Received: May 16, 2023
Accepted: June 10, 2023

Acad Med J 2023;3(2):189-195
UDC:616.857
https://www.doi.org/10.53582/AMJ2332189ds
Case report

MIGRAINE AND PATENT FORAMEN OVALE - CASE REPORT

Deleva Stoshevska Tatjana[1], Nikoloska Sofija[2], Veljanovski Dimitar[3], Nikoloski Marko[4], Stoshevski Bojan[5]

[1]City General Hospital 8th September, Department of Neurology, Skopje, Republic of North Macedonia
[2]University Clinic for Ear, Nose and Throat, Skopje, Republic of North Macedonia
[3]City General Hospital 8th September, Department of Radiology, Skopje, Republic of North Macedonia
[4]University Clinic for Surgical Diseases "St. Naum Ohridski" – Skopje, Republic of North Macedonia
[5]Universiy Clinic for Pulmonology and Allergology, Skopje, Republic of North Macedonia
e-mail: deleva_tatjana@yahoo.com

Abstract

Migraine is a headache disorder, typically characterized by unilateral headache (with or without aura) of pulsating quality, which is associated with nausea, phonophobia and photophobia. The patent foramen ovale (PFO) is a remnant of the fetal circulation. Multiple studies suggest that migraine is more prevalent in subjects with PFO and *vice versa*, suggesting that PFO and migraine may be risk factors for each other.

Case report. We present a 33-year-old female patient with unilateral hemicranial headache, mostly on the right side, pain in the right eye, nausea, vomiting, photo and phonophobia, with previous visual difficulties with the ipsilateral eye. The complaints usually lasted 2-3 days and were associated mostly with the menstrual cycle. There were also occasional bouts of dizziness. Ophthalmological and otorhinolaryngological nature of these complaints was excluded with additional investigations. In addition, nuclear magnetic resonance (NMR) of the brain, color Doppler duplex sonography (CDDS) of carotid and vertebral arteries were performed, all with normal findings. On transcranial color Doppler sonography with Bubble test, a positive finding was obtained for a Grade 4 right-left shunt and the patient was referred for cardiology assessment and evaluation. The patient was diagnosed with migraine with aura (visual) and PFO.

Conclusion. Results from epidemiological studies examining the relationship between PFO and migraine are mixed at best. It is unclear if there is a causal relationship or simply a co-existence of these two conditions. More research of PFO in migraine is clearly needed before we can consider changing our views on the aforementioned conclusions.

Keywords: migraine, patent foramen ovale

Introduction

Migraine is a widespread neurological disorder. Migraine is a common, recurrent and often disabling headache disorder, typically characterized by unilateral headache (with or without aura) of pulsating quality, which is associated with nausea, phonophobia and photophobia. The diagnosis of migraine is made based on criteria laid down in the International Classification of Headache Disorders (ICHD-2) organized by the International

Headache Society[1]. Migraine, one of the most common conditions of primary headache, often occurs in people aged 20-64 years old, with a high disability rate and heavy disease burden[2]. According to the 2013 Global Burden of Disease survey from the World Health Organization (WHO), migraine was the 3rd most common disease and ranked 6th in causing major disability in humans, which was calculated based on the number of years of life lost to disability[3].

The patent foramen ovale (PFO) is a remnant of the fetal circulation. *In utero*, the foramen ovale serves as a conduit for right-to-left shunting of oxygenated blood from the placenta into the systemic circulation. At birth, as the pulmonary circulation establishes, the increasing left atrial pressure causes functional closure of the foramen ovale. The anatomical closure of the atrial *septum primum* and *septum secundum* usually occurs by 1 year of age. If, however, it is not closed after three years of age, it is termed as patent foramen ovale (PFO). When there is incomplete closure of the flap-like opening between the *septum primum* and *septum secundum*, a patent foramen ovale (PFO) ensues.

There is debate within the cardiology and neurology communities as to whether there is a causal relationship between PFO and migraine.

PFO accounts for 95% of all right-to-left shunts[4]. One possible mechanism which implicates a role for the right-to-left shunt in the development of migraine is that subclinical emboli and metabolites from the venous system bypass the pulmonary circulation via the PFO, thus entering the systemic circulation and resulting in irritation of the trigeminal nerve and brain vasculature, which in turn triggers migraine. One such metabolite is serotonin which is normally metabolized by the pulmonary monoamine oxidase enzyme. In the presence of a PFO, serotonin is shunted away from the lungs and is postulated to trigger migraine[5]. Platelet activation and aggregation has been shown to be increased in patients with migraine[6]. Serotonin is released from aggregating platelets. Furthermore, a small double-blind crossover study has shown that aspirin, an anti-platelet drug which might be expected to reduce the formation of platelet-fibrin complexes and thus improve migraine, has a statistically significant prophylactic effect in migraine[7]. Transient hypoxemia due to paradoxical shunting of blood through the PFO causes microinfarcts in the brain, leading to irritation and a tendency for migraine - any etiology that predisposes to hypoxia or thrombosis may be a factor.

Various etiologies that predispose to hypoxia or thrombosis in the presence of a PFO may predispose to migraine by promoting subclinical ischemia and paradoxical embolism[8]. Resting and stress hypoxemia related to left-to-right shunting (paradoxical embolism) across a PFO has been demonstrated in the absence of pulmonary embolism. Moreover, a tiny embolus in the systemic circulation can pass through the PFO and directly into the arterial system. These “paradoxical embolisms”, which lead to tiny brain infarctions, triggering low perfusion or cortical spreading depression, may cause a migraine attack[9] and could be the most probable pathophysiological mechanism on how PFO could lead to a migraine attack.

Others have also found that a RLS (right to left shunt) is correlated with a higher frequency of multiple cortical lesions in DWI sequences, which distinguishes itself from atrial fibrillation-related ischemic stroke that is seen occurring in the cortical-subcortical territory[10]. In migraine patients with PFO when undergoing the Valsalva maneuver, blood flow of the posterior circulation significantly exceeds that of the anterior circulation and the posterior circulation is more likely to be involved[11]. During the aura phase, focal areas of hypoperfusion close to the ischemic threshold in occipital regions, which might be due to these cerebral microinfarcts, can cause visual symptoms.

RLS results in decreased blood oxygen saturation and hypoxia and will trigger cortical spreading depression which can lead to migraines. On the other hand, a decrease in cerebral oxygen saturation increases the expression of plasminogen activator-1 and results in inhibition of fibrinolysis and thus increases the possibility of microembolization.

Genetic factors may also cause these patients to develop both diseases. About 2-fold higher frequency of PFO is seen in migraineurs as compared to the general population, suggesting that a genetic influence could predispose some patients to a higher risk of developing both migraine and atrial septal abnormalities; [12]hereditary associations with migraine have been found in autosomal dominant PFO[13]. Taken together, the pathophysiological mechanisms are complex and migraine is possibly the result of these pathways working synergistically.

Case report

A 33-year-old patient, married, mother of one child, denies habits, food and drug allergy. A reason for a neurological examination is a headache that is usually localized on the right half of the head and around the right eye, but sometimes on the left half of the head. Headache is usually preceded by visual difficulties, such as blurred vision, "seeing through water", sometimes as flashes in part of the field of vision. Sometimes there is nausea, not vomiting. During the headache, light and sounds are considered, there is a feeling of general weakness and adynamia. Headache lasts 2-3 days, with variable response to analgesic therapy (usually takes Tabl. Ibuprofen, Drag. Diazepam a 2mg, Tabl. Vitamin B6). These complaints first appeared about 15 years ago, but in the last few months they have become more frequent, almost every month, in the period before or after the end of the menstrual cycle. Due to the accompanying visual difficulties, the patient was examined by an ophthalmologist with performed tonometry, fundus examination, perimetry and optical coherence tomography (OCT) - with normal findings. Among other diseases, she gives information about lower values of serum iron, hyperplasia of the endometrium, for which she was examined by a gynecologist. Anamnestic data that about 7 years ago she had an inflammation of the left ear with accompanying dizziness, since then, when suddenly turning the neck, she sometimes has short-term (a few minutes) bouts of dizziness that spontaneously subside. For vertigo and rapid heartbeat and feeling of palpitations, she was investigated 5 years ago at the PHI UC for Endocrinology - Skopje, and endocrinological etiology is excluded. She denies any other comorbidity and does not use chronic therapy.

Patient denies current or previous infectious symptomatology. She contracted COVID-19 in November 2020. She is not vaccinated with SARS-CoV-2 vaccine.

Negative family history of migraine and other diseases of neurological interest.

The neurological status of the patient was normal. As a function of etiological resolution of the presented symptomatology, a series of follow-up investigations were carried out according to neurological indication: laboratory analysis of blood with normal findings; brain nuclear magnetic resonance (NMR) (standard pulse sequences and Time-Of-Flight (TOF) series): cerebrum, cerebellum and brainstem without focal lesions. Ventricular system and subarachnoid spaces neatly wide, free. No diffusion restriction is observed. The TOF series is a neat display of the brain's blood vessels.

Color Doppler duplex sonography (CDDS) of carotid and vertebral arteries: right side, common carotid artery (ACC) with regular flow and regular flow velocities, IMT=0.55 mm. Bifurcation with normal morpho-functional characteristics. Internal carotid artery (ACI) with regular flow and flow velocities. External carotid artery (ACE) normal morpho-functionally. Vertebral artery with physiological anterograde flow, regular flow velocities, diameter up to 2.6 mm. Left side, ACC with neat flow and neat flow velocities, IMT=0.45 mm. Bifurcation

with normal morpho-functional characteristics. ACI with ordered flow and flow velocities. ACE normal morpho-functionally. Vertebral artery with physiological anterograde flow, regular flow velocities, diameter up to 3.4 mm.

Transcranial color Doppler sonography (TCCD) for analysis of cerebral blood vessels: right side, trans-temporal window: medial cerebral artery (ACM), M1 and M2 segment with normal flow and flow velocities, anterior cerebral artery (ACA) with ordered flow and velocities, posterior cerebral artery (ACP), P1 and P2 segment with normal flow and flow velocities. Left side, trans-temporal window: ACM, M1 and M2 segment with normal flow and flow velocities, ACA with normal flow and velocities, ACP, P1 and P2 segment with normal flow and flow velocities.

A trans-occipital window was not realized.

Transcranial color Doppler sonography with bubble test: transtemporal approach, about 2 micro-embolic signals were obtained in the ACM after contrast injection. With the Valsalva maneuver, over 50 micro-embolic signals with a shower effect were obtained. The test was positive for right-left shunt of 4th degree.

The patient was diagnosed with migraine with aura (visual) according to the second edition of the International Classification of Headache Disorders (ICHD-2) and PFO.
According to the positive result of the TCCD bubble test for right-left shunt of 4th degree, the patient was referred for cardiology assessment and evaluation. The patient was referred to an interventional cardiologist for further diagnosis and treatment.

Discussion

The idea that migraine and PFO is correlated has only been around for a few decades, and much of the underlying pathophysiology is still based on hypotheses.

Del[14] first proposed the relationship between migraine and PFO in 1998; he found that the incidence of PFO in migraine patients was significantly higher than that in healthy controls. Later, a number of studies found that the incidence of PFO in migraine patients was 14.6-66.5% [15] while the incidence in the general population was 9-27.3%[16]. In turn, in the population with PFO, the incidence of migraine was 9.13-51.7%, which was also higher than the incidence of migraine in the general population[17].

On the other hand, the salient shortcomings of the possible pathophysiological explanations for the PFO-migraine relationship have been expertly reviewed by Gupta[18]. It is unlikely that the passage of subclinical emboli and metabolites would stream into and lodge at exactly the same areas of the brain to cause the typical lateralizing and often cyclical (e.g., menstrual migraine) headaches over decades in patients, as embolic events are characteristically unpredictable phenomena. It is also well known that most patients with PFO are asymptomatic, while not all migraine patients have a PFO[18]. PFO is present at birth and will persist for life if it does not close spontaneously. However, migraine typically does not start at birth, but rather in adolescence or early adult life, thus arguing against the relevance of PFO in migraine. Furthermore, although the size of a PFO increases from the first to the tenth decade of life, migraine attacks generally tend to subside with advancing age. Migraine has been reported to be up to twice as common in women compared to men, but the prevalence of PFO is similar in men and women[19]. In addition, migraine is frequent in young patients with ischemic stroke, but infrequent in older patients with ischemic stroke[20]. This would be against the hypothesis that PFO is a causal factor for migraine, as the younger cohort will have relatively smaller PFO defects. Although white matter lesions are commonly found on brain magnetic resonance imaging of migraine patients, the presence of right-to-left shunting does not increase this lesion load in patients with migraine, arguing

against the importance of the paradoxical embolism theory leading to microinfarcts in the brain in patients with migraine[21].

The frequency of PFO in the population has been reported at 15–35% in autopsy studies, [21] and appears to decrease with age[22]. *In vivo* studies with transesophageal echocardiography (TOE) have reported a prevalence of PFO in the population of 24%, which is similar to that of autopsy studies[23]. It is obvious that PFO and migraine are common conditions in the population. The next question is whether PFOs are found more commonly in people who suffer from migraine which would lend support to the causal relationship between PFO and migraine. Two Italian groups were the first to report in case–control studies using transcranial Doppler ultrasonography (TCD) a significantly higher prevalence of PFO in subjects with migraine with aura[24,25].

Furthermore, a study of young cryptogenic stroke patients assessed by transoesophageal echocardiography (TOE) demonstrated an increased prevalence of migraine in patients with PFO compared to patients without PFO[26]. In a meta-analysis of seven studies it was demonstrated that the prevalence of PFO in migraineurs ranged from 40% to 72%, with an odds ratio ranging from 1.87 to 5.88, leaving the authors to conclude that there was only low-grade evidence supporting the association between PFO and migraine[27]. A study using modern ultrasound technology in combination with a rigorous saline contrast echocardiogram protocol which allowed more sensitive detection of PFO found no significant association between PFO and migraine, or between small- and moderate-size PFO and migraine. This study did not have a large enough sample of large-size PFO to study its association with migraine[28]. In addition, a large case–control study failed to show an association between migraine and PFO assessed by transthoracic echocardiogram (TTE) with second harmonic imaging and TCD[29].

Furthermore, the treatment of migraine with percutaneous closure PFO remains controversial. Lastly, researchers should consider that the closure of PFO may carry a small but relevant risk of serious adverse events including stroke, pericardial tamponade, atrial fibrillation and death[30].

However, until now, no consensus has been reached on the relationship between PFO and migraines. Therefore, this case report aims to further investigate the association between migraine and PFO.

In clinical practice, testing for PFO in patients with migraine, no matter the ethnological correlation with migraine, means also prevention from possible cerebrovascular incidents, especially in young patients, which is of huge medical significance.

Conclusion

Multiple studies suggest that migraine is more prevalent in subjects with PFO and *vice versa*, suggesting that PFO and migraine may be risk factors for each other, but more research is needed to confirm this speculation. Results from epidemiological studies examining the relationship between PFO and migraine are mixed at best. It is unclear if there is a causal relationship or simply a co-existence of these two conditions. Furthermore, the treatment of migraine with percutaneous closure PFO remains controversial. Lastly, researchers should consider that the closure of PFO may carry a small but relevant risk of serious adverse events including stroke, pericardial tamponade, atrial fibrillation and death[30]. More research of PFO in migraine is clearly needed before we can consider changing our views on the aforementioned conclusions.

Conflict of interest statement. None declared.

References

1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004; 24 Suppl 1: 9-160. doi: 10.1111/j.1468-2982.2003.00824.x.
2. Stewart WF, Roy J, Lipton RB. Migraine prevalence, socioeconomic status, and social causation. *Neurology* 2013 Sep 10; 81(11): 948-955. doi: 10.1212/WNL.0b013e3182a43b32.
3. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(9995): 743-800. doi: 10.1016/ S0140-6736(15)60692-4.
4. Weber F, Goriup A. Prevalence of right-to-left shunts in active fighter pilots. Aviat *Space Environ Med* 2007; 78(2): 135-136.
5. Sharma A, Gheewala N, Silver P. Role of patent foramen ovale in migraine etiology and treatment: a review. *Echocardiography* 2011; 28(8): 913-917. doi: 10.1111/j. 1540-8175.2011.01460.x.
6. Borgdorff P, Tangelder GJ. Migraine: possible role of shear-induced platelet aggregation with serotonin release. *Headache* 2012; 52(8): 1298-318. doi: 10.1111/j.1526-4610. 2012.02162.x.
7. Grotemeyer KH, Scharafinski HW, Schlake HP, Husstedt IW. Acetylsalicylic acid vs. metoprolol in migraine prophylaxis--a double-blind cross-over study. *Headache* 1990; 30(10): 639-641. doi: 10.1111/j.1526-4610.1990.hed3010639.x.
8. Prandota J. Migraine associated with patent foramen ovale may be caused by reactivation of cerebral toxoplasmosis triggered by arterial blood oxygen desaturation. *Int J Neurosci* 2010; 120(2): 81-87. doi: 10.3109/00207450903458647.
9. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci.* 2001; 100:215–20.
10. Kim BJ, Sohn H, Sun BJ, Song JK, Kang DW, Kim JS, *et al*. Imaging characteristics of ischemic strokes related to patent foramen ovale. *Stroke* 2013; 44(12): 3350-3356. doi: 10.1161/STROKEAHA.113.002459.
11. He D, Li Q, Xu G, Hu Z, Li X, Guo Y, *et al*. Clinical and imaging characteristics of PFO-related stroke with different amounts of right-to-left shunt. *Brain Behav* 2018; 8 (11): e01122. doi: 10.1002/brb3.1122.
12. Kumar P, Kijima Y, West BH, Tobis JM. The Connection Between Patent Foramen Ovale and Migraine. *Neuroimaging Clin N Am* 2019; 29(2): 261-270. doi: 10.1016/j.nic.2019.01.006.
13. Wilmshurst PT, Pearson MJ, Nightingale S, Walsh KP, Morrison WL. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. *Heart* 2004; 90(11): 1315-1320. doi: 10.1136/hrt.2003.025700.
14. Del Sette M, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, *et al*. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis* 1998; 8(6): 327-230. doi: 10.1159/000015875.
15. Lip PZ, Lip GY. Patent foramen ovale and migraine attacks: a systematic review. *Am J Med* 2014; 127(5): 411-420. doi: 10.1016/j.amjmed.2013.12.006.
16. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci* 2001; 100(2): 215-220.
17. Dao CN, Tobis JM. PFO and paradoxical embolism producing events other than stroke. *Catheter Cardiovasc Interv* 2011; 77(6): 903-909 doi: 10.1002/ccd.22884.

18. Gupta VK. Patent foramen ovale closure and migraine: science and sensibility. *Expert Rev Neurother* 2010; 10(9): 1409-1422 doi: 10.1586/ern.10.125.
19. Gupta V, Yesilbursa D, Huang WY, Aggarwal K, Gupta V, Gomez C, et al. Patent foramen ovale in a large population of ischemic stroke patients: diagnosis, age distribution, gender, and race. *Echocardiography* 2008; 25(2): 217-227. doi: 10.1111/j.1540-8175.2007.00583.x.
20. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. *Neurology* 2001; 57(10): 1805-1811. doi: 10.1212/wnl.57.10.1805.
21. Kurth T, Mohamed S, Maillard P, Zhu YC, Chabriat H, Mazoyer B, *et al*. Headache, migraine and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. *BMJ* 2011; 342: c7357. doi: 10.1136/bmj.c7357.
22. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; 59(1): 17-20. doi: 10.1016/s0025-6196(12)60336-x.
23. Meissner I, Khandheria BK, Heit JA, Petty GW, Sheps SG, Schwartz GL, *et al*. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol* 2006; 47(2): 440-445. doi: 10.1016/j.jacc.2005.10.044.
24. Anzola GP, Magoni M, Guineani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999; 52(8): 1622-1625. doi: 10.1212/wnl.52.8.1622.
25. Del Sette M, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, *et al.* Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis* 1998; 8(6): 327-330. doi: 10.1159/000015875.
26. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, *et al*. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA study. Atrial septal aneurysm. *Stroke* 2002; 33(3): 706-711. https://doi.org/10.1161/hs0302.104543
27. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia* 2008; 28(5): 531-540. doi: 10.1111/j. 1468-2982.2008.01554.x.
28. Woods TD, Harmann L, Purath T, Ramamurthy S, Subramanian S, Jackson S, *et al*. Small- and moderate-size right-to-left shunts identified by saline contrast echocardiography are normal and unrelated to migraine headache. *Chest* 2010; 138 (2): 264-269. doi: 10.1378/chest.09-2797.
29. Garg P, Servoss SJ, Wu JC, Bajwa ZH, Selim MH, Dineen A, *et al.* Lack of association between migraine headache and patent foramen ovale: results of a case–control study. *Circulation* 2010; 121(12): 1406-1412. doi: 10.1161/ CIRCULATIONAHA.109.895110.
30. Steiner TJ, Jensen R, Katsarava Z, Linde M, MacGregor EA, Osipova V, *et al*. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European Headache Federation and Lifting The Burden: the Global Campaign against Headache. *J Headache Pain* 2019; 20(1): 57. doi: 10.1186/s10194-018-0899-2.