Cryptogenic stroke

Kulesh A.A.[1,2], Drobakha V.E.[1,2], Shestakov V.V.[1]
[1]Acad. E.A. Vagner Perm State Medical University, Ministry of Health of Russia, Perm, Russia;
[2]City Clinical Hospital Four, Perm, Russia
[1]26, Petropavlovskaya St., Perm 614990; [2]2, Kim St., Perm 614107

The paper considers the epidemiology and general etiological characteristics of cryptogenic stroke (CS). It discusses the concept of embolic stroke with an unknown source of embolism. It also characterizes the most significant causes of CS, such as paroxysmal atrial fibrillation, atrial cardiopathy, aortic atheroma, non-stenotic cerebral atherosclerotic plaques, and malignant neoplasms. The paper describes approaches to the diagnosis and secondary prevention of CS and proposes etiological and neuroimaging diagnostic algorithms for CI. Clinical cases are also presented.

Keywords: *cryptogenic stroke; aortic arch atheroma; atrial fibrillation; cancer; diagnosis; prevention.*
Contact: *Aleksey Aleksandrovich Kulesh;* ***aleksey.kulesh@gmail.com***
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Cryptogenic stroke (CS) is diagnosed in 10P40% of patients with ischemic stroke (IS) [1]. Depending on the classification used, cryptogenic stroke is a stroke whose cause remained unknown at the maximum possible examination, as well as with an incomplete diagnostic search or identification of several competing mechanisms for the stroke development [1, 2]. It is the first interpretation of CS which seems the most correct and will be used in this article. The complexity of the CS problem is due to more than 200 causes of stroke potentially required to analyze. During a standard examination after having excluded the main etiological factors, such as cardioembolism from major sources, disease of large and small arteries, which take 25%, additional diagnostics most often reveal the following causes: non-stenotic atherosclerosis, non-atherosclerotic arteriopathies (dissection, vasculitis), aortic arch atheroma (AAA), medium-risk cardioembolism (unstable paroxysmal atrial fibrillation – AF, moderate dilated cardiomyopathy), paradoxical embolism on the background of patent foramen ovale (PFO) and hypercoagulation [2]. The occurrence of these factors varies significantly; therefore, the objective of this article is to consider the most common mechanisms of CS development and to introduce an optimal algorithm for diagnostics. The problems of stroke with PFO background and cerebral small vessels disease were discussed in our previous publications [3, 4].

Epidemiology, general etiological characteristics and prognosis

The proportion of patients with CS in a particular study decreases when newer and more detailed classifications CCS (Causative Classification of Stroke System) and ASCOD (Atherosclerosis, Small-Vessel Disease, Cardiac Pathology, Other Causes, Dissection) are applied. In a standard examination, CS is determined in 20P30% of patients, while in an extended study in specialized centers, it occurs only in 10P15% [5]. It is believed that there are some difficulties in identification of the stroke causes at a young age, but CS is more often observed in patients of 50 years and older. This may be due to its heterogeneity, which increases with age, and emphasizes that, in the current meaning, CS is not a pathogenetic entity, but a formal diagnostic construction. This view is confirmed by the results of the largest population-based study OXVASC where the widest approach to the diagnosis of CS was used, namely the one based on the TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment); it did not reveal any convincing similarities or differences with three main subtypes of IS [6]. At the same time, studies aimed to identify the causes of CS demonstrate that PFO is the cause of IS in 48% of cases, a paroxysmal form of AF in 40% and AAA in the remaining 14% of patients [7]. An important factor determining the etiology of CS is age. In patients aged 18P45 years, the most common causes of IS are dissection (28%), cardiogenic embolism (12%), antiphospholipid syndrome (11%), coagulopathy of unspecified origin (6%) and cerebral arteritis (5%) [8]. At the age of 31 – 60 years, early atherosclerosis and acquired structural heart diseases come to the fore, and after 60 years occult AF is considered the main one [2]. The short and medium-term risk of recurrence in CS is intermediate between a high risk for atherothrombotic and a low risk for lacunar stroke: for example, the frequency of recurrent stroke after 5 months reaches 5.6%, after 2 years – 20%, and after 5 years – 33 % [9].

The concept of Embolic Stroke of Undetermined Source of embolism (ESUS)

In clinical studies and (in a less degree) in everyday practice, the ESUS concept proposed in 2014 by RG Hart et al. [5] is used. ESUS is diagnosed in 80P90% of patients with CS and takes 9P25% in the structure of IS. The range of causes of ESUS is the following: 1) cardioembolism from low-risk sources (myxomatous valvulopathy with prolapse, mitral annular calcification, aortic valve stenosis, calcific aortic valve, atrial asystole and sick-sinus syndrome, atrial high-rate episodes, atrial appendage stasis with reduced flow velocities or spontaneous echodensities, atrial septal aneurysm, Chiari network, moderate systolic or diastolic dysfunction (global or regional), ventricular non-compaction, endomyocardial fibrosis) and paroxysmal AF; 2) arteriogenic embolism from vulnerable non-stenotic atherosclerotic plaques (AP) of precerebral arteries or dissection; 3) aortogenic embolism from vulnerable atheroma of the arch or the descending aorta; 4) paradoxical embolism through the PFO, atrial septal defect or pulmonary arteriovenous fistula, and 5) cancer-associated embolism due to hypercoagulation, non-bacterial thrombotic endocarditis and tumour emboli from occult cancer. Low-risk

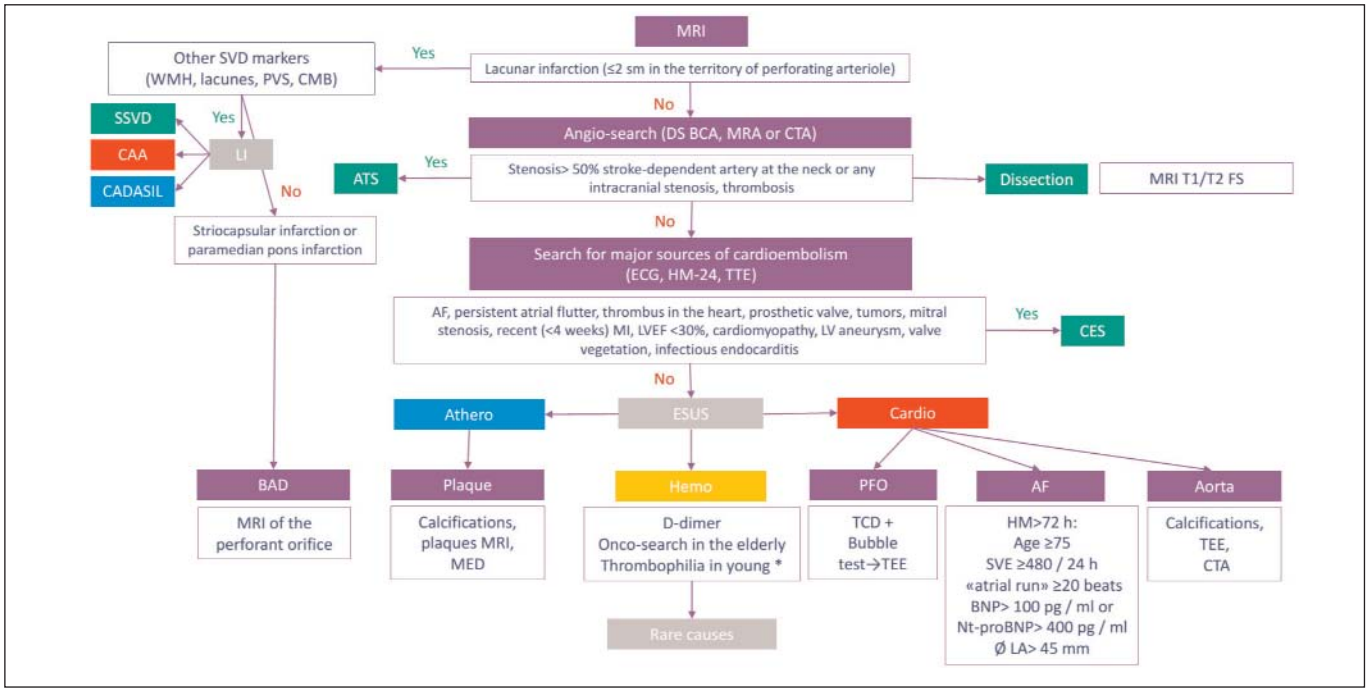

Fig. 1. *CS diagnostic algorithm based on the ESUS concept. SVD – cerebral small vessels disease; WMH – white matter hyperintensity; PVS – perivascular spaces; CMB – cerebral microbleeding; SSVD – sporadic small vessels disease; CAA – cerebral amyloid angiopathy; CADASIL – Cerebral Automosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; LS – lacunar stroke; ATS – atherothrombotic stroke; DS – duplex scanning; BCA – brachiocephalic arteries; HM – Holter ECG monitoring; MI – myocardial infarction; EF – ejection fraction; LV – left ventricle; CES – cardioembolic stroke; BAD – branch atheromatous disease; MED – microembolodetection; TCD – transcranial dopplerography; TTE – transthoracic echocardiogram; TEE – transesophageal echocardiography; SVE – supraventricular extrasystoles in 24 hours; BNP is a B-type natriuretic peptide; LA – left atrium; * – patients without vascular risk factors, with recurrent arterial or venous thrombosis and a positive family history*

sources of cardioembolism are important as a potential cause of stroke at the population level, but evaluating their etiological role in a particular patient is difficult [2, 5, 7, 10, 11].

ESUS is seen in the presence of non-lacunar infarction in combination with non-stenotic extra- and intracranial arteries (stenosis <50%), absence of major sources of cardiac embolism and other specific causes of stroke. The minimal examination necessary for diagnosis includes computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, ECG, transthoracic echocardiography, Holter ECG monitoring for at least 24 hours, examination of depending extra- and intracranial arteries using catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography [5, 10] (Fig. 1).

The main idea of ESUS is the unity of thromboembolism pathogenesis against the background of major (when oral anticoagulants have been proven effective) and minor or occult sources of cerebral embolism. In addition to pathogenetic backgrounds, this view is based on the advantage of warfarin over aspirin shown in a subgroup analysis of WARSS study related to the 2-year risk of recurrent IS or death with a more significant risk reduction in patients with embolic infarction localization or in presence of PFO [5]. Currently, in the framework of the ESUS concept, NAVIGATE ESUS and RE-SPECT ESUS have been completed with no benefits of anticoagulants over aspirin [12].

Cardiac causes of CS

Clinically evident AF serves as the cause of every 4th stroke. Moreover, in 15% of patients, AF is known at the time of a stroke, in another 8% of patients it is first detected on an ECG upon admission to a hospital, and in other 5% – using additional telemetry or 24-hour in-patient Holter monitoring [13]. Innovative technologies in recent years allow to monitor heart rhythm from 1 to 3 years by subcutaneous implantation of an ECG loop recorder, as well as for a longer time by using artificial pacemakers [14]. In existing clinical recommendations, the monitoring period for CS varies from 72 hours to 30 days [15, 16]. Currently, the results of randomized EMBRACE, CRYSTAL-AF and FIND AF randomized trials studied the effectiveness of prolonged ECG monitoring in CS have been published; they demonstrated the dependence of AF detection frequency on the time of observation. So, in the CRYSTAL-AF study, after 6 months monitoring the use of a loop recorder implanted in the first 3 months after a stroke contributed to AF detection in 8.9% of patients versus 1.4% with standard monitoring, after 1 year of monitoring it occurs in 12, 4% versus 2.0% and after 3 years the proportion is 30% versus 3%. A relatively high probability of detecting the first episode of AF after a stroke is associated with the following factors, namely patients' age ⩾75 years; supraventricular extrasystole ⩾480/24 h; longest «atrial run» ⩾20 beats; BNP >100 pg/ml; Nt-proBNP > 400 pg/ml; left atrial diameter >45 mm; stroke etiology with arterio-arterial embolism, cryptogenic stroke or ESUS, cardiac cause other than AF. Therefore, after a 72-hour baseline ECG monitoring, it is advisable to stratify the risk taking into account the above-named factors, and if there is a high probability of AF detection by the second stage, it is possible to conduct non-invasive ECG monitoring for at least 7 days, with a negative result, the search should be stopped [17, 18].

Although for a long time AF has been considered the direct cause of thrombosis and cardioembolism, only in a small proportion of patients AF paroxysm coincides chronologically with a stroke or transient ischemic attack [19]. Therefore, AF can be a marker of atrial dysfunction or TcardiopathyУ, which, in turn, serves as a direct cause of embolic events. The concept of atrial cardiopathy (cardiomyopathy, atriopathy) is that under the various etiological factors influence atrial cardiomyopathy develops; it leads to stroke through mechanical dysfunction and procoagulatory changes, and to AF progress through electrical dysfunction and fibrosis, which also contributes in the pathogenesis of IS [20]. Atrial cardiopathy is observed in 65% of patients with CS, and 35–45% of patients with CS have cardiopathy without AF [9]. Independent markers of atrial dysfunction include paroxysmal supraventricular tachycardia; dispersion of P-wave; increased terminal index; NT-proBNP level; morphology of the left atrial appendix according to heart MRI and its fibrosis; decreased peak systolic blood flow velocity in the appendix; biomarkers of hypercoagulatory status, as well as polymorphism of genes associated with AF [20]. Finding the optimal set of biomarker data seems to be a promising approach in patients with CS.

The prescription of oral anticoagulants for the secondary prevention of stroke is possible only with AF verification [21]. A promising option is an antithrombotic strategy choice based on the signs of atrial cardiopathy assessment. Thus, a subsequent WARSS analysis showed higher warfarin efficacy in patients with NT-proBNP >750 pg / ml [5]. The ARCADIA study is currently evaluating the hypothesis that apixaban is superior to aspirin in the prevention of recurrent stroke in patients with ESUS and atrial cardiopathy seen in the presence of biomarkers [22].

Aortic atheromatosis

AAA is considered as a marker of systemic atherosclerosis and is most strongly associated with peripheral arterial disease, as well as with smoking. Most often, the atheroma is located on the internal curvature of the aortic arch and at the orifice of its three branches. Complicated AAA is considered as AP with a thickness of i4 mm with ulceration or a mobile component. AAA is seen in 22% of patients with a determined cause of a stroke and in 61% of patients with the stroke unknown etiology. In case of TEE, complicated AAA is observed in 21–27% of patients with stroke and 5P9% of people without stroke. The risk of stroke increases with AP thickness, and an AAA i4 mm is considered as an independent risk factor for recurrent stroke along with AF and carotid stenosis >70% [23, 24]. Thus, nowadays AAA, especially if complicated, is considered as one of the risk factors for CS and ESUS.

The development of a stroke on AAA background is possible by the embolic (AP fragments or cholesterol crystals) and hypoperfusion (with localization of atheroma at the orifice of the main branches) mechanism [23]. AAA located in the middle distal part of the arch is prone to embolization in the left carotid circulation. Although atheroma of the ascending aortic arch is the main source of cerebral embolism, atheroma in the distal part of the arch can also cause embolism due to retrograde blood flow from the descending aorta in diastole [24, 25]. According to MRI, embolism in AAA is manifested by small cortical or border zones infarctions scattered within several vascular territories. Larger cortical infarctions may be associated with cleavage of fragments of complicated AAA [26].

The main methods to identify and characterize AAA are TEE and CT angiography. TEE is considered the 3gold standardИ for the diagnosis of AAA; in determining the aortic arch thrombus its sensitivity and specificity are more than 90%, however it has significant limitations, such as invasiveness which is named the main one, poor patient tolerance and sedation necessity. CT angiography is devoid of such limitations and it is easier to perform. When using TEE or CT angiography, unstable (embologous) AAA is considered as AP in the ascending aorta or proximal arch, corresponding to i1 of the following criteria: 1) the thickness of the intima-media complex is i4 mm for TEE or the thickness of the AP adjacent to the aortic wall is i6 mm with CT angiography or 2) ulcerated AB with TEE or soft AP with CT angiography. Inclusion in the diagnosis of these research methods can reduce the incidence of CS from 19.2 to 11% due to an increase in atherothrombotic stroke [7, 25]. The search for AAA is justified in elderly patients: 1) with multiple lesions within different vascular territories; 2) with small infarctions and 3) with cortical lesions or infarctions in the border zones [18] (Fig. 2).

Strict control of cardiovascular risk factors (CVRF) is primarily recommended for stroke patients with AAA [27]. Currently, there is no convincing evidence in favor of antiplatelet agents or anticoagulants use in the secondary prevention of IS in AAA. A comparison aspirin and clopidogrel combination vs warfarin in AAA> 4 mm did not show significant differences in stroke prevention [28]. Rosuvastatin at a dose of 5 mg for 6 months can lead to AAA stabilization in combination with a level decrease of low density lipoproteins in patients with IS [29]. Thus, according to current North American recommendations, patients with IS and AAA should be prescribed antiplatelet agents and statins [16].

Non-stenotic atherosclerosis

To determine a stroke as atherothrombotic, an ipsilateral focal stenosis> 50% (ASCOD) is required. Nevertheless, more and more evidences have recently appeared in favor of the fact that non-stenotic (<50%) atherosclerosis of brachiocephalic arteries serves as a significant risk factor for ESUS [30]. Non-stenotic extracranial AP can become a source of arterial-arterial embolism, and in addition to this mechanism intracranial AP can spread at a perforating artery orifice (*branch atheromatous disease*) [9].

At present, we can talk about a paradigm shift, along with the stenosis degree it has such an effect on embolic risk and treatment as structural parameters of AP, such as the presence of hemorrhage, ulceration, neovascularization, thinning of the fibrous capsule and mainly the volume of lipid necrotic cor. These signs indicate the AP vulnerability and its belonging to V and, especially, to type VI according to the classification of the American Heart Association. Non-stenotic APs on the lesion side are detected in every 3rd patient with CS. Among AP with stenosis ⩾30%, type VI is observed in 54% of cases in patients with stroke and in 20% of cases in patients with asymptomatic course. At the same time, 55% of type VI AP are detected with stenosis <70% [30].

Determination of the embolic potential of AP is possible using high-resolution MRI of the vascular wall, including assessing the contrast enhancement (AP MRI), CT (multislice CT and dual energy CT) and modern ultrasound techniques (three-dimensional scanning, micro-bubble contrast, MED).

MRI allows to determine an atherosclerosis activity degree and AP vulnerability. The most informative and often used are the T1 3D MRI sequences using the FSE (fast spin echo) data acquisition technique and the gradient echo sequence, which allows to

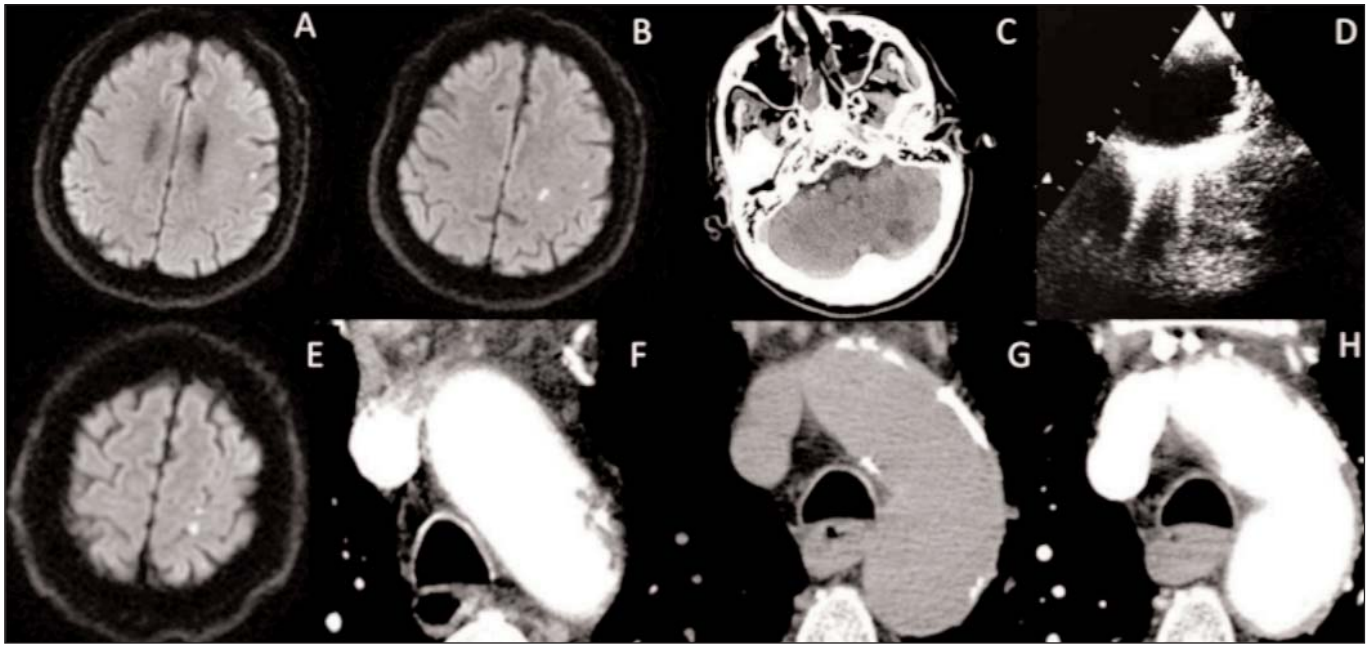

Fig. 2. *IS on the background of AAA. Patient A., 72 years old, suffers from hypertension and coronary heart disease. In 1998, he suffered a myocardial infarction, in 2007 coronary artery bypass grafting was performed. The patient was admitted to the hospital with complaints of clumsiness in his right hand. MRI of the brain revealed small scattered lesions with high signal on diffusion-weighted images (DWI) in the cortical parts of the left middle cerebral artery territory (a, b, e). According to duplex scanning, stenosis of the left common and internal carotid arteries was determined (25%); no intracranial artery stenosis was detected with MR angiography. According to the results of transthoracic echocardiography, an increase of the left atrium and the diameter of the ascending aorta was recorded. During Holter ECG monitoring, supraventricular ectopic activity was observed in the form of single, paired and group extrasystoles and paroxysm of supraventricular tachycardia (4 episodes) with a heart rate of up to 152 per minute, for a total duration of 25 s. The bubble test is negative. According to CT angiography, the diameter of the aorta in the root region is 40 mm, in the ascending region 40 mm, in the arch region 37 mm. In the area of the aortic arch, APs with calcium are visible, extending into the lumen up to 9 mm. APs have irregular shapes, with streaks of contrast medium, the formation of thrombotic masses (complicated atheroma, f).*

Patient B., 72 years old, suffers from hypertension. Admitted to the hospital complaining intense vertigo and instability when walking. CT scan of the brain revealed left cerebellar infarction (c). Sinus rhythm, according to the transthoracic echocardiography of the heart cavity is normal. According to the results of thoracic aortography, stenoses of the internal carotid artery on the right (80%) and left (40%), vertebral artery on the right (90%) were visualized. The left subclavian and vertebral arteries are normal, the aortic circuit is irregular. According to CT angiography, intracerebral arteries are not stenotic. Complicated atheroma of the aortic arch was visualized (g, h), which is also visualized with TEE – heterogeneous AP with irregular surface and a crater-like hollow (d)

identify the intraplaque hemorrhage and the lipid necrotic cor. In addition, the 3black bloodИ technique can be applied. All of these sequences should be accompanied by suppression of the signal from fat. Contrast enhancement with gadolinium is necessary for AP components differentiation (for example, necrotic cor and fibrotic tissue), neovascular zones and inflammation areas identification [9, 31]. Thus, high-resolution MRI of the vascular wall may be required for patients: 1) with recurrent stroke in the same vascular territory; 2) with small disseminated infarctions within the same vascular zone; and 3) with suspected BAD [18].

Transcranial Doppler with the determination of cerebral microembolic signals (microembolic signals, MES) is informative to identify unstable AP [31]. MES is observed in 43% of patients with clinically manifest carotid stenosis compared with 10% of patients with asymptomatic stenosis; the presence of at least one MES increases the risk of cerebral events in patients with stroke by 7.5 times and embolic events in patients without stroke by 13.4 times, while the absence of MES indicates a very low likelihood of clinical manifestation of stenosis [32].

Clinical studies have not documented the benefits of anticoagulants over antiplatelet agents in the secondary prevention of stroke in patients with intracranial atherosclerosis. Surgical treatment of non-stenotic APs also does not exceed conservative therapy in secondary prevention. Therefore, as with AAA occurence, antiplatelet agents hold the main place in the secondary prevention of CS in non-stenotic atherosclerosis, including intracranial [27]. Prescribing statins (especially in high doses) is associated with a decrease in AP thickness. Changing the lipid core volume is considered as the most informative indicator of statin therapy effectiveness. Thus, the use of rosuvastatin in asymptomatic small and moderate stenosis leads to a decrease of the necrotic cor volume by 41% per year [30, 33]. In general, as in the case of asymptomatic stenosis, it is believed that a lipid necrotic core, hematoma and ulceration of AP is the optimal clinical situation for high doses of statins prescription. Moreover, such patients require ultrasound monitoring and monitoring of clinical and MRI signs of embolism, they may also need revascularization, despite a small percentage of stenosis [34].

The occult cancer

Cardiovascular and oncological diseases make the main contribution to the structure of mortality, and more and more

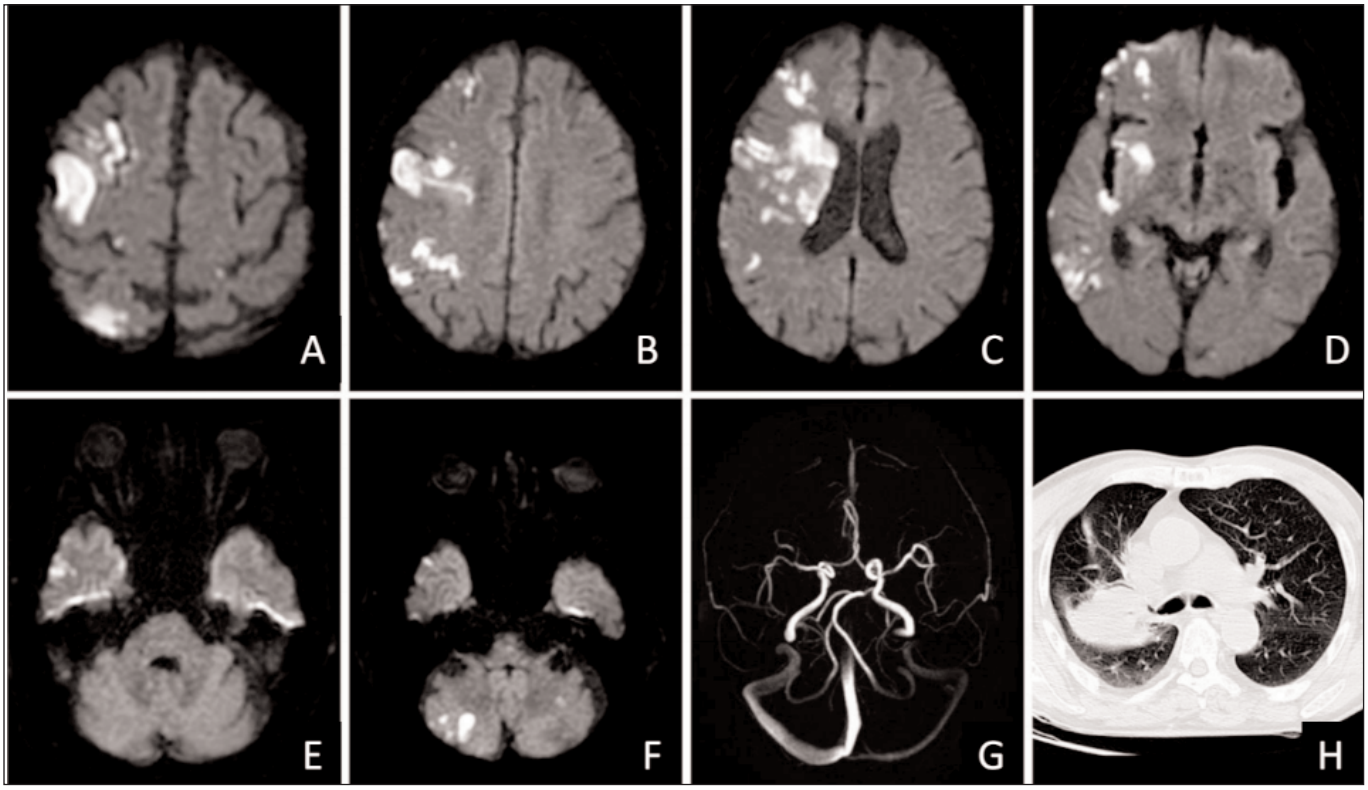

Fig. 3. *Cancer-associated IS. Patient S., 73 years old, suffers from lung cancer (peripheral squamous cell disease of the upper lobe of the right lung with centralization, T3NxM1). At 10 a.m., he acutely developed weakness in the left extremities and speech impairment. In addition to a stroke, thrombosis of the brachial artery on the right was diagnosed, thrombectomy was performed. MRI of the brain revealed multiple foci of white and gray matter infarction with hyperintensive signal characteristics on DWI b-1000 (a–f) scattered within both carotid and basilar (mainly right) territories without stenosis of intracerebral vessels according to MR angiography (g). Duplex scanning of carotid arteries revealed stenosis (I35%), vertebral arteries are normal. We did not reveal the source of embolism. A central right lung cancer was diagnosed with chest CT (h)*

experts are paying attention to their comorbidity. IS develops in 7P15% of patients with malignant neoplasms (MN) usually in the first months after the cancer diagnosis. At the same time, in half of patients with MN there is a CA. MN is observed in every 10th hospitalized patient with a stroke, the oncological process is accompanied by an increased risk of IS, as well as its more severe course, recurrence and mortality [35].

The mechanisms of IS in patients with MN include hypercoagulation, non-bacterial thrombotic endocarditis, paradoxical and tumor embolism, as well as classic stroke causes potentiation (atherosclerosis and AF). Hypercoagulation in MN is caused by cell adhesion molecules activation with mucin secreted by adenocarcinomas; tissue coagulation factors release leading to the activation of factors VII and XII; endothelial cells damage by cytokines; platelet activation; suppression of protein C production; intravascular lymphomatosis, as well as an increase in blood viscosity in myeloproliferative diseases. A special clinical variant of hypercoagulation associated with cancer is Trusso syndrome, spontaneous recurrent or migrating episodes of arterial embolism due to non-bacterial thrombotic endocarditis, venous thrombosis, or its combination. In half of patients with stroke and MN, microembolism is revealed according to transcranial dopplerography associated with a high level of D-dimer. Thrombotic events are especially characteristic for patients with adenocarcinomas, tumors of the lungs, pancreas and mammary glands, as well as the stomach [1, 9, 35, 36].

In patients with CS and occult cancer an increased level of D-dimer, fibrinogen and CRP, multiple lesions in several vascular territories, as well as nutritional deficiency are noted, whereas infarctions in the border zones of the cerebral hemispheres and cerebellum are typical [4] 35, 37, 38] (Fig. 3). In such patients, a neurological deficit has gradually developed over several hours or days. Encephalopathy in patients with a cancer-associated stroke occurs due to the presence of multiple infarctions. They also have a history of systemic arterial or venous thromboembolism. In the majority of patients, stroke develops at the advanced stage of MN with metastases, although in some cases it may be the first manifestation of disease [35, 37].

Evaluation of the level of D-dimer and oncological search are appropriate for patients, especially the elderly ones who are: 1) with insufficient severity of traditional risk factors for stroke; 2) with atypical symptoms; 3) with multiple infarctions in different vascular territories. Oncological search is individual and it depends on age and in most cases includes the level of D-dimer, CRP, and the chest, abdomen and pelvis CT assessment [18].

The question of an optimal variant of antithrombotic therapy in patients with cancer-associated stroke remains open [35]. Particular attention in the treatment of this group of patients should be given to deep vein thrombosis and thromboembolism prevention [39].

Diagnostic Algorithms. According to Bang et al. [18] and our own ideas, the first stage of CS diagnosis consists in a

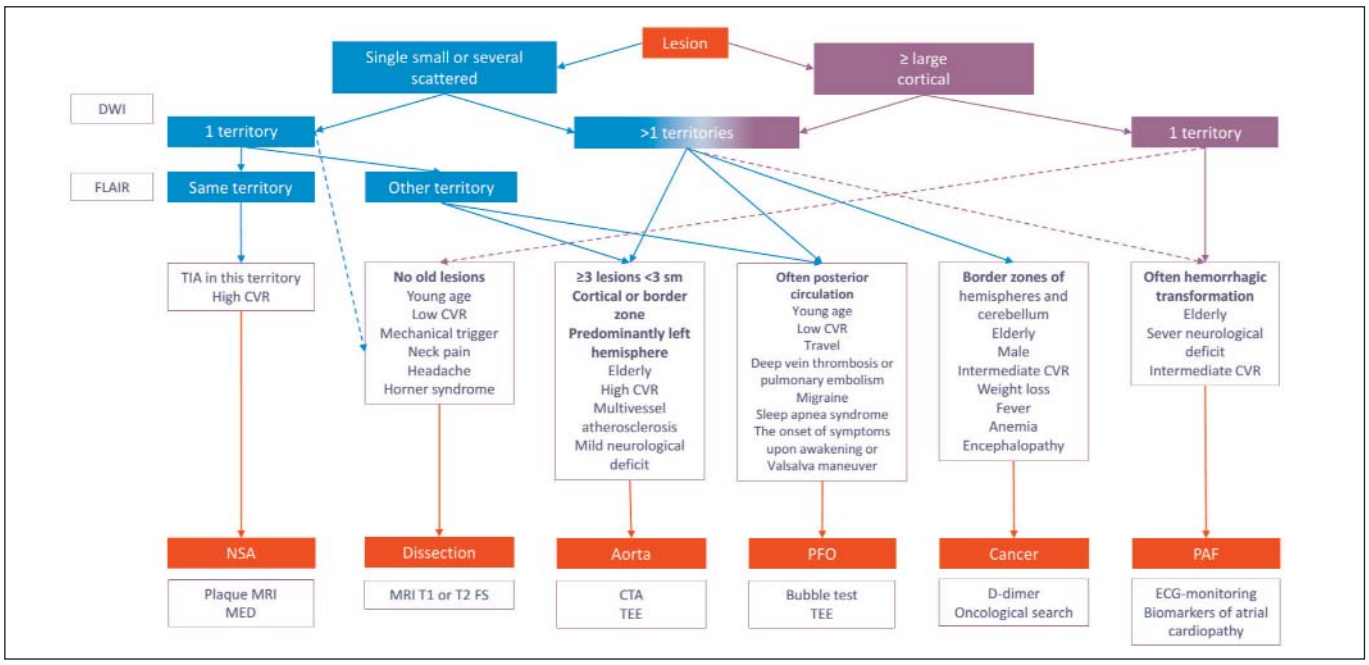

Fig. 4. *Screening algorithm for CS, based on the MRI pattern of the lesions. The dashed arrow indicates a less likely cause; HT – hemorrhagic transformation; VBT – vertebrobasilar territory; PE – pulmonary embolism; NSA – non-stenotic atherosclerosis; PAF – paroxysmal atrial fibrillation*

detailed analysis of the MRI pattern of stroke with the distribution of infarctions assessment on DWI and FLAIR (Fig. 4). Ryoo et al. [7] have shown that CS in PFO develops in young patients with a relatively low CVRF; in this case infarctions are often located in the vertebrobasilar territory, as well as in AAA, IS occurs in old age on the high CVRF background, small lesions are located in cortical or border zones. Patients with IS in AF are characterized by old age, relatively low CVRF and large cortical infarctions [7].

In addition to the studies shown in Fig. 1 and 4, some authors propose to carry out hematological testing with arterial (for all patients) and venous (in the presence of a right-to-left shunt) coagulation tests assessment at the second (expanded) stage of diagnosis, and to exclude genetic causes (MELAS, CADASIL, Fabry disease), cerebral vasculitis, oncological search, as well as ECG monitoring prolonged up to 1–3 years at the third stage (specialized examination) [2]. Hypercoagulatory status occurs in 3P21% of patients with IS and, excluding antiphospholipid syndrome, it is associated with venous thrombosis [9]. Tests for thrombophilia in young patients without vascular risk factors but with recurring arterial or venous thrombosis and a positive family history are diagnostically valued [40].

Conclusion

Thus, patients with CS are the most difficult category of patients with acute cerebrovascular accident for diagnosis, and this type of stroke determination is the starting point for further diagnostic searches based on a thorough analysis of neuroimaging data, as well as in-depth angio- and cardiac search. The use of diagnostic algorithms will increase the percentage of identifying CS causes and, consequently, choose an adequate secondary prevention, reducing recurrent strokes incidence.

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