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# ANTIPHOSPHOLIPID SYNDROME AS A CAUSE OF ISCHEMIC STROKE IN YOUNG AGE

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## ABSTRACT

Hypercoagulation syndrome is an actual multidisciplinary problem of the last decade. Hemostasis disorders leading to hypercoagulation syndrome are manifested by various diseases in neurology, obstetrics, rheumatology, surgery. Antiphospholipid syndrome is the most common form of hypercoagulation syndrome and most often develops at a young age, in children and even newborns, and in females 5 times more often than in males. The causes and mechanism of antiphospholipid syndrome are not completely clear. The defeat of the central nervous system in this syndrome can have both ischemic (violation of cerebral circulation) and non-ischemic (primary immune-mediated damage to the nervous system) genesis. The spectrum of neurological disorders associated with antiphospholipid syndrome is very wide: from cerebral circulatory disorders, migraines and migraine headaches to chorea and epileptic seizures. Thus, antiphospholipid syndrome requires special attention for timely and early diagnosis for the prevention of severe complications.

**Keywords:** antiphospholipid syndrome, antiphospholipid bodies, ischemic stroke, neurological manifestations.

## INTRODUTION

One of the urgent problems of modern medicine is the study of pathogenetic mechanisms underlying vascular damage and impaired blood coagulation (Nasonov E.JI. et al., 1995, 1999; Barkagan Z.S., 1988, 2000). The intensive development of clinical immunology allows a new approach to assessing the participation of autoimmune reactions in the implementation of these changes. Antiphospholipid syndrome (APS) was first described by G.R.V. Hughes et al. in 1986 and attracts the attention of clinicians in various fields of medicine (Demin A.A. et al., 2000, 2001; Azeem T. et al., 2000; Dourakis S.P. et al., 2001; Tanne D., Hassin-Baer S ., 2001; Daugas E. et al., 2002; Espinosa G. et al., 2002). Since then, the number of published papers on the study of APS has steadily increased.

Antiphospholipid syndrome (antiphospholipid antibody syndrome, lupus antibody syndrome, Hughes syndrome) is a systemic autoimmune disease associated with hypercoagulation and caused by the synthesis of antiphospholipid antibodies (aPL): anticardiolipin antibodies (aCL, lupus anticoagulant (LA), antibodies to b2-glycoprotein I ( anti-b2-GP I) [5, 12, 13].Despite the fact that APS is most often considered in the context of gynecological pathologies as one of the causes of abortion, its definition as exclusively gynecological is incorrect: the disease occurs in any population groups and has an erased clinical picture.The alertness of a doctor of any specialization in relation to this condition is especially important, since timely prescribed

therapy improves the quality of life of patients and long-term prognosis, preventing the development of life-threatening complications.

International incidence statistics are not maintained; remains unknown and the exact prevalence of APS among the population. The disease is typical for young people (in the literature there are descriptions of the diagnosis of APS in a patient of 8 months of life [14]) and middle age, it is rare in the elderly. There was no significant correlation with race; secondary APS affects women more often, but the exact percentage between the sexes has not been identified.

However, Cervera et al. found the most common manifestations of APS: deep vein thrombosis (38.9%) [2], thrombocytopenia (29.6%), stroke (19.8%), pulmonary embolism (14.1%), superficial thrombophlebitis (11.7 %), transient ischemic attack (11.1%), hemolytic anemia (9.7%), epilepsy (7%) and obstetric morbidity [11].

Currently, it is customary to distinguish three subgroups of antiphospholipid syndrome (APS):

1. Primary antiphospholipid syndrome (PAPS) - is diagnosed in patients without concomitant rheumatological pathology. PAPS accounts for up to half of all cases of the disease.
2. Secondary antiphospholipid syndrome - develops in patients with an established rheumatological diagnosis (most often systemic lupus erythematosus) as a complication of the underlying disease [3]. Less commonly, secondary APS may occur in other disorders (eg, lymphoproliferative disorders, autoimmune disorders; hepatitis C, HIV, syphilis, and other infectious diseases) or be associated with long-term use of certain drugs (procainamide, quinidine, hydralazine, fentoin, chlorpromazine, oral contraceptives). ).
3. Catastrophic antiphospholipid syndrome (CAPS syndrome, Asherson's syndrome) is an acute condition diagnosed in the presence of three or more thromboses (regardless of location) of arteries and / or veins in patients with APS of any etiology, developing over a period of several days to several weeks. The exact mechanism for the development of this condition, as well as provoking factors, is not completely clear at the moment; mortality is approximately 50% due to multiple organ failure [2].

In the pathogenesis of APS, the leading role belongs to organ-specific autoantibodies that react with antigenic determinants of phospholipids - antiphospholipid antibodies (aPL) (Reshetnyak T.M. et al., 1998; Rand J.H., 2002). The aPL family includes a diseased group of antibodies: antibodies that cause a false positive Wasserman reaction (reagins); antibodies that promote in vitro inhibition of phospholipid-dependent coagulation reactions - lupus anticoagulant (LA); antibodies that react with cardiolipin (aCL) immobilized on the solid phase, with other negatively charged or neutral phospholipids or complex phospholipids and various protein molecules that are detected using radioimmunological or enzyme immunoassay methods (Nasonov E.L. et al., 1987 - 2000; Ordi-Ros J. et al., 2000; Lieby P. et al., 2001; Setty Y.N., Komatireddy G.R., 2001).

Although traditionally associated with autoimmune diseases, autoantibodies are present in minimal amounts in all healthy individuals. According to the immunologist P. Macinger, the main function of the immune system is precisely the recognition of harmful antigens, regardless of infectious or non-infectious nature, and exogenous or endogenous origin [5].

With the study of the problem and the accumulation of experience, there was a refinement of the criteria for the diagnosis of APS. The last revision of the APS classification was carried out

at the 11th International APL Congress in 2006 in Sydney [22]. According to this classification, the diagnosis of APS can be made if the patient has at least one clinical and one laboratory criterion.

Clinical criteria include arterial or venous thrombosis of various localization (peripheral venous thrombosis, myocardial infarction, ischemic stroke, infarction of any organ, etc.), objectified by imaging (ultrasound, angiography) or histological methods [2]. Another clinical criterion is obstetric pathology, namely:

- unexplained fetal death (≥1) after 10 weeks of pregnancy in the absence of its morphological pathology according to ultrasound or morphology;
- premature birth (≥1) - before 34 weeks of gestation due to eclampsia or placental insufficiency with a morphologically normal fetus;
- repeated (≥3) spontaneous abortions (up to 10 weeks of pregnancy) in the absence of anatomical, hormonal or chromosomal pathology in the parents [22, 23].

Laboratory criteria include:

- positive lupus anticoagulant (LA), studied in accordance with the recommendations of the International Society for Thrombosis and Hemostasis [8, 24, 25];
- positive anticardiolipin antibodies in titer more than 40 GPL, MPL;
- positive antibodies to ß2-glycoprotein I (aß2GP-1) isotypes G or M (>99th percentile).

In this case, a prerequisite is to obtain positive results in at least two studies conducted at least 12 weeks apart. This requirement is dictated by the need to exclude false positive results. Knowledge and observance of these diagnostic criteria is of fundamental importance, since, according to the results of the experience and research of foreign colleagues, there is currently an unjustified overdiagnosis of APS in the field of neurology [8, 24]. The neurological manifestation of APS is represented by stroke (19.8%), myelopathy (less than 1%), Sneddon syndrome, convulsive syndrome (7%), chorea (1.3%), headache and migraine (20.2%), dementia (2 .5%), eye syndromes (15-88%), multiple sclerosis, Guillain-Barré syndrome and peripheral neuropathy [16]. The most severe neurological complication of APS is stroke.

The frequency of IS caused by the production of aPL among other causes in young patients according to the latest data is 11-12.5% [6, 17], according to earlier studies, it reached 25% [7, 18, 19].

Cerebral circulation disorders, combined with the production of aPL, in most cases debut at a young age (up to 45 years) at an age, much less often in childhood or older [6]. According to G. Kenet et al. (2009), aPL, along with the Leiden mutation, are the main cause of thrombophilia and ischemic stroke in children [20]. Women get sick more often (81%), which is associated with the specifics of their hormonal background, which favors the development of an immunopathological process and a procoagulant state. Pregnancy, the postpartum period, dysmenorrhea, and premenopause can be provoking factors for NMC in APS in women, which clinically confirm the importance of hormonal changes in the implementation of the procoagulant state present in APS [6].

To date, the presence of aPL is considered as a risk factor for IS. It is known that the risk of IS increases by 2.31 times in patients with aPL detected in the blood [21]. A recent Framingame study showed that high levels of anticardiolipin antibodies in the blood serum are a predictor of the risk of recurrent stroke in women, but not in men [16].

Although traditionally, autoantibodies are associated with autoimmune diseases, they are present in minimal amounts in all healthy individuals [1]. According to the immunologist P. Macinger, the main function of the immune system is precisely the recognition of harmful antigens, regardless of infectious or non-infectious nature, and exogenous or endogenous origin [1, 4].

The main mechanism for the development of ischemic CVD in APS is cerebral artery thrombosis in situ due to a hypercoagulable state induced by aPL production. Some authors attach importance to the mechanism of arterio-arterial and cardiac embolism, taking into account microemboli often recorded during transcranial Doppler sonography and the presence in patients with APS according to ECHO-CG of heart valve pathology (cusp thickening, local marginal thickening, calcification, regurgitation, valvular stenosis) [28 ]. According to Kalashnikova L.A., Nasonov E.L., Aleksandrova E.N. the mechanism is not significant in the genesis of NVC in APS, since valvular heart disease is not present in all patients with APS with IS, and the presence of valvular pathology does not correlate with the frequency of ischemic strokes and MICC (Kalashnikova L.A., Nasonov E.L., Alexandrova E.N. Ischemic cerebrovascular accidents and heart valve lesions in primary antiphospholipid syndrome, 1996)

The clinical spectrum of ischemic brain lesions in APS is extensive and includes manifestations from transient ischemic attacks to focal lesions such as amaurosis, extensive cerebral infarction, ataxia, and dementia [26]. Most often, a vascular lesion in APS affects the territory of the middle cerebral artery [27].

A tendency to recurrence of stroke in APS is noted, it is often preceded by transient ischemic attacks. Rapid regression of symptoms is characteristic.

Some cerebrovascular accidents occur without symptoms and turn out to be an incidental finding in the study of magnetic resonance imaging. Recurrent strokes lead to the development of multi-infarct dementia [9, 10]. It is the tendency to stroke that distinguishes and differentiates APS from other less dangerous hypercoagulable syndromes, such as factor V Leiden mutation [26].

Focal neurological symptoms in IS usually develop very quickly, consciousness usually remains intact, and headache is absent in most cases. Usually (about 2/3 of cases) there is a good recovery of impaired functions, since brain infarcts, according to neuroimaging data, as a rule, are small and medium in size. The latter, in turn, is due to thrombosis of small or medium diameter cerebral arteries. The degree of regression of focal neurological deficit in repeated strokes is reduced. In the absence of secondary prevention with indirect anticoagulants and aspirin, strokes recur [9].

Diagnosis of NMC associated with the production of aPL is based on their clinical features: young age of patients, intact main arteries of the head, small or medium sizes of cerebral infarcts. Of great diagnostic importance is the presence in patients of the main and additional systemic manifestations of APS [7].

Differential diagnosis of APS is carried out with a wide range of diseases occurring with vascular disorders [11,29].

It is believed that APS should be suspected in the development of thrombotic disorders (especially multiple, recurrent, with unusual localization), thrombocytopenia, obstetric pathology in young and middle-aged individuals in the absence of risk factors for these

pathological conditions [19, 30, 31]. It should be excluded in unexplained neonatal thrombosis, in cases of skin necrosis during treatment with indirect anticoagulants, and in patients with prolonged activated partial thromboplastin time at screening.

Treatment and prevention of NMC in APS are associated with the main mechanisms of action of aPL - their interference in the coagulation cascade. The basis for the treatment and prevention of recurrent cerebral ischemia is the use of indirect anticoagulants, aspirin and heparin [6, 7]. In the acute period of a stroke, direct-acting anticoagulants are used - heparin, fraxiparin, clexane. Treatment with indirect anticoagulants is carried out under the control of the international normalized ratio (INR), which is recommended to be maintained at the level of 2-3 [32]. Anticoagulants of indirect action, small doses of aspirin, or a combination of both are also used to prevent recurrent NMC and MIMC. At the same time, the effectiveness of anticoagulants is much higher than that of aspirin.

The presence of concomitant aPL-associated thrombocytopenia is not a contraindication for the secondary prevention of CVD, however, clinical and laboratory monitoring of patients should be more thorough [33]. In some cases, in the presence of side effects from taking these drugs, treatment with Plavix was effective. Preventive antithrombotic treatment is carried out continuously and its cancellation is associated with the development of repeated NMC.

In conclusion, we note once again that APS is one of the causes of ischemic CCI, CIMC, multi-infarct dementia, and thrombosis of the veins and sinuses of the brain in young patients [19]. Diagnosis is based on a comprehensive assessment of neurological and systemic manifestations of the disease in conjunction with the detection (at least twice) of at least one of the diagnostically significant aPL. Early diagnosis and timely administration of anticoagulants can prevent the development of recurrent strokes and dementia.

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