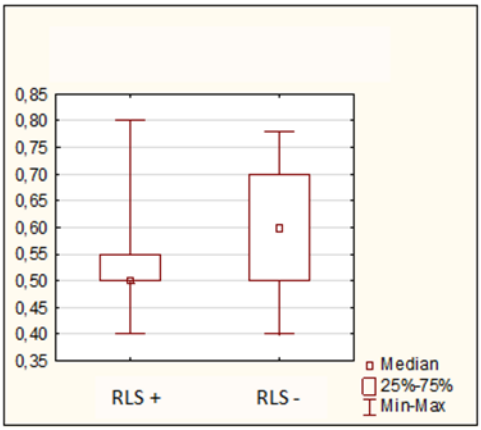

Figure 2. Graphical representation of intimal media thickness values in patients with and without RLS in CS/TIA

Table 2 presents the findings from both univariate and multivariate logistic regression models assessing the predictive significance of CS compared to stroke of known cause in relation to the presence of RLS. In the unadjusted univariate model, the odds ratio was 5.870 (95% CI: 2.079–16.574, p < 0.0001). After adjustment, the odds ratio decreased to 4.012 (95% CI: 1.323–12.171, p = 0.014), suggesting that individuals with CS/TIA are roughly four times more likely to exhibit RLS than those with strokes of identified etiology. Multivariate regression confirmed that RLS presence independently correlates with CS/TIA.

Table 2. Binary logistic regression analysis for RLS

	Univariate				Multivariate			
	p	**Odds ratio**	**95% CI for Exp (B)**		**p**	**Odds ratio**	**95% CI for Exp (B)**	
			Lower	**Upper**			**Lower**	**Upper**
All Stroke	Ref.	Stroke with known cause						
Cryptogenic stroke	0.000	5.733	2.734	12.021	0.001	3.949	1.802	8.653
Stroke	Ref.	Stroke with known cause						
Cryptogenic stroke	0.001	5.870	2.079	16.574	0.014	4.012	1.323	12.171
Odds Ratio for the presence of RLS in patients with CS/TIA versus those with stroke/TIA of known cause. Odds Ratio was adjusted for age, arterial hypertension, and coronary artery disease.								

A statistically significant disparity was observed in the occurrence of migraine as a comorbid condition between patients with RLS and CS/TIA versus those without RLS and CS/TIA, with a significant association of migraine with RLS ($p < 0.04$). A migraine attack history was documented in 33.33% of patients possessing RLS, whereas just 8.7% of patients lacking RLS reported such a history (Figure 3, Table 3).

Table 3. Prevalence of migraine in patients with CS/TIA and RLS

Cryptogenic stroke/TIA				
	n	RLS (%)	Without RLS (%)	
yes	21	10(33.33)	2 (8.7)	Fisher's exact p=0.04
no	32	20(66.67)	21 (91.3)	

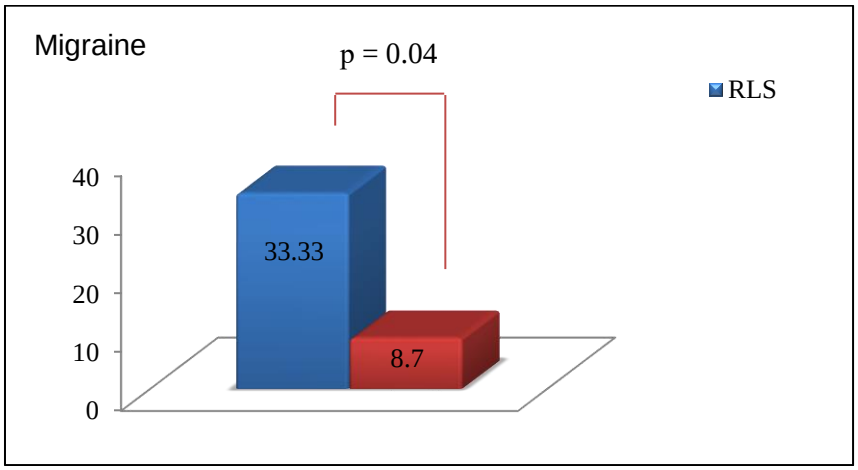

Figure 3. Visual illustration of migraine prevalence among patients with CS/TIA with RLS compared to those without RLS

4. Discussion

Over the past two decades, a multitude of investigations has revealed that PFO is markedly more prevalent among individuals experiencing CS than in the broader population, especially in younger cohorts where PFO has been validated as a CS risk factor. In our study, we focused on participants aged 60 or below, since CS are diagnosed more often in this age population and the association between PFO and CS has been consistently confirmed in this group.

In our investigation, a notably greater occurrence of RLS was observed among patients with CS/TIA compared to those experiencing stroke/TIA of identified etiology (56.6% versus 18.18%, $p = 0.0004$). This aligns with prior research demonstrating a strong correlation between PFO and CS in patients under 55 years (Rus Mansilla et al., 2008; Overell et al., 2000; Lamy et al., 2002). For example, Overell and colleagues' meta-analysis reported an odds ratio (OR) of 6.00 (95% confidence interval [CI]: 3.72–9.68) for PFO presence in cryptogenic stroke patients compared to those with stroke of known origin (Overell et al., 2000). Similarly, Koutroulou et al. (2020) identified PFO prevalence rates of 58.1% using contrast transcranial Doppler and 48.9% via transesophageal echocardiography in CS cases. Patients with both RLS and CS/TIA demonstrated fewer traditional stroke risk factors, a reduced prevalence of comorbidities such as hypertension, diabetes mellitus, and coronary artery disease, and markedly lower IMT - an indicator of atherosclerosis - than those experiencing strokes or TIAs of established etiology. Such observations imply that these traditional risk factors likely do not contribute to stroke pathogenesis in PFO patients, supporting the hypothesis that PFO represents a standalone element predisposing to cerebral infarction of unknown origin and brief cerebral ischemic episodes.

Prior observational studies, neuroimaging findings, and genetic evidence indicate that migraine, particularly migraine accompanied by aura, elevates the risk of stroke. The mechanisms linking stroke and migraine are vascular and metabolic abnormalities such as endothelial dysfunction, paradoxical embolism via RLS, hypercoagulability, cervical artery dissection, adverse lifestyle factors, and obesity. Additionally, genetic predispositions may heighten susceptibility to cortical spreading depression - a phenomenon that sensitizes brain tissue to ischemia (Mawet et al., 2014). Migraine with aura may also increase ischemic risk via migraine - related infarction, vasoconstrictive medication effects, or platelet aggregation (Mawet et al., 2014). 3 major meta-analyses (Etminan et al., 2005; Schurks et al., 2009; Spector et al., 2010) confirmed a significant association between migraine and stroke, with stronger correlations observed in women, individuals under 45 years of age, smokers, and women using oral contraceptives. Furthermore, MacClellan et al. (2007) found that this association was particularly pronounced in patients with CS.

Epidemiological data further emphasize a strong connection between migraine and PFO. Numerous studies have reported a higher incidence of migraine in patients diagnosed with PFO (Schwedt et al., 2008; Tang et al., 2022). For example, a cross-sectional investigation conducted in China found that 12.83% of individuals with PFO experienced migraine without aura, with PFO markedly increasing the likelihood of migraine occurrence (Tang et al., 2022). Additionally, Schwedt et al. (2008) conducted a meta-analysis of 18 studies, which demonstrated a significant association between PFO and migraine, presenting an odds ratio of 5.13 (95% CI: 4.67–5.59). Taken together, the existing evidence consistently confirms the link between migraine and PFO. Del Sette and colleagues found that RLS occurs more frequently in patients with migraine accompanied by aura than in healthy subjects, with a prevalence comparable to that seen in young stroke patients (Del Sette et al., 1998). The mechanism underlying the migraine - PFO relationship remains unclear. One hypothesis suggests a shared genetic basis for both migraine and atrial septal abnormalities (Arquizan et al., 2001). An alternative hypothesis, suggested by Wilmshurst et al. (2000), proposes that vasoactive agents

such as serotonin and endothelin circumvent the pulmonary filtration through a PFO and enter the cerebral bloodstream, possibly provoking migraine episodes. Serotonin, released during platelet activation (Cloutier et al., 2018), and endothelin, elevated during migraine (Farkkila et al., 1992), are both normally metabolized in the lungs. The RLS mechanism allows these substances to bypass metabolism and enter cerebral circulation, initiating cortical spreading depression and potentially causing migraine (Deen et al., 2019; Sevgi et al., 2012).

Despite extensive studies, there remains limited information regarding the prevalence of migraine specifically in stroke patients with PFO. Our study revealed a significant association between migraine and CS accompanied by RLS ($p < 0.04$). A history of migraine was recorded in 33.33% of patients with RLS, whereas only 8.7% of those without RLS reported migraine. These findings align with earlier research (Del Sette et al., 1998; Anzola et al., 1999; Wilmshurst et al., 2000). Additionally, the Italian Project on Stroke in Young Adults identified a significantly greater occurrence of RLS among patients with ischemic stroke (IS) and migraine with aura, reporting an odds ratio (OR) of 2.41 (95% CI 1.47–3.95) (Pezzini et al., 2011).

While migraine has been extensively researched, data on its prevalence in patients with PFO-related stroke remain limited. Our results revealed a statistically significant association between migraine and stroke connected to PFO ($p < 0.04$). Similarly, Lamy et al. identified an increased occurrence of migraine among CS patients with PFO (27.3%) versus those lacking PFO (14.0%), yet they did not observe a significant association between migraine and either shunt size or isolated atrial septal aneurysm (Lamy et al. 2002). Experimental animal models further support the RLS - migraine - stroke connection. Dreier et al. (2007) demonstrated that endothelin-1 crossing an RLS induces cortical spreading depression via endothelin A receptors, triggering vasoconstriction, hypoperfusion, and ultimately infarction.

Together, these findings clarify the complex interplay between migraine and strokes related to PFO, highlighting a specific subgroup of PFO-associated strokes in individuals with migraine. Although the impact of PFO closure on decreasing migraine episodes and improving life quality is still unclear, the advantage of percutaneous PFO closure for secondary stroke prevention in carefully chosen patients with PFO-related stroke is well documented. Additional studies are needed to more precisely characterize and validate the connection between migraine and PFO-related stroke. Such investigations may also prompt critical questions, including whether percutaneous PFO closure should be considered for migraine sufferers -particularly those experiencing migraine with aura - and what additional factors should be evaluated to devise optimal stroke prevention strategies.

5. Conclusion

Our study confirmed a significant association between migraine and PFO-related stroke among young patients. This work contributes to the growing body of evidence, strengthening the connection between migraine, PFO, and stroke, and deepening the understanding of the underlying mechanisms that link these conditions.

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