Paradoxial embolism as a cause of ischemic stroke in patient with *sinus venosus* atrial septal defect

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We present a case report of a middle-aged patient with a rare sinus venosus atrial septal defect (ASD) and ischemic stroke that developed due to paradoxical embolism. Occlusion of the anterior cerebral artery led to a stroke with cognitive impairment, acalculia, and apraxia. Diagnostic ultrasound features of this anomaly in suspected cases are discussed. In the presented case, verification of the stroke cause became possible due to the contrast-enhanced computed tomography of the heart. ASD detection made it possible to refer the patient to the surgical treatment necessary to prevent both recurrent cerebral accidents and the progression of pulmonary hypertension, and the prevention of the development of right ventricular heart failure.

Keywords: *stroke; atrial septal defect; sinus venosus; paradoxial embolism.*
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Introduction. In young patients, the second cause of ischemic stroke (IS) after cervical/cerebral dissection is paradoxical embolism against the background of patent foramen ovale (PFO) or, less often, an atrial septal defect (ASD). Taking this into account, the standard diagnostic algorithm in young patients with IS as a screening method includes transcranial doppler ultrasound with contrast enhancement (bubble test), with a positive result, transesophageal echocardiography (TEE) is performed [1, 2, 3, 4, 5, 6]. In the overwhelming majority of cases, this approach is sufficient to verify the atrial septal abnormality. However, there is a rare variant of ASD of the sinus venosus type, which requires the use of TEE with modification of standard positions in order to examine the interatrial septum (IAS) along its entire length or perform a computed tomography of the heart. The article describes a clinical case of ischemic stroke on the background of sinus venosus-type ASD, the verification of which proved to be difficult and included, in addition to TEE, computed tomography (CT) of the heart.

Clinical case

Patient *47 years old, supervisor. Earlier, from the age of 15, migraine headaches were worried; cardiovascular history was not burdened. In April 2020, an episode of shortness of breath and swelling of the lower extremities was recorded, for which he did not seek medical help. On September 26, 2020, the patient flew by plane with a total duration of 5.5 hours. The next morning, while working at the computer, suddenly developed weakness and numbness in the right limbs, speech impairment. This condition lasted for about two hours. The patient applied for outpatient medical care two days later, the diagnosis "transient ischemic attack" was established, hospitalization was recommended, which the patient refused. On the morning of October 1, relatives noted a decrease in intellectual functions and drowsiness caused by an ambulance team, the patient was taken to the regional vascular center, hospitalized.*

On physical examination, the condition was assessed as moderate, overweight was noted (height 170 cm, weight 80 kg, body mass index 28 kg/m^2), blood pressure on both arms 125/80 mmHg, pulse 72 per minute, rhythmic. The neurological status revealed pronounced cognitive impairments (acalculia, apraxia), the strength in the right extremities was reduced to 4 points. Other neurological areas are intact. On admission, MRI of the brain was also performed: foci of acute infarction were visualized in the basin of the left anterior cerebral artery against the background of its occlusion (Fig. 1).

During the inpatient stage, a detailed examination was carried out to verify the causes of ischemic stroke. According to the resting ECG in dynamics and 24-hour Holter ECG monitoring, atrial fibrillation/flutter were not detected. Transthoracic echocardiography (TTE) revealed dilatation of the right chambers of the heart (Fig. 2A), mild mitral regurgitation and moderate tricuspid regurgitation (Fig. 2B), signs of pulmonary hypertension of I degree (systolic pressure in the pulmonary artery 40 mmHg). At the same time, the valve structures of the heart were intact, regional wall motion abnormalities have not been established, and the systolic function is satisfactory. Duplex scanning of brachiocephalic arteries, veins of the lower extremities – no pathology. General clinical and biochemical blood tests without significant abnormalities, PCR for SARS-CoV-2 is negative.

To exclude paradoxical embolism, transcranial doppler ultrasonography with contrast enhancement was performed: 15 high-intensity signals (HITS) were recorded in the middle cerebral artery (Fig. 2B). During gray-scale scanning of the TEE (Fig. 2 D, E, F), no additional formations were found in the chambers of the heart, atrial auricles, the phenomenon of spontaneous echo contrast in all parts of the heart attracted attention, with an unchanged rate of expulsion from the auricle of the LA equal to 0,52 m/s. In standard positions, IAS looked intact; color doppler mapping showed no signs of blood shunting. With intravenous injection of 10 ml of aerated

saline after tight filling of the right chambers with straining, an instant (during the first cardiocycle) massive release of microbubbles into the left atrial cavity was recorded. It is important to note that the appearance of microbubbles was noted not from the side of the IAS, which made it possible at that time to exclude the presence of ASD, PFO. Based on the results of TEE, a conclusion was made about the presence of ultrasound signs of a pronounced right-left shunt, probably of extracardiac localization.

The absence of an established cause of ischemic stroke, suspicion of the presence of an extracardiac right-left shunt required an extended examination. According to the results of CT of the lungs in S2, 10 on the right, S10 on the left, areas of consolidation of the lung tissue are visualized, with a wide base adjacent to the paracostal pleura, as well as a small amount of fluid in the pleural cavities with diastasis of its leaves up to 4–5 mm, subpleural compaction of the dorsal parts of the lungs. These changes were regarded as a CT picture of the consequences of myocardial pneumonia. In order to exclude pulmonary arteriovenous malformation as the cause of the right-left shunt, CT angiography of the pulmonary artery was performed; no pathology was visualized.

On the background of ongoing therapy (rivaroxaban, antihypertensive therapy, atorvastatin), a complete restoration of cognitive functions was achieved. The patient was discharged on the 14th day with a diagnosis of "cryptogenic stroke. Postponed pulmonary embolism, infarction pneumonia". Due to the established postponed venous thromboembolic event, suspicion of paradoxical embolism as a cause of stroke, rivaroxaban was prescribed at a dose of 20 mg per day.

At the next visit after 5 months, the patient did not show any complaints, when performing TTE, no significant dynamics was noted, dilatation of the right heart chambers remained, pulmonary hypertension remained at the same level. Screening for thrombophilia (antiphospholipid syndrome, antithrombin III, protein C) is negative, D-dimer is within the criteria of the age norm.

To verify the cause of the right-left shunt, indications were established for performing a CT of the heart, the results of which revealed an ASD of the sinus venosus type with a diameter of 16 by 11 mm, partial abnormal drainage of the pulmonary veins, and the confluence of the right upper pulmonary veins into the superior vena cava. The dilatation of the right chambers of the heart (right atrium 70×47×73 mm) and the consequences of viral pneumonia (subpleural area of reticular deformity of the interstitial pattern) were also visualized (Fig. 3).

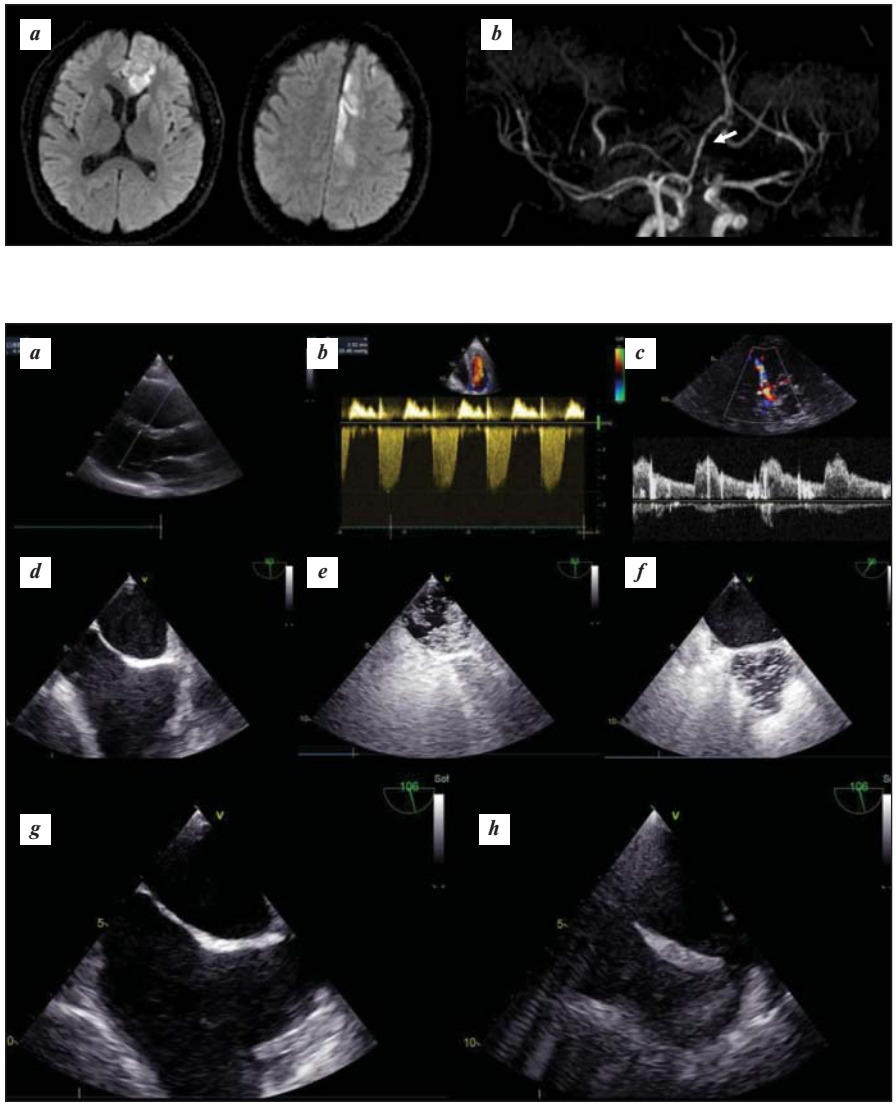

Fig. 2. *Images obtained with ultrasound methods for examining the patient's M heart. a – transthoracic echocardiogram (TTE), parasternal long-axis plane: right ventricular dilatation, with a predominance of its size over the left; b – TTE, CW, tricuspid regurgitation with signs of increased systolic pressure in the pulmonary artery; c – transcranial duplex ultrasonography, control PW volume is set in the middle cerebral artery. Against the background of a normal signal, hyperechoic signals from microbubbles (HITS) are seen; d – transesophageal echocardiography (TEE), standard bicaval position, the atrial septum looks intact; e – TEE with contrast, standard bicaval position. During the Valsalva maneuver a massive discharge of microbubbles into the left atrium is seen, the source is not visualized; f – TEE with contrast, middle third of the esophagus, short axis views in the vicinity of the aortic valve. After agitated saline injection in the right chambers, a large number of microbubbles appear in the left chambers (already fixed in the aorta), the interatrial septum looks intact; g – follow-up TEE after CT-verification of sinus venosus. Standard bicaval position does not allow visualization of the defect; h – TEE, modified bicaval position, a sinus venosus atrial septal defect is visualized on the right side of the screen*

Repeated TEE (Fig. 2 G, H), according to the results of which, in a modified bicaval position (counterclockwise rotation of the transducer, slight extraction, anteflexio), an ASD (15 mm in diameter) was visualized with a left-to-right discharge of the sinus venosus type at the level superior vena cava.

After 6 months, the patient had no neurological deficits and functional impairments, and returned to work. A consultation with a

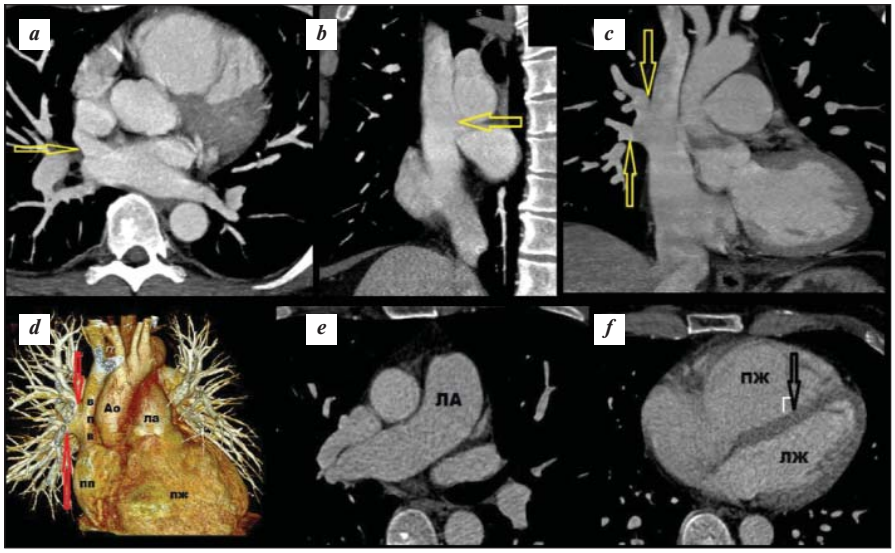

Fig. 3. *Contrast-enhanced CT of the heart of patient M. a – axial plane: the arrow shows sinus venosus ASD, the defect is located between the left (LA) and right atrium (RA) at the level of the orifice of the superior vena cava (SVC); b – sagittal reformation: the arrow shows sinus venosus ASD, located between LA and RA (closer to the orifice of SVC); c – coronal (frontal) reconstruction: abnormal drainage of the right pulmonary veins into the SVC, abnormally draining pulmonary veins are shown by arrows; d – volumetric (3D) reconstruction: partial abnormal drainage of the right pulmonary veins into the SVC (indicated by arrows); e – axial slice at the level of the pulmonary artery (PA) trunk: dilatation of the PA trunk (the diameter is increased in comparison with the ascending aorta) is 35 mm – a sign of pulmonary hypertension; f – axial slice at the level of the ventricles: signs of increased pressure in the right ventricle (RV): dilatation of the RV, bending of the interventricular septum towards the left ventricle (LV). The arrow shows the interventricular septum bended towards the LV. Ao – aorta*

through the left hand leads to the appearance of contrast, first in the left, then in the right atrium.

Many patients with ASD in childhood remain asymptomatic, however, during their life they usually develop a number of clinical manifestations in the form of decreased exercise tolerance, atrial fibrillation (AF), paradoxical embolism, pulmonary hypertension, and decompensation of right ventricular failure. The development of stroke in patients with ASD may be associated with both paradoxical embolism and AF [7, 8, 9, 10].

In the presented case, the patient had a partial anomalous pulmonary vein drainage (PAPVD) in the form of the inflow of the right pulmonary veins into the superior vena cava. PAPVD is a defect that leads to the formation of a right-left shunt, which, according to autopsy data, is found in 0.4% of people in the population. The isolated form of PAPVD is rare, in 90% of cases this defect is accompanied by ASD of the sinus venosus type [11], which aggravates the hemodynamic overload of the right atrium. As a rule, if less than 50% of blood is redirected from the pulmonary veins to the SVC system, the defect remains clinically asymptomatic, while with a more massive shunt, patients develop a clinically manifest overload of the right heart chambers with their dilatation, signs of pulmonary hypertension and congestion in the lungs, which and was observed in a patient [12].

cardiac surgeon was performed, and surgical treatment of congenital heart disease was recommended. On May 7, 2021, the patient underwent a successful Warden operation (cutting off the superior vena cava (SVC), making an anastomosis between the abnormal drainage of the pulmonary veins and the left atrium through the ASD using an autopericardial patch, dissecting the apex of the right atrium and forming an anastomosis with the distal end of the SVC).

Discussion. ASD is the third most common type of congenital heart anomaly. There are four types of ASD – ostium secundum (80%), ostium primum (10%), sinus venosus (5–10%) and coronary sinus defect (1–5%) [7,8].

The most common defect, ostium secundum, is located in the fossa oval region and is true. It does not merge with other structures and is most often associated with paradoxical embolism and the development of stroke. After PFO, secondary ASD is the most common cause of atrial shunt.

Sinus venosus is a communication between one or more right pulmonary veins and the cardiac end of the superior vena cava (superior vena cava type) or the posterior-inferior atrial wall just above the junction of the inferior vena cava and the right atrium (inferior sinus venosus defect). Most often, the defect is located between the **right superior** pulmonary vein and SVC as a result of insufficient tissue separating these structures. The defect is usually associated with abnormal flow of the pulmonary veins, especially the right superior pulmonary vein.

An uncovered sinus defect of the coronal sinus is the rarest variant of ASD. In this case, the introduction of microbubbles

Hemodynamic overload leads to electrophysiological remodeling of the right chambers of the heart and the formation of atrial cardiac arrhythmias, primarily AF [13]. In a study of 1168 patients with ASD, it was shown that the risk of developing AF in such patients is higher than in the age- and sex-matched control group (for a cohort of patients without surgical ASD closure: adjusted RR 11.9%) [14]. With age, the risk of developing atrial arrhythmia in patients with ASD increases [15]. According to Jost et al., Among 115 candidates for sinus venosus-type ASD surgery, the incidence of AF was 4%, 28% and 53% in the age groups 1.5–40 years old, 41–60 years old and 60–80 years old. respectively [16].

Empirically, it is expected that the risk of vascular catastrophes in patients with ASD will be higher due to the increased incidence of cardiac embolism. Indeed, it has been shown that the risk of developing stroke and AF in patients with ASD verified in childhood is higher than in a control group comparable in terms of sex and age (RR 3.8 and 18.2, respectively), however, the relationship between these risks remained unproven, since in the study cohort, no patient with stroke had AF [17]. This, at first glance, paradoxical result gives ground for thought: on the one hand, one cannot but take into account the limitations of the study (the median age of patients at the end of the follow-up is 29 years; exclusion from the analysis of cases of strokes that developed before the diagnosis of ASD) and the limits of the possibilities of diagnostic methods (the limited duration of ECG monitoring does not always allow to

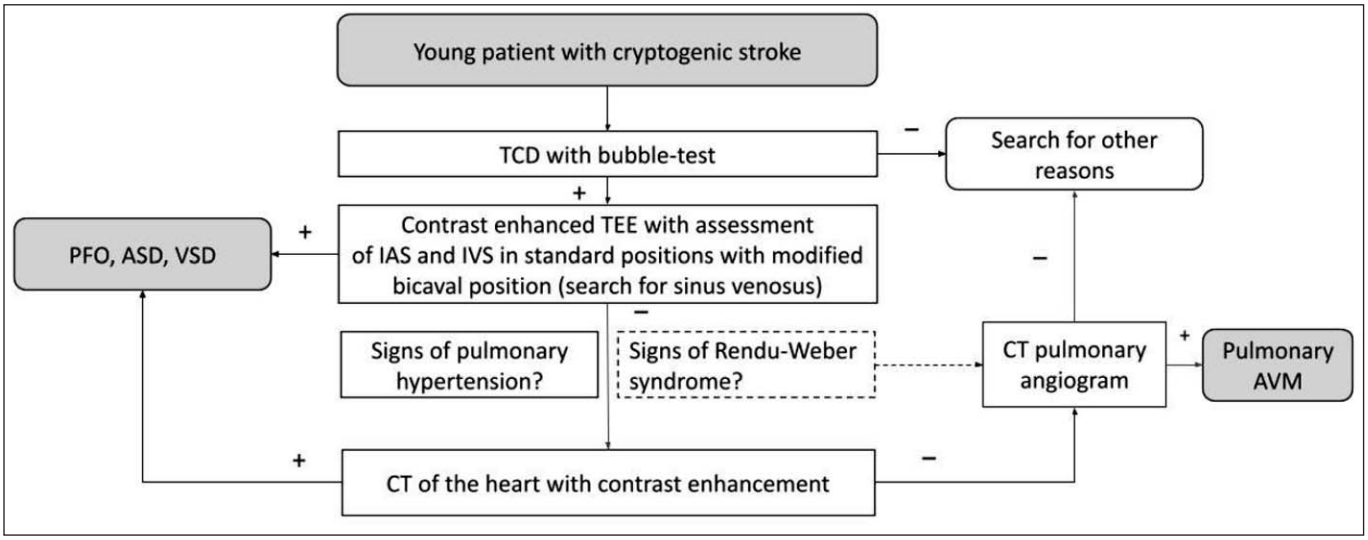

Fig. 4. *Algorithm for verifying the cause of a right-left shunt*

catch AF paroxysms). On the other hand, given the young age of patients, it is reasonable to consider another mechanism of stroke development – paradoxical embolism. This idea is clearer in the already mentioned study [14] involving 1168 adult patients with ASD (median age at diagnosis 47.7 years, the proportion of patients with sinus venosus – 4%). In this study, the risks of AF and stroke in the ASD cohort were predictably higher than in the comparison group. However, of greater interest is the fact that AF occurred in only 28% of patients with ASD who had a stroke prior to surgical closure of ASD, while in the group of patients who developed a stroke after surgery, the frequency of AF was 77%, thus, it can be assumed that the risk of stroke with an open defect in some cases is mediated by paradoxical embolism, and after its closure, AF becomes more important [14].

Although the risk of paradoxical embolism in ASD is not as high as in PFO, it is generally recognized at 14% [10, 18]. It is difficult to say what proportion of cases of paradoxical embolism in ASD occurs precisely in the sinus venosus defect, but given its low prevalence, it is probably not high. In the literature, there are separate descriptions of cases of myocardial infarction and ischemic strokes by the mechanism of paradoxical embolism through ASD of the sinus venosus type [19, 20]. In all cases, the authors emphasize the particular importance of an extensive and informal diagnostic search, supported by the potential curability of the cause of ischemic events.

It should be borne in mind that AF and paradoxical embolism are not mutually exclusive mechanisms. Transient rhythm disturbances can force the migration of blood clots that form directly in the area of the septal defect, including after its closure [21, 22].

It is not known how the risks of stroke, AF, and paradoxical embolism change depending on the type of ASD. Probably, at this stage, the risks of cerebrovascular events in ASD of the sinus venosus type should be conditionally considered on a par with the corresponding risks for other types of defects.

Ultrasound diagnosis of sinus venosus ASD is associated with a number of difficulties. TEE, in contrast to TTE, has a high sensitivity in the diagnosis of ASD, including such a rare variant as sinus venosus [23]. However, there are peculiarities, which include the location of this defect in the high parts of the IAS and the insufficient experience of the echocardiographer in the diagnosis of rare congenital heart defects in adult patients. The standard bicaval position with simultaneous visualization of both vena cava as landmarks for correct visualization of the IAS, used to diagnose PFOs and the most common ASDs, is not optimal for visualizing sinus venosus defects due to their location in the high part of the IAS [24]. The echocardiographer should be particularly alert about this pathology, especially if there are signs of unexplained pulmonary hypertension [25,26]. To assess the presence, localization, number, morphology of ASD, indications for occluder placement, the IAS should be visualized in a number of positions [27], namely, the four-chamber at the level of the middle third of the esophagus (ME 4C), the short axis of the aortic valve at the level of the middle third of the esophagus (ME AV SAX), the inflow and outflow tracts of the right ventricle at the level of the middle third of the esophagus (ME RV In-Out) and the bicaval position at the level of the middle third of the esophagus (ME bicaval). The standard transesophageal echocardiography protocol must be supplemented with a modified bicaval position in order to exclude a possible sinus venosus ASD by gently rotating the transducer counterclockwise, displacing the transducer to the level of the upper or lower third of the esophagus.

For the timely verification of a sinus venosus as a cause of ischemic stroke, it is possible to use the following algorithm (Fig. 4).

Conclusion. The presented clinical case illustrates the possibility of ischemic stroke in a middle-aged patient by the mechanism of paradoxical embolism, which is realized through a rare ASD – sinus venosus. Verification of the cause of the stroke became possible thanks to the CT of the heart. Ultrasound diagnostics of this type of ASD is also possible, but requires the use of a special protocol. The source of the paradoxical embolism remained unknown, however, taking into account the provoking factors (long flight), it can be assumed that they were the veins of the lower extremities. The identification of ASD as the cause of ischemic stroke made it possible to refer the patient to surgical treatment, which is necessary both for the prevention of recurrent cerebral accidents and for the prevention of the development of heart failure.

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