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72-year-old patient with cryptogenic ischemic stroke and with patent foramen ovale and concomitant atrial septum aneurysm

72-letnia pacjentka z kryptogennym udarem niedokrwiennym mózgu z towarzyszącym tętniakiem przegrody międzyprzedsionkowej i drożnym otworem owalnym

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Abstract

Ischemic stroke is the leading cause of morbidity and mortality in developed countries. In 40% of cases etiology of stroke is unclear. Patent foramen ovale (PFO) is present in more than half, while atrial septum aneurysm (ASA) appears in 25% of patients with cryptogenic stroke. However, available data on the correlation between a cryptogenic stroke and the coexistence of PFO and ASA are limited. A lack of knowledge and recommendations in this field makes clinicians unsure in terms of their approach to a patient with a stroke and PFO with concomitant ASA.

The authors describe the case of a 72-year-old patient with ischemic stroke and PFO with concomitant ASA. The diagnostic process and treatment methods are presented. The approach is discussed in detail.

Key words: ischemic stroke, cryptogenic stroke, patent foramen ovale, atrial septum aneurysm, oral anticoagulant therapy, PFO closure

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Introduction

Ischemic stroke is one of the most common causes of morbidity and mortality in developed countries [1]. In 40% of cases the etiology of the stroke is unclear (cryptogenic stroke) [2]. Patent foramen ovale (PFO) is present in more than half, while atrial septum aneurysm (ASA) appears in 25% of patients with cryptogenic ischemic stroke [3].

PFO is a remnant of the fetal circulation. Within the first year of life after birth PFO closes. However, in about 25% of adults foramen ovale persists. The prevalence of PFO in the general population decreases with age, from 34% in the first three decades to 20% in the ninth decade. In most of these patients, PFO never causes symptoms and is considered as a normal variant as it is found only incidentally during echocardiographic investigation performed for other reasons [4].

ASA is a fixed displacement or a mobile excursion of the fossa ovalis region of the atrial septum with a total amplitude exceeding 10mm from the mid-line [5]. ASA has been identified by transesophageal echocardiography in up to 10% of patients.

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The postulated pathogenetic mechanism of stroke in patients with PFO/ASA is due to paradoxical embolus from the venous side. However, deep venous thrombosis is found only in 5–10% of stroke patients with concomitant PFO. Another hypothesis is that the thrombus forms in situ either in PFO or on the surface of the aneurysm. It also may be related to the atrial vulnerability to arrhythmia with regard to PFO and ASA presence [6]. Finally, the coexistence of PFO and ASA change the geometry, shape and hemodynamics of the atria, and affects the coordinated cooperation of atria, left atrial appendage and the other chambers of the heart. This is why coexistence of PFO and ASA is believed to promote similar conditions as in atrial fibrillation (AF) with left atrial dysfunction, which promotes thrombus formation [7]. Available data on the correlation between cryptogenic ischemic stroke and PFO with concomitant ASA are limited [3, 8, 9].

A lack of knowledge and recommendations on how to manage patients with ischemic stroke accompanied by coexisting PFO and ASA leads to a diagnostic and therapeutic dilemma.

The present paper describes the case of a 72-year-old patient with ischemic stroke and PFO with concomitant ASA.

Case report

A 72-year-old woman was admitted to the stroke unit at Nicolaus Copernicus Memorial Hospital in Lodz in the acute phase of ischemic stroke. Neurological examination revealed speech disorders and paresis of the left arm. Using the National Institutes of Health Stroke Scale (NIHSS) the patient gained 3 points, which means slight clinical symptoms of stroke. Incident of stroke was preceded by a transient ischemic attack presenting with weakness of the right upper and lower limbs.

She was a non-smoker, without a family history of neurological and cardiovascular diseases.

Her medical history was notable only for rheumatoid arthritis, depression and glaucoma.

She was taking wenlafaxin 75mg once a day and methylprednisolone 2 mg once a day.

Her body temperature was 36.5°C, cardiac activity was regular (80/min) and atrial blood pressure was 140/80 mm Hg; lung auscultation revealed a symmetrical normal vesicular sound, but with weakness over the base of the right lung. Neurological examination revealed left paresis of the upper limb 4+/5, discreet central paresis of nerve VII on the left.

All laboratory tests were normal except for elevated levels of platelets and C-reactive protein (Table 1). Resting electrocardiography (ECG) reported no irregularities. The chest X-ray revealed a linear atelectasis in the right lung base.

Transthoracic echocardiography (TTE) showed: dilated cavities of both atria, neither wall thickness nor left ventricle wall motion abnormalities, proper left and right ventricular function with ejection fraction of left ventricle — ejection fraction (EF) 60%, a mild mitral and tricuspid regurgitation, possibility of pulmonary hypertension, ASA without leakage. Transesophageal echocardiography (TEE) displayed the presence of ASA with left-to-right shunt on the PFO at rest (diameter of shunt from 2 mm to 5 mm); occasional spontaneous reversal of the shunt direction and the right-to-left shunt was increased by the Valsalva maneuver; slightly marked left ventricular spontaneous echo contrast (SEC); no thrombus was seen in the left atrium or in the left atrial appendage; the function of the left atrial appendage was normal on Doppler evaluation (Fig. 1).

Holter ECG did not report significant arrhythmia and conduction abnormalities.

A cranial computed tomography without contrast demonstrated multiple, diffuse vascular lesions. Carotid and vertebral arteries were free of atherosclerotic lesions without thickness of intima–media complex on Doppler scans and cerebral arteriography displayed no occlusion of cerebral arteries.

Table 1. Laboratory parameters

Parameter	Value	Range
Hemoglobin [g/dl]	12.5	11.4–15.5
Erythrocytes [T/l]	4.08	3.5–5.2
Hematocrit [%]	37.6	34.0–46.0
Leukocytes [G/l]	10.28	4.4–11.3
Platelets [G/l]	550	150–400
Troponin T [ng/ml]	0.03	< 0.1
Total cholesterol [mg/dl]	190	140–200
LDL-cholesterol [mg/dl]	142	< 115
HDL-cholesterol [mg/dl]	30	> 65
Triglycerides [mg/dl]	90	< 200
Creatinine [mg/dl]	0.99	0.5–0.9
Glucose [mg/dl]	87	60–99
Urea [mg/dl]	42	10–50
CRP [mg/l]	60→26	0.0–5.0
PCT [ng/ml]	0.05	0.00–0.50
AST [U/l]	25	< 31
ALT [U/l]	39	< 31
Potassium [mEq/l]	4.2	3.5–5.1
Sodium [mEq/l]	138	136–145
TSH [uIU/ml]	3.88	0.270–4.2

LDL — low-density lipoprotein; HDL — high-density lipoprotein; CRP — C-reactive protein; PCT — procalcitonin; AST — aspartate transaminase; ALT — alanine transaminase; TSH — thyrotropic hormone

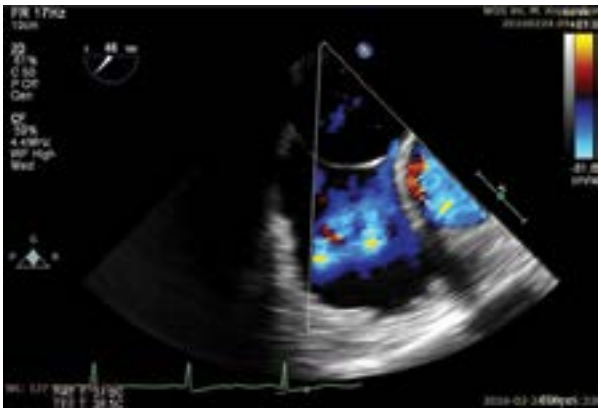

Figure 1. Atrial septum aneurysm with left-to-right shunt in transesophageal echocardiography

Doppler study of the lower extremities was negative for thrombosis.

The patient did not have any complications while she was hospitalized. The patient was discharged after 9 days with final diagnoses: ischemic stroke, hypercholesterolemia, PFO, ASA, rheumatoid arthritis, depression, glaucoma.

The patient received anticoagulant therapy with acenocumarol and she was referred for further assessment for percutaneous PFO closure.

Discussion

Available data on the correlation between the coexistence of PFO with cryptogenic stroke are limited. Some clinical and anatomical risk factors have been proposed to increase the likelihood of this correlation, such as: the presence of ASA, an amplitude of PFO > 4 mm, Chiari network, recurrent cryptogenic stroke, deep venous thrombosis or hereditary prothrombotic alterations, prolonged immobilization or extensive travel preceding the event.

In this regard, in patients with isolated PFO, the overall risk of recurrent stroke is low.

But when PFO coexists with other prothrombotic factors the risk of embolization can be substantial.

According to current guidelines for patients with an ischemic stroke or transient ischemic attack (TIA) and coexisting PFO, only antiplatelet therapy is recommended for secondary stroke prevention.

In the absence of available data, it is hard to establish a preferred therapy in patients with cerebrovascular event and the coexistence of PFO and ASA.

European Stroke Organization Guidelines for Management of Ischemic Stroke recommends in this case anticoagulation therapy and percutaneous PFO closure [10]. In contrast, guidelines of the American Heart Association/ /American Stroke Association for the prevention of stroke in patients after stroke or TIA recommend antiplatelet therapy. Anticoagulation with interventional treatment is recommended only for patients with PFO and concomitant deep venous thrombosis [11].

Meta-analysis of 21 clinical trials has demonstrated superiority of anticoagulant therapy over antiplatelet therapy for secondary cerebrovascular events prevention in the case of PFO coexistence (event rates 7.7% vs. 9.8%, respectively, p = 0.003). Nevertheless, anticoagulant therapy was associated with over six-fold higher risk of major bleeding events (7.15 vs. 1.3%, respectively, p = 0.03). The efficacy and safety of PFO closure were also evaluated. PFO closure was associated with 50% relative reduction of recurrent cerebral events versus antiplatelet therapy without difference in the occurrence of major bleeding. Compared with anticoagulant therapy, PFO closure showed the same risk reduction of recurrent neurological events, whereas the incidence of major bleeding was reduced by almost 82% (15 vs 7.1%, respectively, p < 0.00001) [12].

Unfortunately, the results were obtained almost exclusively from observational trials. Only one randomized-controlled trial comparing the efficacy of anticoagulant and antiplatelet therapy (warfarin vs acetylsalicylic acid dose 325 mg) is available. The result of this study demonstrated that there was no significant difference in recurrence of cerebrovascular events regardless of PFO size, the presence of ASA or pharmacological strategy. Nevertheless, among the cryptogenic population there was a trend toward event reduction (in patients with and without PFO), but the statistical power was not adequate enough to reveal superiority of warfarin over aspirin. The limitation of this study is that it included mostly elderly patients (age of study group 59 ± 12.2 years). The mean international normalized ratio (INR) in the warfarin group was 2.04, which suggests that more aggressive anticoagulant therapy might have given different results. The primary end point in this study was death that was caused not only by recurrent ischemic stroke but also from any other cause [13].

Three interventional trials on endovascular PFO closure versus medical management have been published — CLOSURE I, RESPECT and PC TRIAL [14–16]. Unfortunately, none of these studies demonstrated a significant benefit for interventional treatment. Subgroups analysis of the RESPECT trial showed a significant efficacy of device closure among patients with ASA. This was not supported by other trials.

In described case, anticoagulant therapy with acenocumarol was recommended until PFO closure. The main reason for the therapeutic decision was the coexistence of PFO and ASA with high risk of embolic stroke (symptoms involved bilateral middle cerebral artery territories on the same day). The other conditions that encouraged our decision to apply anticoagulant treatment were: cryptogenic stroke, large size of PFO with occasional spontaneous

right-to-left shunt, the slightly marked LV spontaneous echo contrast (SEC), presence of predisposing factors for venous thromboembolism such as age > 40 years, ischemic stroke with paresis, autoimmune disease with chronic steroid therapy. No deep venous thrombosis and chronic steroid therapy were inconsistent with the strategy selected by us.

Considering the risk of thromboembolic events and the expected benefit/risk ratio of advantages and complications, the heart/brain team in our hospital decided to implement anticoagulant treatment until endovascular PFO closure.

Conclusion

Treatment decisions for patients with stroke and PFO with concomitant ASA should be individualized with evaluation of stroke risk recurrence and bleeding complications.

In the absence of clear data it may be reasonable to consider anticoagulant therapy in patients with cryptogenic stroke and PFO with ASA. Those patients represent a group with high embolic stroke risk of undetermined source.

However, there is no consensus on the preferred therapeutic options in patients with stroke and both PFO and ASA. The available evidence is based almost exclusively on observational trials. More randomized trials are needed to better define and treat these patients. In the meantime an optimal medical therapy for patients with cryptogenic stroke and both PFO and ASA is unknown and no medical therapy can be considered as a "gold standard". A local heart/brain team should take all the decisions regarding the treatment of these patients.

Conflict of interest(s)

None declared.

Streszczenie

Udar mózgu jest jedną z głównych przyczyn chorobowości i umieralności na świecie. W blisko 40% przypadków etiologia udarów niedokrwiennych mózgu pozostaje nieznana. Badania wskazują, że 50% udarów kryptogennych wiąże się z obecnością drożnego otworu owalnego (PFO), a 25% z obecnością tętniaka przegrody międzyprzedsionkowej (ASA). Jednak wyniki badań dotyczących korelacji obecności PFO i ASA z kryptogennym udarem mózgu są sprzeczne, a postępowanie terapeutyczne w udarze mózgu ze współistniejącymi PFO i ASA pozostaje nieustalone.

W pracy opisano przypadek 72-letniej pacjentki hospitalizowanej z powodu udaru niedokrwiennego mózgu z towarzyszącym świeżo rozpoznanym ASA i z PFO.

Słowa kluczowe: udar niedokrwienny mózgu, udar kryptogenny, drożny otwór owalny, tętniak przegrody międzyprzedsionkowej, leczenie doustnym antykoagulantem, zamknięcie PFO

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