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Neurological disorders associated with patent foramen ovale

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ABSTRACT

The foramen ovale between the right and left atria remains open in 15–25% of people over 18 years of age and in most of them it does not manifest itself clinically. At the same time, the defect is associated with a number of diseases and conditions: the development of atrial fibrillation, worsening the degree of hypoxemia in patients with pulmonary diseases, etc. There are studies devoted to the influence of a patent foramen ovale on the occurrence and course of cryptogenic stroke, migraine, syncope, dizziness, transient global amnesia, visual impairment and ocular movement disorders. However, the actual contribution of patent foramen ovale to the development of neurological disorders remains a matter of debate. The purpose of this work was to assess the significance of a patent foramen ovale in the development of neurological disorders in adults and children by analyzing literature data for the period from 2012 to 2022. In the process of studying the literature, a high prevalence of the defect was identified among patients with stroke and migraine (especially migraine with aura). At the same time, data from randomized clinical trials in patients with stroke and migraine showed selectively high effectiveness of closure of the patent foramen ovale in certain groups of patients. The association of patent foramen ovale with transient global amnesia, syncope, and dizziness has been confirmed in a limited number of studies. Cases of visual impairment and ocular movement disorders associated with the presence of a patent foramen ovale have been described. Thus, it was concluded that a patent foramen ovale is a risk factor for the development of neurological disorders only in certain groups of patients with stroke and migraine. The connection between the defect and the development of transient global amnesia, syncope, dizziness, visual impairment, as well as the development of neurological pathology in children requires further research.

Keywords: patent foramen ovale; stroke; migraine; transient global amnesia.

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Неврологические нарушения, ассоциированные с открытым овальным окном

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АННОТАЦИЯ

Овальное окно между правым и левым предсердиями остаётся открытым у 15–25% людей старше 18 лет и у большинства не проявляется клинически. В то же время, дефект ассоциируют с рядом заболеваний и состояний: развитием фибрилляции предсердий, ухудшением степени гипоксемии у пациентов с лёгочными заболеваниями и др. Существуют исследования, посвящённые влиянию открытого овального окна на возникновение и течение криптогенного инсульта, мигрени, синкопальных состояний, головокружения, транзиторной глобальной амнезии, нарушений зрения и глазодвижения. Тем не менее, реальный вклад открытого овального окна в развитие неврологических нарушений остаётся предметом споров. Целью данной работы была оценка значимости открытого овального окна в развитии неврологических нарушений у взрослых и детей посредством анализа литературных данных за период с 2012 по 2022 г. В процессе изучения литературы была выявлена высокая распространённость дефекта среди пациентов с инсультом и мигренью (особенно мигренью с аурой). В то же время, данные рандомизированных клинических испытаний у пациентов с инсультом и мигренью показали избирательно высокую эффективность закрытия открытого овального окна у отдельных групп пациентов. Связь открытого овального окна с транзиторный глобальной амнезией, синкопе, головокружением подтверждалась в ограниченном числе исследований. Описаны случаи нарушений зрения и глазодвижения, связанных с наличием открытого овального окна. Таким образом, был сделан вывод о том, что открытое овальное окно — фактор риска развития неврологических нарушений лишь у определённых групп пациентов с инсультом и мигренью. Связь дефекта с развитием транзиторной глобальной амнезии, синкопе, головокружения, нарушений зрения, а также с развитием неврологической патологии у детей требует дальнейших исследований.

Ключевые слова: открытое овальное окно; инсульт; мигрень; транзиторная глобальная амнезия.

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ЭКО•ВЕКТОР

INTRODUCTION

The foramen ovale is a communication channel between the right and left atria during intrauterine development. It ensures the flow of oxygenated blood from the mother to the fetus, bypassing the nonfunctioning pulmonary circulation. In 70%–75% of cases, the foramen ovale closes completely during the first 2 years of life [1]. However, the patent foramen ovale (PFO) remains present in 15%–35% and 15%–25% of individuals according to autopsy data and echocardiographic studies (echocardiography), respectively [2].

Most individuals with PFO do not experience any clinical symptoms. However, this defect is linked to atrial fibrillation [1, 3], worsening hypoxemia in patients with pulmonary diseases [4], and various neurological conditions and symptoms. Numerous studies have investigated the impact of PFO on the occurrence and progression of cryptogenic stroke and migraine.

Patients with PFO may experience syncope [5, 6], vertigo [7], transient global amnesia (TGA) [8], and visual [9–13] and oculomotor [14, 15] disorders. These occurrences are usually attributed cerebral artery embolism [3, 16–18] and the influence of vasoactive substances such as serotonin, nitric oxide (NO), and prostaglandin PGI2. This is due to incomplete filtration of these substances from the blood in the lungs [16–17, 19, 20]. In the pathogenesis of migraine, impaired cerebral autoregulation and a common genetic basis for the development of migraine in PFO are speculated [16, 17].

The clinical significance of PFO is potentially high. However, PFO involvement in the development of neurological disorders remains debatable.

This study aimed to evaluate the role of PFO in the development and progression of neurological disorders in adults and children. We conducted a comprehensive review of medical literature between 2012 and 2022 using the electronic databases PubMed and Google Scholar. Our search terms included “open foramen ovale,” “cryptogenic stroke,” “migraine,” “platypnea–orthodeoxia,” “syncope,” “vertigo,” “visual disturbances,” “sensory disorders,” “ataxia,” and “temporary global amnesia.”

CRYPTOGENIC STROKE

Cryptogenic stroke refers to a stroke whose cause has not been determined through comprehensive patient evaluation and accounts for 15%–45% of all strokes [21]. PFO prevalence in stroke patients is 46% and is higher in individuals below 55 years old. However, one-third to half of diagnosed PFOs are incidental and not related to the stroke event [3, 22, 23], and the risk of a first cryptogenic stroke in individuals with PFO is relatively low (0.1%) [21].

The RoPe scale is used to evaluate the pathogenicity of PFO in stroke patients (Table 1). The criteria of this scale assess the probability of PFO influence on stroke development. These criteria include young age, cortical localization of brain infarction on neuroimaging, and absence of traditional risk factors of stroke such as arterial hypertension, diabetes mellitus, acute cerebral circulatory failure, and transient ischemic attack in the patient’s history and smoking [22, 24]. The RoPe score increases as the patient meets more criteria, indicating a higher potential significance of PFO in the development of stroke.

A study showed that the significance of PFO for cryptogenic stroke is 0% for a score of 0–3 points, 62% for 6 points, and 88% for 9–10 points [22]. Patients with the maximum score (10 points) were 18–29-year-old individuals without arterial hypertension, diabetes mellitus, and a history of stroke or transient ischemic attack and with cortical localization of brain infarction confirmed by neuroimaging [23].

Studies validating the use of the scale in practice have found a significantly higher association between stroke and PFO in patients with a RoPe score >7 [25]. Additionally, the RoPe score was an independent predictor of recurrent ischemic cerebrovascular events [26]. A multicenter study revealed the scale’s usefulness in assessing the association between PFO and stroke [27].

Favilla et al. presented a random-effects meta-analysis of six randomized clinical trials comparing the efficacy of PFO closure to drug therapy in patients with stroke and PFO. The data indicated that closure results in a 0.6% reduction in the absolute risk of recurrence per year in selected young patients [28].

Age, concomitant atrial septal aneurysm, shunt size, and depth and extent of cerebral infarction were identified as factors influencing closure efficacy. Patients older than 60 years old were not included in all closure studies except DEFENSE-PFO; hence, the results of these studies may not be applicable to this age group. Closure may be a feasible option for carefully

Table 1. RoPe Scale (Risk of Paradoxical Embolism) [23]
Таблица 1. Шкала RoPe (от англ. Risk of Paradoxical Embolism) [23]

Predictor	Score
Arterial hypertension (none)	1
Diabetes mellitus (none)	1
Acute cerebral circulation disorder or transient ischemic attack history (none)	1
A nonsmoking patient	1
Cortical infarction	1
Age, years	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0

selected patients over 60 years old who do not have extensive vascular risk factors and underlying atrial fibrillation.

The RESPECT study found that PFO closure was beneficial for patients with atrial septal aneurysm (odds ratio [OR], 0.20; 95% confidence interval [CI], 0.06–0.70; p = 0.005) compared to those without aneurysm (OR, 0.86; 95% CI, 0.42–1.76; p = 0.68).

The CLOSE trial found that closure did not significantly benefit patients with aneurysm (OR, 0.05; 95% CI, 0.00–0.36) compared to those without atrial septal aneurysm (OR, 0.10; CI, 0.00–0.91; p = 0.73). However, the study was unable to assess the impact of concomitant interatrial septal aneurysm because of the requirement for patients without an interatrial septal aneurysm to have a large shunt through the PFO.

Most trials have reported that closure is more beneficial in patients with a large right-to-left shunt. In the RESPECT study, closure was significantly more beneficial in patients with a large shunt (OR, 0.26; 95% CI, 0.10–0.71; p = 0.005) than in those without a large shunt (OR, 0.96; 95% CI, 0.44–2.11; p = 0.93). In CLOSE study, approximately two-thirds of patients had a large shunt, and closure was similarly beneficial in patients with and without a large shunt, although all patients had an atrial septal aneurysm.

The REDUCE, CLOSE, and DEFENSE-PFO trials excluded patients with small deep brain infarcts to increase the possibility that the initial event was related to PFO. In RESPECT, closure reduced the risk of stroke recurrence after superficial infarction (OR, 0.43; 95% CI, 0.19–0.96; p = 0.03) but was ineffective after small deep infarction (OR, 2.25; 95% CI, 0.41–12.32; p = 0.34) [28].

Small studies with limited samples have investigated PFO prevalence in pediatric patients [29, 30]. A cohort study evaluated PFO prevalence in healthy children and those with a history of stroke. The study found a higher PFO prevalence in patients who had a stroke of unspecified etiology (28%) compared to healthy controls (11.5%; p = 0.03) and children with a known cause of stroke (5.6%; p = 0.009). Furthermore, it was observed that the 2-year recurrence rate did not differ significantly between children with and without PFO (hazard ratio, 2.0; 95% CI, 0.4–9.3; p = 0.39) [29].

Menon et al. conducted a study of 153 patients below 20 years old who underwent PFO closure. The indications for closure included migraine headache (104; 68%), nonmigraine headache (24; 16%), visual symptoms (110; 72%), transient ischemic attack symptoms (42; 28%), and stroke-like symptoms (24; 16%). The mean duration of follow-up was 12 months.

Symptoms improved in 143 (92%) patients. However, the authors noted that PFO closure is an expensive procedure with unknown long-term effects and that much of the improvement may have been due to psychosocial factors and the placebo effect. Menon et al. further highlighted the lack of strict standards in PFO evaluation and treatment in children.

The study was limited by its retrospective design and the fact that only half of the patients consulted a neurologist. Therefore, the initial neurological diagnosis was possibly inaccurate, which could have affected the underlying physiology and response to treatment. Therefore, Menon et al. concluded that treatment with PFO closure cannot be considered evidence-based. This aspect should be evaluated with a rigorous prospective analysis [31].

MIGRAINE

A meta-analysis investigated the effectiveness of PFO closure in migraine therapy. The study found a high PFO prevalence in migraine patients, ranging from 30%–40%, with the frequency increasing to 48%–70% in migraine with aura. This is twice as high as the prevalence in the normal population [32].

Further, Liu et al. conducted a review of studies on the association between PFO and migraine. The review data shows that patients with migraine have a proportion of 67%–72% for permanent shunt, which occurs during normal breathing, and a proportion of 28%–33% for hidden shunt, which only occurs when the pressure in the right atrium increases (during the Valsalva test) [33]. However, the authors noted that among patients with migraine, the ratio of large and small shunts was 75% and 25%, respectively. Additionally, permanent and large shunts are more common in patients with aura [33].

The amount of right-to-left atrial bleeding does not always correspond with the anatomical size of the PFO. In clinical practice, it is evaluated by the number of bubbles detected during transthoracic or transesophageal echoCG with contrast agent [34]. According to Liu et al., blood flow through PFO is diagnosed when microbubbles are detected during 3–5 cardiac cycles during transthoracic examination [33].

Moreover, Kuzhel et al. showed that the amount of blood discharge through PFO can be classified as small if 3–9 contrast bubbles are present in the left atrium, medium if 10–30 contrast bubbles are present, and large if >30 contrast bubbles enter the left atrium [34].

The efficacy of PFO closure compared to drug therapy has been investigated in randomized controlled trials; however, the results varied. None of the three trials (MIST, PREMIUM, PRIMA) reached their primary endpoints, as the results were not statistically significant (Table 2).

Additional analysis of results from the PREMIUM and PRIMA trials suggests that closure may be effective for some patients. Further analysis of patients in the PREMIUM trial who experienced aura in more than 50% of their migraine attacks showed a significant difference in attack frequency between the PFO closure and control groups, i.e., 49% (19/39) vs. 23% (9/40), respectively (p = 0.015) [35]. This indicates that PFO closure may be suitable for this patient group when standard drug therapy is ineffective.

The PRIMA trial revealed a significant reduction in the number of days and frequency of migraine attacks with aura in the PFO closure group. Specifically, there was a reduction of –2.4 days compared to –0.6 days (p = 0.141) and –2.0 attacks compared to –0.5 attacks (p = 0.003) [35]. These

Table 2. Characteristics of randomized clinical trials of patent foramen ovale (PFO) closure in patients with migraine [35–38]
Таблица 2. Характеристики рандомизированных клинических испытаний по закрытию открытого овального окна (ООО) у пациентов с мигренью [35–38]

Study	Comparison groups	Inclusion criteria	Primary endpoint
MIST (n = 147), a randomized prospective, double-blind, and mock-controlled clinical trial over 6 months	Closing of PFO with false procedure	Patients with aura 5 or more migraine days per month for at least 1 year 2 or more failed attempts at prophylaxis Moderate or large right-to-left shunt	Complete cessation of migraine headaches from 91 to 180 days after treatment Outcome: – PFO closure group: 3/74 – Control: 3/73 – p = 5.51
PREMIUM (n = 230), a randomized prospective double-blind clinical trial (10–12 months)	Closure of PFO versus drug therapy and false procedure	Patients with and without aura 6–14 days of migraine per month Lack of effect of at least three medications for migraine prophylaxis Right-to-left shunt of class 4–5 according to the results of transcranial Dopplerography	Reducing the frequency of migraine attacks by 50% Results: – Closure group: 45/117 (38.5%) – Control: 33/103 (32%) – p = 5.32
PRIMA (n = 107), a multicenter prospective randomized open clinical trial for 1 year	Closure of PFO compared to medication-assisted treatment	Patients with aura younger than 50 years old 3 or more migraine attacks per month or five or more migraine days per month (but no more than 15 days) within 3 months prior to enrollment Resistance to the two most prescribed medications	Reduction in migraine days per month during months 9–12 after randomization compared with months 1–3 before randomization Results: – PFO closure group: 2.9 migraine days per month – Control: 1.7 migraine days per month – p = 5.097

findings show that PFO closure may provide significant relief for patients with migraine with aura who are under 50 years old and resistant to drug therapy.

Data on the effect of PFO on migraine in children is limited. The results of one observational study of 63 children (32 with migraine, with and without aura, and 31 healthy controls) indicate that PFO prevalence was higher in children with migraine than in controls; however, the difference was not statistically significant (46.9% vs. 25.8%; p = 0.084). However, PFO prevalence was significantly higher in children with aura than in children without aura (71.4% vs. 27.8%; p = 0.031) and healthy children (p = 0.0074) [39].

Another study examined PFO prevalence in children with migraine (109 patients with migraine, 38 with aura and 71 without aura). The study found that PFO prevalence in children with migraine was comparable to that in the general population (35% vs. 25%; p = 0.13). However, PFO prevalence was significantly higher in children with aura (50%; p = 0.004) than in the general population (25%) and similar to that in children without aura (27%; p = 0.73) [40].

Both studies investigated the impact of the blood shunt size across the atrial septum on migraine. The first study used transthoracic echoCG with the administration of sodium chloride foam as contrast to assess the shunt size. The size of the shunt was determined based on the number of microbubbles that penetrated the left atrium: small shunt, 3–9 microbubbles; moderate shunt, 10–30; and large shunt, >30 [39]. The second study evaluated the presence and size of the shunt using echocardiography and transcranial Doppler ultrasound (TCD) with sodium chloride foam contrast. To perform contrast TCD, a 4 or 5 MHz transducer was placed over the temporal bone, and the flow velocity in the middle cerebral artery was recorded during the injection of sodium chloride foam solution into the cubital vein [40].

In the presence of PFO, increased cerebral artery blood flow velocity is associated with the penetration of contrast bubbles from the venous channel into the arterial channel due to paradoxical embolism. Short and high-amplitude signals with specific characteristics appear on the Doppler spectrogram of cerebral artery blood flow [41]. Blood flow was diagnosed by identifying spikes superimposed on the velocity curve for a duration of 10 seconds. The shunt size was determined based on the number of spikes, following TCD standards:

1) No spikes (no right-to-left shunt)
2) 1–10 spikes (small shunt)
3) >10 individual spines (middle shunt)
4) Individual spikes cannot be identified from each other (large shunt)

If the results of TCD and echoCG were inconsistent (i.e., contrast echoCG was negative and contrast TCD was positive),

echoCG was considered a more reliable technique owing to its direct visualization of microbubbles crossing the atrial septum [40]. None of the studies found that shunt size had an effect on migraine [39, 40].

TRANSIENT GLOBAL AMNESIA

TGA is characterized by the sudden onset of anterograde amnesia lasting up to 24 hours [42]. It typically affects individuals around 60 years old and is indicated by marked anterograde amnesia and a pronounced degree of retrograde amnesia, but without personality disorder [18]. The clinical picture includes temporal and spatial disorientation and almost frequent repeated stereotyped questions on the part of the patient. No neurological disorders are observed except for transient memory impairment. On average, the episode ceases after 4–6 hours, leaving behind lacunar amnesia for the episode and the period immediately preceding the attack onset. TGA is typically an isolated syndrome, and recurrent episodes are infrequent [18].

Neuroimaging studies, particularly magnetic resonance imaging (MRI), determined that hippocampal dysfunction is associated with TGA [18]. However, the exact mechanism of TGA development remains unclear. Several hypotheses have been proposed, including an epileptogenic mechanism, spreading cortical depression (neurochemical), and vascular mechanisms [18, 43].

Most studies have shown that TGA survivors do not share the risk factors and prognosis of patients with cerebrovascular disease. Therefore, TGA cannot be considered as a form of ischemic stroke associated with atherosclerosis or cardiogenic embolism. Among alternative vascular mechanisms for the development of TGA, paradoxical embolism via PFO has been proposed. This mechanism is associated with a high PFO incidence in patients who have experienced an episode of TGA [18].

In a retrospective study, Noh et al. assessed the potential influence of paradoxical embolism on TGA development in patients with PFO. TCD was used to confirm the presence of a right-to-left shunt and transesophageal echoCG. The study found that 58.6% of the 128 patients with TGA had a right-to-left shunt, as identified by TCD. During the 4-year follow-up, 5% of the study patients experienced TGA recurrence, whereas patients without PFO did not experience any recurrences.

However, individuals with PFO had fewer or no major vascular risk factors, such as arterial hypertension and diabetes mellitus, compared to those without PFO. Additionally, patients with PFO had fewer foci of chronic cerebral ischemia on MRI than the PFO-negative group. Therefore, the authors concluded that TGA may be caused by paradoxical embolism, which is not associated with traditional risk factors of stroke development [42].

A recent study on cerebrovascular circulation in neurological patients with TGA concluded that an embolic mechanism of TGA development can be excluded [44]. Blood flow was determined using TCD and confirmed by transesophageal echoCG. The study results showed a low frequency of microembolic signals in patients with and without PFO (OR, 2.34; 95% CI, 0.63–8.63; p = 0.201); however, the difference was not statistically significant [44].

SYNCOPE

We found a single case of syncope associated with PFO. Liu et al. investigated the association between right-to-left blood shunting and unexplained cases of syncope. All patients with syncope underwent a standard initial evaluation, including a thorough history taking (according to the European Society of Cardiology guidelines), a thorough physical examination, an active orthostatic test, and standard 12-lead electrocardiography. Based on this evaluation, the patient received a presumptive diagnosis of reflex, orthostatic, or cardiogenic syncope.

Additional tests, including cardiac and autonomic function tests, were performed based on the diagnosis. Patients who did not receive further diagnosis underwent 24-hour Holter monitoring, echoCG, electroencephalography, brain MRI, and TCD according to the European Society of Cardiology guidelines for further evaluation or differential diagnosis.

Unexplained syncope was diagnosed during a consultation involving a neurologist and cardiologist. To determine shunting, a TCD–ultrasonographic bubble test was used, and the degree of blood shunting was classified into four classes based on the number of microemboli penetrating the left atrium (<10, 11–25, and >25 microemboli represented by single bubbles, and microemboli in the form of a "shower" when it is impossible to distinguish individual contrast bubbles).

The study included patients aged 15 years and older. The main group consisted of 52 individuals who met the diagnostic criteria for unexplained syncope, whereas the comparison group comprised 52 patients with vertigo. Of 104 total participants, 36 had shunts classified as class 1 (n = 13), 2 (n = 4), 3 (n = 7), and 4 (n = 12). Right-to-left shunt prevalence was 48.1% (25/52) in the main group and 21.2% (11/52) in the comparison group (p = 0.004). The frequency of class 3 and 4 shunts was significantly higher in the main group than in the comparison group (16/52 vs. 3/52; p = 0.001). No difference (p = 0.323) was found in the prevalence of class 1 and 2 shunts between the main (n = 9) and comparison (n = 8) groups.

The authors found an association between blood shunting and syncope (OR, 1.988; 95% CI, 1.233–3.25; p = 0.005). Therefore, right-to-left blood shunting may be strongly associated with syncope [19].

VERTIGO

Cao et al. conducted a large single-center prospective controlled study to evaluate the association between PFO and unexplained vertigo [20]. The study included 244 patients below 75 years old with vertigo as the primary symptom. The cause

of vertigo was identified in 123 patients (50.4%), whereas it remained unexplained in 121 patients (49.6%).

The patients in the "explainable" group had a clear cause based on internationally recognized diagnostic criteria, including benign positional paroxysmal vertigo, vestibular neuritis, vestibular migraine, Meniere's disease, bilateral vestibular dysfunction, vestibular paroxysm, orthostatic hypotension, stroke, cerebellar ataxia, sudden deafness, cervical spondylosis, and brain lesions causing intracranial hypertension. Conversely, the diagnosis could not be established for patients with unexplained vertigo.

To diagnose PFO, patients underwent TCD with contrast. If the TCD test was positive, transesophageal echoCG or right heart catheterization was used to confirm the diagnosis. Further, the patients were classified based on the degree of blood shunting. In the "explainable" group, 14 patients were in class 1, seven in class 2, six in class 3, and seven in class 4. In the "unexplained" group, 27 patients were in class 4, 26 in class 3, 12 in class 2, and 14 in class 1.

In the "explainable" group, PFO prevalence was 34 (27.4%) compared to 79 (64.7%) in the "unexplainable" group. The authors concluded that PFO is an independent risk factor for vertigo based on the statistically significant factors of age (OR, 0.97; 95% CI, 0.95–0.99) and prevalence (OR, 4.37; 95% CI, 2.50–7.63) identified through multiple regression analysis [20].

Reports of a series of patients whose vertigo symptoms disappeared after PFO closure have attracted attention [7, 45]. However, no additional larger studies have been found.

VISUAL DISTURBANCES

Several studies have presented cases of visual impairment associated with embolism through PFO. The most common presentations are occlusion of the central retinal artery and its branches [9–13]. Moreover, there are isolated reports of visual impairment associated with brainstem stroke and oculomotor nerve involvement [14, 15]. Of particular interest is a case of paramedian thalamic infarction associated with PFO that manifested visual symptoms, which is discussed below [46].

In all cases, patients underwent a thorough examination to differentiate and exclude other causes of visual symptoms and diagnose any concomitant conditions that may indicate an increased risk of thrombosis, such as systemic vasculitis, carotid artery thrombosis, large vein thrombosis in the lower extremities, thrombophilia, and others.

Ophthalmoscopy did not reveal any ocular changes in patients with symptoms not related to retinal artery occlusion. However, in cases of retinal arterial occlusion, ophthalmoscopy showed retinal edema, optic disc pallor, and arterial filling defects. Patients with PFO experienced visual symptoms, including decreased visual acuity [9–13], visual loss [9, 11], diplopia [14, 42], loss of visual fields [9, 13], central scotoma [9], and transient monocular blindness [10].

In cases where visual symptoms were caused by a brainstem stroke, characteristic symptoms of the third cranial nerve included ptosis [14, 15], ophthalmoplegia, exotropia, and inability to raise the eye upward (supraduction), lower the eye downward (infraduction), and bring the eye inward (adduction) [14, 15] and symptoms associated with trigeminal and facial nerve damage [14]. In addition to visual symptoms, the patient presented with sensory disturbances [46] and limb dysmetria [14].

Šekarić et al. reported a case of paramedian thalamic infarction in a patient with PFO. The patient exhibited visual symptoms including diplopia, left-sided hemianopsia, central right-sided prosoplegia with deviation of the tongue to the right, left-sided hemihypesthesia, trunk ataxia, and mild memory deficit. Subsequently, the patient developed discrete right-sided hemiparesis. During drug treatment, the patient's neurological symptoms gradually subsided, except mild diplopia and memory deficit. Upon discharge, the patient was advised to undergo PFO closure, which was performed 6 months after stroke onset [46].

Amblyopia associated with PFO is common among children and adolescents. In a case study by Mazurkiewicz-Bełdzińska et al., a 16-year-old adolescent presented with brainstem stroke symptoms, including visual disturbances such as restricted left eye movement, diplopia, horizontal nystagmus of the right eye when attempting to look with the right eye, and vertigo [47]. In a study by Lyons et al., amblyopia resulted from central retinal artery occlusion in an adolescent with PFO. Percutaneous PFO closure was performed in both cases, resulting in the resolution of symptoms.

A review of available literature on neurological symptoms and PFO-associated conditions in adult and pediatric patients enabled to integrate researchers' opinions on the defect's influence on the development of neurological pathology into several general mechanisms.

A paradoxical embolism occurs when an embolus, such as a blood clot, air bubble, or fat particle, travels from the deep veins to the systemic arterial circulation. This is not a normal occurrence, as blood typically passes through and is filtered in the pulmonary vessels. PFO functions as a conductor, allowing unfiltered blood to flow freely from the right to the left atrium. From there, the blood enters the left ventricle and continues through the aorta to the cerebral vessels.

Embolism of vessels in various brain regions and associated local cerebral blood flow restriction contribute to the development of ischemia and the appearance of neurological symptoms. Additionally, ischemia is associated with the occurrence of spreading cortical depression, which triggers the flow of nociceptive impulses in migraine patients [16, 17].

It is hypothesized that spreading cortical depression may activate the pannexin-1 neuronal pathway, resulting in the release of pro-inflammatory factors such as prostaglandins and NO. These factors act on the trigeminal nerve vasculature, leading to migraine with aura [16].

Cortical depression is a mechanism of both TGA [18] and syncope [19]. In TGA, cortical depression is caused by transient hippocampal dysfunction [18], whereas in syncope, it is

caused by impaired cerebral autoregulation and local hypoperfusion [19].

Another mechanism of PFO action is related to inadequate filtration of vasoactive substances in the lungs due to the fact that some blood does not pass through them. Abnormal cerebral vascular tone changes caused by excessive vasoactive substances are associated with impaired cerebral autoregulation and cerebral hypoperfusion in patients with syncope, particularly in specific brain regions responsible for maintaining consciousness [19]. Activation of dura mater pain receptors in migraine has been associated with the effects of serotonin, NO, and prostaglandin PGI2 [16, 17]. Additionally, the action of serotonin on the receptors of vestibular nuclei has been linked to vertigo [20].

Based on the search results, PFO may be considered as a pathogenetic factor in selected patient groups. Neurological symptom development is influenced by various factors, including the presence of PFO, age, concomitant cardiovascular diseases, metabolic disorders, hemostasis system status, heredity, and anatomical characteristics of the orifice.

When evaluating the efficacy of PFO closure in patients with stroke and migraine, comorbid factors should be considered. Some investigators emphasized that the procedure is justified only in selected patients [2, 3, 21, 22] and that further studies are warranted to identify those who would benefit from closure [33, 35].

Current data on pediatric patients with PFO and on patients with TGA, syncope, and visual impairment are limited to a small number of studies and case reports of individual patients in whom PFO caused symptoms. Therefore, it cannot be concluded that PFO is a significant risk factor in all patients with this pathology. However, these findings indicate the need for greater vigilance against the defect. Considering PFO in combination with other factors that act on the patient simultaneously can contribute to more effective diagnosis and treatment of neurological patients.

CONCLUSIONS

1. PFO is a risk factor of neurological symptoms in patients with stroke and migraine with aura.

2. Criteria determining the significance of PFO in the pathogenesis of migraine development have not been established. Furthermore,

3. The association between PFO and TGA, syncope, vertigo, visual disturbances, and neurological pathology in pediatric patients is unclear and requires further research.

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