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Etiology of Cryptogenic Stroke

G.R. Ramazanov[1]*, T.A. Magomedov[1], L.T. Khamidova[1], N.V. Rybalko[1], S.S. Petrikov[1], N.A. Shamalov[2]

Department of Emergency Neurology and Rehabilitation
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department
3 Bolshaya Sukharevskaya Square, Moscow 129090, Russian Federation
[2] Federal Center for Cerebrovascular Pathology and Stroke, the Ministry of Health of Russian Federation
1 b. 10, Ostrovityanova St., Moscow 117513, Russian Federation

*** Contacts:** Ganipa R. Ramazanov, Head of the Department of Emergency Neurology and Rehabilitation, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department. Email: ramazanovgr@sklif.mos.ru

ABSTRACT Ischemic stroke is a heterogeneous syndrome with a plurality of potential etiological factors. The routine diagnosis does not always allow the cause of acute cerebrovascular accident to be found, in such cases we talk about cryptogenic ischemic stroke, which incidence is 20-40%. The category of patients with cryptogenic stroke was first characterized and assigned to a separate group in the database of the National Institute of Neurological Diseases and Stroke in the USA, and later in the TOAST study. The diagnosis of cryptogenic stroke is usually based on the exclusion of well-known causes of acute cerebrovascular accidents, such as atherosclerosis, cardiac arrhythmias, arterial hypertension. Due to the considerable variability of concepts for cryptogenic stroke, the term ESUS (Embolic Stroke of Undetermined Source) appeared in 2014 and formulated criteria which accurately characterized these patients: non-lacunar cerebral infarction by CT and/or MRI, no atherosclerotic lesion stenosing a stroke-associated artery of more than 50%, no sources of high-risk cardioembolism, no other causes of stroke such as dissection of the artery supplying the area of infarction in the brain, migraine, arteritis. Among the potential causes and sources of cerebral embolism in patients with cryptogenic stroke are heart, veins of lower extremities and pelvis, nonstenosing atherosclerosis of brachiocephalic artery, atheroma of aortic arch, paradoxical embolism non-atherosclerotic vasculopathy, monogenic diseases, hypercoagulable states, and others. We should note that there is a lot of studies on the possible causes of cryptogenic stroke in the available literature, but no common approach to classification of etiologic factors and examination algorythms were developed. The high incidence of cryptogenic stroke, the significant heterogeneity of its etiopathogenetic mechanisms and the need for differentiated approaches to the secondary prevention of this type of acute cerebrovascular accident determine the relevance of further studies in this field.

Keywords: cryptogenic stroke, paradoxical embolism, open oval window, Fabry disease, aortic atheroma

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Affiliations

Ganipa R. Ramazanov	Head of the Department of Emergency Neurology and Rehabilitation, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, Cand. Med. Sci., ORCID https://orchid.org/0000-0001-6824-4114
Timur A. Magomedov	Neurologist of the Department of Neurology for Patients with Acute Cerebrovascular Accident with ICU, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orchid.org/0000-0002-0804-3190
Layla T. Khamidova	Head of the Scientific Department of Ultrasound and Functional Diagnostics, Cand. Med. Sci., N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orchid.org/0000-0002-6299-4077
Natalya V. Rybalko	Leading Researcher, Scientific Department of Ultrasound and Functional Diagnostics, Dr. Med. Sci., N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orchid.org/0000-0001-6973-4430
Sergey S. Petrikov	Director of N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, Professor of Russian Academy of Sciences, Doctor of Medical Sciences, https://orchid.org/0000-0003-3292-8789
Nikolay A. Shamalov	Deputy Director of the Federal Center for Cerebrovascular Pathology and Stroke of the Ministry of Health of Russian Federation, Professor, Doctor of Medical Sciences, https://orchid.org/0000-0001-6250-0762

AA — antinuclear antibodies
ACVE— acute cerebrovascular event
AF — atrial fibrillation
AP — atherosclerotic plaque
APS — antiphospholipid syndrom
BA — brachiocephalic arteries
CIS — cryptogenic ischemic stroke
CT — computed tomography
ECG — electrocardiography
EchoCG — echocardiography
FD — Fabry disease
IAS — interatrial septum
IS — ischemic stroke
MRI — magnetic resonance imaging
PE — pulmonary embolism
PFO — patent foramen ovale
PxE — paradoxal embolism
SCA — sickle cell anemia

TE EchoCG — transesophageal echocardiography
TIA — transient ishemic attack
TTR EchoCG — transthoracic echocardiography

Ischemic stroke (IS) is a heterogeneous syndrome with many potential etiological factors. Routine diagnosis does not always allow us to establish the cause of acute cerebrovascular event (ACVE), in such cases it is customary to talk about cryptogenic ischemic stroke (CIS), which incidence is 20–40% [1–4]. The category of patients with CIS was first characterized and assigned to a separate group in the database of the National Institute of Neurological Diseases and Stroke in the USA, and subsequently in the *TOAST* study [1, 5, 6]. The diagnosis of CIS is normally based on the exclusion of well-known causes of stroke, such as atherosclerosis, cardiac arrhythmias, arterial hypertension [3]. In connection with the considerable variability of the concept of CIS, in 2014 the term *ESUS* (*Embolic Stroke of Undetermined Source*) was introduced and criteria were formulated that clearly characterize such patients:

- non-lacunar infarction of the brain according to computer (CT) and/or magnetic resonance imaging (MRI);
- the absence of an atherosclerotic lesion stenosing a stroke-associated artery by more than 50%;
- lack of sources of high risk cardioembolism;
- the absence of other causes of stroke, such as dissection of the artery that feeds the area of cerebral infarction, migraine, arteritis.

Among the potential causes and sources of cerebral embolism in patients with CIS, the heart, veins of the lower extremities and pelvis, non-stenotic atherosclerosis of the brachiocephalic arteries (BA), atheromas of the aortic arch, paradoxical embolism, non-atherosclerotic vasculopathy, monogenic diseases, hypercoagulable conditions, etc. [7].

According to various studies, the incidence of recurrent IS in patients with CIS is significantly higher than with the established pathogenetic variant of stroke. *S. Bal et al.* (2012) found that by day 30 and 90 from the onset of the disease clinically silent foci of ischemia were detected in the new vascular pool in 6.6% and 14.5% of patients with CIS, respectively (according MRI of the brain). Repeated IS within 90 days develops in 1.2% of patients with CIS [8]. In patients with CIS, the incidence of recurrent stroke within a year is significantly higher than in patients with atherothrombotic, cardioembolic, lacunar stroke (30% versus 16%, 14% and 2%, respectively) [9]. According to *G. Ntaios et al.* (2015), the risk of recurrent AI within 31 months in patients meeting *ESUS* criteria is comparable to that in patients with cardioembolic AI (29% and 27%, respectively), but higher than in patients with atherothrombotic (13%) and lacunar (13%) strokes. At the same time, favorable functional outcomes (2 points or less on the modified Rankin scale) occur more often in patients with *ESUS* (62.5%) than in patients with cardioembolic stroke (32.2%) [10]. However, in a population study of *L. Li et al.* (2015) the frequency of development of repeated IS over 10 years in patients with CIS and non-cardioembolic stroke was not significantly different (32% versus 27%) [3].

CARDIOEMBOLISM

The heart as a source of cerebral embolism was first described in 1875 on the example of a patient with an embolism of the retinal arteries and the middle cerebral artery. Currently, more than 20 different cardiological diseases are considered as potential sources of cerebral embolism [1]. Recent studies show that continued electrocardiographic (ECG) monitoring reveals paroxysmal atrial fibrillation (AF) in some patients with CIS [11]. The frequency of detection of AF paroxysms in patients after IS varies from 3.2 to 30% depending on the duration of ECG monitoring (from 24 hours to 36 months) [12-14].

Subclinical AF and patent foramen ovale (PFO) are the leading risk factors for the development of CIS [14–16]. An *EMBRACE* study found that 30-day non-invasive ECG monitoring compared to standard 24-hour Holter ECG monitoring improved the detection of AF episodes by 5 times[15]. *T. Sanna et al.* (2014) reported that an implantable device for continued ECG monitoring for 6 months better revealed AF paroxysms in patients with CIS than the standard technique (8.9% versus 1.4%) [14]. According to *H. Kamel et a* . (2013), the cumulative risk of IS in patients with paroxysmal supraventricular tachyarrhythmia is much higher than in patients without this type of arrhythmia [17]. In the *MOST* study, atrial acceleration of more than 220 beats/min in was associated with a 2-fold increase in the risk of death, and a 6-fold increase in the risk of non-fatal stroke [18]. However, recent studies cast doubt on the fact that is itself is the main cause of cardioembolic complications. A number of researchers believe that IS is a marker of atrial cardiopathy, which is the direct cause of cardioembolism [19–21]. At present, predictors of IS have been established in patients with CIS: elderly age, previous embolic strokes, enlargement of the left atrium according to echocardiography and early atrial complexes (according to ECG) [22-24]. Moreover, enough evidence has been accumulated indicating the association of markers of atrial cardiopathy and IS regardless of the presence of AF. Signs of left atrial dysfunction detected during a routine ECG are associated with an increased risk of IS. Dispersion of the *P* wave according to ECG data is another marker of left atrial dysfunction associated with the risk of IS [25]. So, in the *NOMAS* study, it was found that moderate (for women 43–46 mm, for men 47–51 mm) and significant (for women 47 mm and more, for men 52 mm and more) left atrial expansion is associated with a risk of repeated cardioembolic or CIS [26]. The *SPORTIAS* study showed that markers of left atrial dysfunction are present in more than 65% of patients with CII [27].

Increased blood concentration of *B*-type natriuretic peptide may be an independent risk factor for ischemic stroke (regardless of the presence of atrial fibrillation) [28]. In a meta-analysis of *V. Lombart et al.* (2015) it was shown that the levels of cerebral natriuretic peptide and *N*-terminal cerebral natriuretic propeptide were significantly higher in patients with cardioembolic stroke [29].

Transesophageal echocardiography (TE EchoCG) more efficiently reveals cardiogenic sources of cerebral embolism compared with transthoracic echocardiography (TTR EchoCG) [30]. In more than one of 8 patients who did not show any pathology according to the data of TTR EchoCG, risk factors for cardioembolism of high degree are revealed in case of TE EchoCG. In patients with normal TTR EchoCG, when performing TE EchoCG, risk factors for cardioembolism are detected in 40% of cases [31]. Magnetic resonance imaging (MRI) is better than TTR EchoCG reveals transmural myocardial scars, which are an independent risk factor for the formation of thrombotic masses [32]. The use of heart MRI is highly sensitive with respect to the detection of thrombotic masses in the left ventricle, especially in patients after myocardial infarction [33]. In patients with CIS, the use of heart MRI allows a direct or potential source of cardioembolism to be established in 27.1% of cases [34]. In a study by *A. Baher et al.* (2014) the use of heart MRI allowed us to verify the pathogenetic version of IS in 39.1% of patients with the initial CIS [34].

NON-STENOTIC ATHEROSCLEROSIS

In the 40s of the XX century, most experts believed that cerebral vasospasm was the main cause of IS. This theory had dominated until the 50s of the twentieth century when the neurologist Miller Fisher emphasized the importance of atherosclerosis

as the main cause of IS [35]. In 79% of patients with *ESUS*, non-stenotic atherosclerosis is detected [7]. With stenosis from 1 to 15%, the prevalence of carotid arteries complicated by atherosclerotic plaques (ASP) ipsilateral to the focus of acute cerebral ischemia, is 8.1% [36]. In patients with CIS and non-stenotic atherosclerosis of the stroke-associated artery, signs of hemorrhage in the plaque on the side of the stroke are detected in 25% of cases. In a study by *T. Freilinger et al.* (2012) complicated atherosclerotic plaques of type VI according to the classification of cardiomyopathies AHA (2006) were detected using high-field MRI in 37.5% of patients with CIS. The most common signs that characterized complicated plaques were: hemorrhage into the plaque (75%), ulceration of the fibrous lining (50%) and parietal thrombosis (33%) [37].

ATEROMA OF THE AORTIC ARCH

For the first time, the dependence between IS and the atheroma of the aortic arch was suggested by *W.J. Jr. Winter* in 1957, which described two cases of IS in patients with this formation [38]. The absence of atherosclerotic lesions of the carotid arteries does not exclude the presence of atheroma of the aortic arch [39]. Ateroma of the aortic arch should be considered as a potential cause of cerebral embolism in the absence of other sources. *P. Amarenco et al.* (1992) revealed a dependence between atherosclerotic lesions of the aortic arch and and IS in a post-mortem study of 500 patients. Upon autopsy, in 28% of patients who died of IS, atherosclerotic lesions of the aortic arch were revealed. Ateromas of the aortic arch were detected only in 5% of cases in patients who died due to other neurological diseases [40]. According to *Kanjana et al.* (2016), an aortic arch atheroma is detected in 29% of patients with *ESUS* [7] with TE EchoCG, and according to *F. Knebel et al.* (2009), TE EchoCG better detects ASP of the aortic arch than TTR EchoCG [41]. A number of researchers showed high informativeness of MRI to detect atheroma of the aortic arch [42]. The size of the ASP of the aortic arch is directly related to its thrombogenity [43]. According to transcranial microemboli detection, embolic signals were detected in 78% of patients with large plaques and only in 29% of patients with little plaques or without them [43]. The thickness of the ASP of the aortic arch is more than 4 mm, and its ulceration, the presence of the movable part are factors that increase the likelihood of thromboembolism [40, 44]. So, in a study by *D.A. Stone et al.* (1995) it was found that complex ASP of the aortic arch (plaques with signs of ulceration,2 mm or more in diameter and/or in depth) and/or with a movable part (thrombotic masses) are more often detected in patients with CIS than in patients with stroke of known etiology or in healthy respondents (39%, 8% and 7%, respectively) [45]. The frequency of repeated IS in patients with ASP thickness of the aortic arch of 4 mm or more is significantly higher than in patients with plaque thickness of 1–3.9 mm and less than 1 mm (11.9 per 100 patients/year, 3.5 per 100 patients/year and 2.8 per 100 patients/year, respectively) [44]. In a study by *M. Di Tullio et al.* (2009) large or complex ASP of the aortic arch in patients with *ESUS* were associated with an increased risk of recurrent IS or death within 2 years (risk ratio 6.42; 95% CI, 1.62–25, 46, and 9.50; 95 % CI, 1.92–47, 10, respectively) [46].

INTRACRANIAL ARTERIAL STENOSIS

Intracranial stenosis of the arteries can be the cause of IS and should be considered as a potential cause in patients with CIS [47].

The prevalence of this pathology in patients with IS varies significantly from 2.2 to 51% [48, 49]. This significant variety is most likely associated with various diagnostic methods, as well as the ethnic component of the respondents. High-field MRI with the ability to assess vascular wall can be a reliable tool in the diagnosis of intracranial ASP. Diffuse thickening of the wall of the intracranial artery can be a marker of active atherosclerosis even in the absence of narrowing of the lumen of the artery [30].

PARADOXICAL EMBOLISM

Paradoxical embolism (PxE) is a condition where a blood clot formed in the venous channel enters the arterial system of the pulmonary circulation. In 1877, *J. Cohnheim* first described PxE in a patient with PFO [50]. This condition may develop in patients with PFO, atrial septal defect (ASD), pulmonary arteriovenous fistulas. The incidence of PFO in the population exceeds 25% [51]. A meta-analysis of 23 studies showed that the incidence of OOW in patients with CIS is 2.9 times higher than in patients with an established pathogenetic variant, and reaches 40% [52]. Risk factors for the development of cerebral embolism in patients with PFO are the size of the PFO and the intensity of blood shunt from right to left, the presence of IAS aneurysm, as well as the degree of IAS excursion ≥10 mm during the cardiac cycle [53–55].

A fairly difficult task is to prove the existence of a dependance between PFO and the IS. The most likely cause of IS in patients with PFO is PxE from the veins of the pulmonary circulation (veins of the lower extremities and pelvis). It should be noted that the frequency of detection of venous thrombosis of the lower extremities in patients with IS and PFO is 7.6–9.5% [16, 56, 57]. In patients with CIS and PFO, pelvic vein thrombosis was detected in 1.5–13% of cases [56–58]. In 2013, criteria for the probability of dependance between PFO and CIS were suggested, *ROPE (Risk of Paradoxal Embolism) scale* [59]. The maximum *ROPE* score is 10 points. The higher the score, the closer the relation of PFO with CIS [59].

Pulmonary embolism (PE) is the most common cause of cardiac shunt from right to left through PFO [60]. The frequency of PxE in patients with pulmonary embolism is 60% [60]. *C. Thanislav et al.* (2011) showed a high prevalence of clinically undeveloped pulmonary embolism which was up to 37% in patients with CIS and PFO, especially when PFO was ombined with IAS aneurysm or its hypermobility [61]. Other causes of increased pressure in the right atrium are acute respiratory failure and myocardial infarction in the right ventricle [62].

Echocardiography using foamed sodium chloride solution is used for diagnostics of both PFO and arteriovenous pulmonary shunts [63]. Valsalva's maneuver can increase the information content of this diagnostic method, as it increases the pressure in the right heart [64].

In a study by *H. Schuchlenz et al.* it was shown that the diameter of PFO more than 4 mm is an independent risk factor for the development of TIA, especially in patients with a history of two or more strokes [65].

K. Kimura et al. (1999) showed that paradoxical cerebral embolism can be observed in patients with CIS with isolated arteriovenous pulmonary fistula provided there is a blood shunt from the right heart to the left [66]. The first pathoanatomical description of pulmonary arteriovenous fistula belongs to *T. Churton* and is dated 1897 [67]. Currently, there are no clear statistics on the frequency of IS in patients with pulmonary arteriovenous fistulas, but there are a large number of clinical observations. Therefore, any patient with CIS should be examined for the presence of arteriovenous pulmonary fistula. The best diagnostic tool is CT of the lungs with contrast enhancement [68].

Magnetic resonance imaging can also help diagnose May–Thurner syndrome, another potential cause of PxE in patients with PFO [69]. May–Thurner syndrome is compression of the common iliac vein (usually the left) with the common iliac artery. This syndrome in the population occurs with a frequency of up to 20%, more often in women [70]. *T.J. Kiernan et al.* (2009) revealed May–Thurner syndrome in 6.3% of patients with CIS and PFO [71].

NONATHEROSCLEROTIC VASCULOPATHY

Nontherosclerotic vasculopathy, according to *J. Varona et al.* (2007), is the cause of about 17% of all IS [72]. Nontherosclerotic vasculopathy usually includes dissection of the arteries, Takayasu's arteritis, giant cell arteritis, fibromuscular displasy, Moyamoya disease, and others. About a quarter and IS in younger patients (under 45 years) are associated with dissection of BA [73]. The absence of a neck injury in the history should not exclude dissection, since in the vast majority of cases it is nontraumatic [73]. In addition to the standard duplex study of BA in cases of suspected dissection, it is necessary to perform an MRI scan using the T1 *Fat Saturation* mode, which has maximum sensitivity and specificity for this pathology [74]. Vasculopathy, associated with varicella-zoster virus, has a wide spectrum of clinical manifestations and may be the cause of transient ischemic attack (TIA), IS, hemorrhagic stroke, the formation of cerebral aneurysms and subarachnoid hemorrhage [75]. About a third of TIA and IS in pediatric practice are associated with chickenpox virus [76]. Over a third of adult patients infected with chickenpox virus are affected by stroke during the year [77]. Serological examination of cerebrospinal fluid with determination of titers of chickenpox virus IgG is the most effective diagnostic method (sensitivity 93%) [73]. Neuroborreliosis or syphilis can also be the cause of vasculopathy in patients with CIS [78].

According to *P. Sajedi et al.* (2017), in 21.2% of patients with CIS, when performing CT angiography of extracranial arteries, a network is revealed in the carotid bulb on the side of the focus of acute cerebral ischemia. The data demonstrate a statistically significant correlation between the network in the bulb of the carotid artery and IS [79].

Stroke is a common complication of sickle cell anemia (SCA) [80]. According to *K. Ohene-Frempong et al.* (1998), the highest risk of IS in patients with the *SS* genotype [81]. The main mechanism for the development of IS in patients with SCA is arteriopathy, which develops as a result of chronic trauma to intima [82]. The presence of OOW in patients with SCA is considered as a factor that increases the risk of IS [83]. Protein *C* and *S* deficiency in patients with SCA increases the risk of IS [68]. The risk of developing primary IS in patients with SCA over 20 years old is over 11%, over 30 - 15%, over 45 - 24% [81]. The risk of repeated IS in patients with SCA (provided that the first stroke developed at the age of ≥20 years) is 1.6 per 100 patients per year [81].

HYPERCOAGULABLE STATES

The prevalence of hypercoagulable states in patients with IS is 3–21%. Such hereditary thrombophilia as protein deficiency *C* deficiency, protein *S* deficiency, antithrombin III deficiency, mutation of factor V Leiden, mutation of prothrombin *G*20210*A*, methylenetetrahydrofolate reductase mutation *(MTHFR) C*677*T*, are rare IS causes in adult patients [12, 53 , 84–86]. A united analysis of 18 case-control studies in adult patients with IS younger than 50 years showed that factor V Leiden mutation was detected in 7.5% of patients with IS compared to 4.1% in the control group [53]. Two small studies have shown a correlation between the mutation of the prothrombin *G*20210*A* gene and IS [87, 88]. However, during the last metanalysis, which results were published in 2010, no relationship between the prothrombin gene mutation and the increased risk of IS was revealed [86].

In 5 meta-analyzes, the dependance of increased risk of IS on *MTHFR C*677*T* mutation was evaluated [85, 89–92]. The first meta-analysis from 2002 did not reveal this association [91]. In the following 4 meta-analyzes, a correlation was found between *MTHFR C*677*T* mutation and the increased risk of IS.

A. Pezzini et al. (2009) investigated the association of three genetic factors (prothrombin *G*20210*A*, *MTHFR C*677*T* and Leiden factor V mutations) with a risk of developing myocardial infarction, IS and TIA in young patients aged 18 to 45 years. It was found that in patients with a single gene mutation, the risk of repeated cerebrovascular events is lower than in the presence of a 2 gene mutation [93].

The value of protein *C* and *S* deficiency, acting as independent risk factors for stroke or TIA, has not yet been established, although there are a large number of published clinical examples of the development of IS in patients with this pathology [94].

Antiphospholipid syndrome (APS) is one of the most common forms of acquired hypercoagulable conditions associated with an increased risk of IS or TIA. A case-control study revealed a correlation between APS and an increased risk of IS development in women under the age of 50 [95]. The results of studies in elderly patients are heterogeneous [46, 96]. In the case-control study, which included 255 patients of an average age of 66 years, the presence of antibodies to cardiolipin was associated with a significant increase in the risk of IS [97]. However, these results were not reproduced in a prospective cohort study [96]. A few studies of the relationship of APS with the risk of repeated IS and TIA are also contradictory [98, 99, 100]. Only one study, which included young patients under the age of 50 years, showed the association of increased risk of repeated IS and APS [100]. Other studies, which included patients of different age groups, showed significantly varying prevalence of APS (from 6 to 46%) in patients with IS [98, 99].

HYPERHOMOCYSTEINEMIA

The relationship between hyperhomocysteinemia and *ESUS* is currently not fully understood [101]. So, in a study by *A. Vaya et al.* (2011) it was shown that in patients with CIS homocysteine levels are higher than in the control group [102]. Other studies obtained inconclusive data on this kind of connection [101, 103]. Some researchers believe that elevated homocysteine level is a marker of atherosclerosis and cardiovascular diseases that cause stroke [101]. It was found that the relationship between CIS and hyperhomocysteinemia increases in the presence of obesity [102]. Genetic defects such as gene mutations of cystathionine beta-synthase and methyl entetragidrofolat reductase, as well as chronic renal failure, reducing the concentration of vitamin B_6, B_9, B_{12} may be the cause of hyperhomocysteinemia [104-106].

MONOGENIC DISEASES

Despite the fact that monogenic diseases considered to cause the IS less, than 1%, their detection becomes an important task [34]. The prevalence of these diseases in patients with CIS and *ESUS* has not yet been established [107]. Cerebral autosomal dominant arteriopathy with subcortical heart attacks and encephalopathy *(CADASIL)* is a non-atherosclerotic lesion of small vessels. The presence of *CADASIL* may be indicated by a multi-infarction lesion of the brain (according to MRI) with a symmetric increase in signal intensity by T 2 VI from the inner and outer capsules, thalamus, white matter of the frontal lobe, basal ganglia [108]. According to *M. O'Sullivan et al.* (2001), the pathognomonic MRI criterion for this syndrome is a symmetric increase in signal intensity at *FLAIR* and T 2 VI from the temporal lobe pole, which does not occur in patients with arterial hypertension with leukoaraiosis [109]. The key point in the diagnosis is the determination of the *NOTCH* 3 gene mutation [34]. The average age of the first cerebrovascular event in patients is 46 years.

Cerebral autosomal recessive arteriopathy with subcortical heart attacks and encephalopathy *(CARASIL)* is a rare disease described in several dozen patients in the world [110]. The exact prevalence is not known. Unlike *CARASIL*, the onset of the disease is 20–40 years. Neuroimaging reveals a picture similar to *CARASIL*. According to *S. Yanagava et al.* (2002), more than half of *CARASIL* patients suffer a stroke or TIA [63].

A potential cause of IS, especially in young women, may be *SUSAC* Syndrome, an autoimmune endotheliopathy that affects the small arteries of the retina, inner ear, and brain. A triad is characteristic: occlusion of the retinal arteries, progressive hearing loss, encephalopathy [111].

Hereditary endotheliopathy with retinopathy, nephropathy and strokes *(HERNS)* is a rare hereditary autosomal dominant disease, manifested by generalized multi-infarction syndrome. The exact prevalence of the disease is not known [112]. The disease gene is located on the chromosome 3 *p* 21.1 - *p* 21.3 [113]. The debut of the disease occurs in the third or fourth decade of life. The following symptoms are characteristic: progressive decrease in visual acuity, psychosis, migraine-like headaches, strokes, nephropathy [112].

Fabry disease (FD) is a hereditary X-linked lysosomal disease associated with congenital deficiency or lack of activity of the enzyme alpha-galactosidase *A*, which leads to a progressive accumulation of globotriosylceramide (*GL*- 3) and other glycosphingolipids in lysosomes of various body tissues, including endothelium of the vascular wall [114]. Vasculopathy, which develops with FD as a result of progressive accumulation of sphingolipids in the endothelium of intracranial arteries, is considered as the main cause of IS [115]. The main diagnostic marker of the disease is the determination of blood concentrations of the enzyme alpha-galactosidase *A*. The diagnosis of FD is confirmed by the determination of a mutation of the *GLA* gene located on the long arm of the 22 *X* chromosome [116]. A characteristic feature of FD is dolichoectasia of the basilar artery [117]. A specific MR sign for FD is an increase in signal intensity in T1-weighted images of the pulvinaria, which is detected in 24% of patients [118]. In a study by *A. Rolfs et al*. (2005) it was shown that in patients with CIS the prevalence of FD was 4.9% in men and 2.4% in women. Fabry disease should be suspected in a young patient with an unknown cause of stroke, especially with the formation of a focus of ischemia in the posterior basin and the presence of proteinuria [119]. The average age of patients with FD when they experience the first stroke is 39 years for men and 45.7 years for women. In the vast majority of patients (70.9% of men and 76.9% of women), no cardiovascular events or renal failure were noted before the onset of IS. The stroke is experienced before the diagnosis by 50% of men and 38% of women [120].

ONCOLOGICAL DISEASES AND STROKE

According to *W. Grisold et al*. (2009), IS may be the first manifestation of cancer [121]. In an autopsy study, *F. Graus et al*. (1985) showed that 15% of cancer patients had signs of cerebrovascular pathology, and in half of them the clinical signs of IS were revealed during life [122]. Cancer is a common cause of coagulopathy. It was found that the level of *D*-dimer in patients with known cancer is 20 times higher than in patients without this pathology. Radiological pattern in patients with CIS in the course of cancer usually shows multiple small foci of ischemia in more, than one vascular basin [123]. An increase in the concentration of *D*-dimer may be a consequence of hypercoagulation syndrome on the background of cancer. *C. Schwarzbach et al*. (2012) found that cancer was associated with a higher incidence of CIS (48% versus 27%), as well as with significantly higher *D*-dimer rates (6.15 μg/mL versus 1.39 μg/m) [124] . Similar data were obtained by *S.J. Kim et al*. (2012), which revealed higher values of *D*-dimer in patients with CIS and oncological pathology compared with patients with CIS without cancer, as well as compared with patients with cancer without IS [123]. According to *S. Kim et al*. (1999), the determination of the *D*-dimer in the blood is indicated for patients with CIS who have no risk factors for SI, patients with atypical IS and in the presence (according to neuroimaging) of multiple foci of ischemia in different vascular basins [125].

Non-bacterial thromboendocarditis is one of the most common causes of IS in patients with oncologis disease [126]. Diagnosis of this condition is possible with TE EchoCG [126]. In a large autopsy study, it was shown that out of 171 observations in 59% of cases, non-bacterial thromboendocarditis was associated with malignant neoplasms of a solid organ [127]. Most often, non-bacterial thrombendocarditis has been associated with pancreatic adenocarcinoma [128].

In conclusion, it should be noted that in the literature available to us there are a large number of studies devoted to describing the possible causes of CIS, however, there are no unified approaches to the systematization of etiological factors and the protocol for examining patients. The high incidence of CIS, the significant heterogeneity of its etiopathogenetic mechanisms, the need for differentiated approaches to the secondary prevention of this type of stroke, determine the relevance of further research in this field.

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