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CONTEMPORARY PICTURE OF NERVOUS SYSTEM DISORDERS IN ANTIPHOSPHOLIPID SYNDROME IN CHILDREN. THROMBOTIC MANIFESTATIONS: ISSUES OF DIAGNOSIS, PATHOGENESIS, CLINICAL PICTURE AND TREATMENT

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Abstract

Antiphospholipid syndrome is an acquired autoimmune thrombophilia, the main diagnostic criteria of which is vascular thrombosis and/or pregnancy pathology arising due to the presence of antiphospholipid antibodies. Thrombosis in antiphospholipid syndrome can occur in vessels of any caliber and localization, which would explain the significant variability of its clinical manifestations. Ischemic stroke and other types of cerebral thrombosis are a characteristic manifestation of antiphospholipid syndrome and can occur in patients of any age, starting from the neonatal period. The pathogenetic mechanisms of various neuropsychic syndrome development in antiphospholipid syndrome are complex and not completely deciphered. It is believed that in addition to thrombosis itself, some patients have vasculopathy due to pronounced intimal hyperplasia. Besides, there might be a possibility of direct interaction of antiphospholipid antibodies with antigens of various cells of the nervous system.

At present, vitamin K antagonists, heparins and aspirin, still have the same leading role in the treatment of antiphospholipid syndrome, but the difficulties of monitoring point to the need for the introduction of new oral anticoagulants and antiplatelets. At the same time, the formation of insights about the multifactorial nature of antiphospholipid syndrome shapes the prospects for the use of drugs of other classes: statins, biological agents, complement inhibitors, etc. Features of the hemostasis and immunity system at different periods of childhood, incomplete formation of the central nervous system, the absence of traditional thrombotic risk factors such as atherosclerosis, hypertension, smoking, obesity, the use of oral contraceptives, etc. in most children point out to the differences of antiphospholipid syndrome in children and adults. This review is devoted to the clinical realities, the course of thrombotic manifestations, primary and secondary antithrombotic preventive measures, and treatment of antiphospholipid syndrome in children. We have analyzed a large volume of literature with a particular focus on contemporary understanding of thrombosis and aniphospholipid syndrome, leading to the formation of neuropsychiatric pathology.

Keywords: *antiphospholipid antibodies, antiphospholipid syndrome, nervous system, thrombotic manifestations, antithrombotic therapy, children.*

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by venous and/or arterial thrombosis and/or recurrent fetal loss syndrome due to the presence of persistent antiphospholipid antibodies (aPL) [*Miyakis S et al., 2006*]. Currently, APS is recognized as the most common form of acquired thrombophilia [*Koike T, 2015*].

The main aPL targets are phospholipid-binding plasma proteins, such as β2-glycoprotein 1 (β2-GP1) and prothrombin. Among other ligands are cardiolipin, annexin V, activated protein C,

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thrombin, antithrombin, tissue plasminogen activator, plasmin, annexin 2, etc. In addition, aPLs can bind to phospholipid complexes, such as phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol [*Chen P, Giles I, 2010; Peluso S et al., 2012*]. The APS diagnostic criteria list includes 3 types of aPL: Anti-cardiolipin antibody (ACL) lupus anticoagulant (LA) and Anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies which is a natural plasma anticoagulant composed of 5 short consensus repeating domains [*de Laat B et al., 2008*]. It should be noted that antibodies to the cryptogenic epitope of the first domain (anti-β2GP1-D1) are significantly associated with a high risk of thrombosis, in contrast to antibodies against epitopes of domains 4 and 5 (anti-β2GP1-D4/5) [*Khamashta M et al., 2016 ; Pericleous C et al., 2016*].

The pathogenesis of APS has not been fully studied, but it probably has a multifactorial nature, which is particularly indicated by the multi-target orientation of aPL [*Tarango C, Palumbo J, 2019*]. To explain the mechanism of blood clots in APS, the "two hit" hypothesis was proposed [*Wincup C, Ioannou Y, 2018*]. The "first hit" is a direct effect of aPL exposure , leading to the activation of endothelial cells, monocytes, platelets, and the complement system [*Krone K et al., 2010; Giannakopoulos B, Krilis S, 2013; Merashli M, 2015*]. The formation of prothrombotic status is also measured by resistance to activated protein C, inhibition of Tissue factor pathway and impaired fibrinolysis, in particular, a decrease of tissue plasminogen inhibitor activity [*Garcia D, Erkan D, 2018*]. The "second hit" involves an action of an additional factor, such as inflammation, which, in combination with aPL, induces thrombosis [*Meroni P et al., 2004*].

In addition, the occurrence of arterial occlusion and the pathology of pregnancy in APS can be reasoned by vasculopathy due to pronounced intimal hyperplasia, leading to vascular stenosis [*Khamashta M et al., 2016*]. The pathogenetic mechanisms that are the cause of non-thrombogenic manifestation of APS probably include a direct interaction of aPL with antigens of various cells. The diversity of pathogenetic mechanisms would partially explain the variability of APS manifestations, but not all of them proved to be resulted from thrombosis. Thus, this fact expands the prospects for rational therapy, which should not be limited by including only anticoagulants [*Sammaritano L, 2019*].

APS is diagnosed in children of any age, starting from the neonatal period. Neonatal thrombosis can be caused not only by the occurrence of aPL de novo, usually in the presence of other risk factors [*Gordon O et al., 2014*], but also by the (transplacental) passage of aPL from mothers [*Motta M et al., 2012*].

APS at different age periods is characterized by certain features of clinical and laboratory parameters [*Berkun Y et al., 2006; Avcin T et al., 2008*], which is probably linked to both the age-related features of the hemostatic system and the additional risk factors, such as overweight, hypodynamia, smoking in adolescents, oral contraceptives, arterial hypertension, etc. [*Rao A et al., 2017*]. The most severe option is catastrophic APS (CAPS), characterized by the development of multiple organ failure (damage to 3 or more organs) due to thrombosis of predominantly small vessels for no more than 7 days [*Sammaritano L, 2019*].

APS criteria in children are based on the Classification criteria for adult (Sapporo, 2006) [*Myakis S et al., 2006*] except for the pregnancy pathology (Table 1). They are not validated enough, so they should not be considered perfect [*Tarango C, Palumbo J, 2019*]. It is widely known that aPL patients often have various clinical and laboratory signs that are not included in the list of diagnostic criteria: thrombocytopenia, hemolytic anemia, heart valve damage, renal (thrombotic) microangiopathy, Livedo reticularis (LR) and some neurological disorders [*Avcin T et al., 2008; Garcia D, Erkan D, 2018*]. APLs that are not considered to be diagnostically significant might persist for a long time. In particular, anti-β2GP1-D1 is detected in the so-called "seronegative" patients without other aPLs [*Cousins L et al., 2015*]. Experts indicate that the proposed criteria are more intended for the selection of homogeneous groups of patients during sci-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Table 1

Diagnostic criteria for antiphospholipid syndrome in children
[*adapted from Miyakis S. et al.,2006*]

Clinical criteria (mandatory)	Laboratory criteria (at least one required)
Vascular thrombosis: one or more clinical episodes of arterial, deep vein thrombosis or small blood vessel thrombosis in any tissue or organ, except for superficial venous thrombosis verified by instrumental imaging or histological examinatio	Detection in plasma for 2 or more times with an interval of at least 12 weeks and no more than 5 years 1. Lupus anticoagulant: two tests based on different principles (test with Russells viper venom (RVV) and sensitive activated partial thromboplastin time (APTT). 2. Anticardiolipin IgG and / or IgM isotypes of anticardiolipin, in medium or high titers (> 40 GPL or MPL or> 99 percentiles) detected by the standardized method (ELISA). 3. Antibodies against β2-glycoprotein 1 IgG or IgM isotypes in the titer > 99 percentiles detected by the standardized method (ELISA)

entific research, thus enabling clinicians to diagnose a particular patient with APS based on the associated symptoms.Both children and adults can have primary and secondary APS. Primary APS is caused by the production of aPL de novo, while secondary one occurs against various underlying diseases, among which 83% of the cases are systemic lupus erythematosus (SLE) and lupus-like diseases. The proportion of primary APS in children is 38-50% of cases. Children with primary APS are younger, and they are more likely to have arterial thrombosis. Children with secondary APS are older; they often have venous thrombosis, dermal and hematological manifestations **[***Avcin T et al., 2008*]. The transformation of primary APS into secondary is possible, and it is much more common in children than in adults. **[***Gattorno M et al., 2003; Gomez-Puerta J et al., 2005*].

The incidence of APS is approximately 5 cases per 100,000 people a year, and the prevalence is 40-50 cases per 100,000 **[***Schreiber K et al., 2018*], while children under the age of 15 account for only 2.8% of cases **[***Cervera R et al., 2002*].

ACL and anti-β2GP1 are found in low titers or transient in 3-28% and 3-7% of healthy children, respectively, most often after vaccination or infections **[***Avcin T et al., 2001; Aguiar C et al., 2015*]. Lupus anticoagulant is detected in 2% of children, usually during the APTT evaluation before a surgery **[***Aguiar C et al., 2015*]. These aPLs are usually non-thrombogenic and transient **[***Male C et al., 1999; Soybilgic A, Avcin T, 2020*]. A significant difference in the frequency of aPL detection and the diagnosed APS in children indicates that not all aPL-positive children develop thrombosis, which is a clinical criterion for diagnosing APS. This is probably due to several reasons:

1. a high frequency of aPL carriage is observed in children after infections and vaccinations, which is related to the phenomenon of molecular mimicry, but these antibodies are not thrombogenic [*Mizumoto H et al., 2006; Avcin T, Toplak N, 2007*];
2. children, except for adolescents, do not have additional risk factors for thrombosis (smoking, oral contraceptives, arterial hypertension, atherosclerosis, etc.);
3. anti-β2GP1 in children can be formed in response to exogenous intake of β2-GP1 with milk and meat, and they are mainly directed to the epitopes of the V domain **[***Ambrozic A et al., 2002*];
4. the low incidence of thrombosis in newborns is resulted from the low placental passage of the aPL IgG2 isotype from mothers;
5. there is a special aPL spectrum in children, for example, anti-β2GP1 in newborns from mothers with systemic autoimmune diseases are mainly presented with antibodies to the IV and V domains of β2GP1 **[***Andreoli L et al., 2011*].

It should be emphasized that most children with aPL-mediated thrombosis usually have other prothrombotic risk factors: acute or chronic diseases, the presence of a central venous catheter, injuries,

surgical interventions [*Briley D et al., 1989; Soybilgic A, Avcin T, 2020*], some children have other traditional additional risk factors [*Avcin T et al., 2009*]. Markers of genetic thrombophilia are detected in children significantly more often than in adults [*Avcin T et al., 2008*].

The range of clinical and laboratory manifestations of APS in children is very wide. In addition to thrombotic manifestations, it includes a large number of non-thrombotic symptoms: hematological (thrombocytopenia, autoimmune hemolytic anemia, Evan's syndrome, leukopenia, LA-associated hypoprothrombinemia syndrome), cutaneous (Livedo reticularis (LR), Raynaud syndrome, Purpura fulminans, skin ulcers, pseudovasculitis syndrome, Chronic urticaria rash), cardiac (valve damage, myocardial infarction), pulmonary (pulmonary hypertension, interstitial fibrosis), renal (antiphosphilipid syndrome nephropathy, Thrombotic microangiopathy), endocrine (adrenal insufficiency due to infarction) [*Madison J et al., 2020*]. The presence and nature of damage to nervous system is highly important for the prognosis [*Ricarte I et al., 2018*]. It is the second most frequent disorder after obstetric pathology in adults with APS [*Hughes G, 2018*], and it is central in the pathology pattern in children with APS [*Avcin T et al., 2009*]. Current data on aPL-associated pathology of nervous system in children are presented in this review.

Nervous system involvement in Antiphospholipid syndrome

According to G. Hughes, nervous system is especially vulnerable due to the fact that the surface pattern and antithrombotic properties of endothelium of cerebral vessels are different from others, which points to a high risk of thrombosis. However, not all neurological manifestations of APS can be explained by thrombosis [*Hughes G, 2018*]. The rapid positive dynamics after the start of anticoagulation therapy in a number of patients with mini-strokes, seizures and memory loss probably indicates a reversible "sludge" phenomenon in the blood vessels of the brain rather than the presence of irreversible thrombosis or infarctions[*Hughes G, 2018*]. In addition, neurological disorders in APS may occur due to immuno-mediated vasculopathy, inflammation, or direct impact of aPL on neurons and glial cells [*Muscal E, Brey R, 2010; Gris J, Brenner B, 2013; Gris J et al., 2015*].

To date, it has not been established what determines the nature and localization of damage to nervous system in various APS patients. Perhaps this depends on the type of aPL, individual sensitivity or genetic predisposition [*Fleetwood T et al., 2018*]. But, for example, in 89% of adults with neurological manifestations of APS, persistence of various aPL types was noted: LA in 16% of patients, ACL-IgG in 41%, ACL-IgM in 42%, anti-β2-GP1 IgG in 17% and anti β2-GP1 IgM in 15% [*Sahebari M et al., 2019*].

Based on the alleged pathogenetic mechanisms, the neuropsychic manifestations of APS are divided into thrombotic and non-thrombotic, although, taking into account the complexity of the pathogenesis, this distinction is to some extent unjustified [*Sanna G et al., 2006; Muscal E, Brey R, 2010; Yelnik C et al., 2016*; *Hughes G, 2018; Fleetwood T et al., 2018*] (Table 2).

Nervous system disorders of thrombotic nature

According to the International Ped-APS registry [*Avcin T et al., 2008*], cerebrovascular disorders in the pattern of APS manifestations take up a larger share in children than in adults.

Ischemic stroke (IS) and transient ischemic attack (TIA). Ischemic stroke caused by cerebral artery thrombosis is the most common thrombotic manifestation, and one of the leading causes of severe condition and death in APS [*Levine J et al., 2002; Schreiber K et al., 2018*]. According to the EuroPhospholipid Project Group Study [*Cervera R et al., 2002*], the total frequency of IS and TIA in a cohort of 1000 patients with APS from 0 to 81 years old was 19.8% and 11.1%, respectively. According to the International Ped-APS registry, IS was an initial thrombotic event in 25% of the cases among children with APS [*Avcin T et al., 2008*]. IS can develop in aPL patients of any age [*Cervera R et al., 2002; Hughes G, 2018*], including newborns [*Alshekaili J et al., 2010; Berkun Y et al., 2014; Saliba E et al., 2016*]. Thus, the analysis of 21 cases of neonatal thrombosis allowed to detect arterial thrombosis in 17 children, of which 12 had IS with localization of a thrombus in the middle cerebral artery [*Peixoto M et al., 2014*].

Sometimes IS is preceded by intensifying headaches [*Hughes G, 2018*] and TIA. The incidence of

Table 2

Neurological and psychiatric manifestations of antiphospholipid syndrome

Thrombotic manifestations	Non-thrombotic manifestations
➢ Ischemic stroke ➢ Transient disorders of cerebral blood circulation ➢ Cerebral venous sinus thrombosis (CVST) ➢ Sneddon's syndrome ➢ Reversible cerebral vasoconstriction syndrome ➢ Acute ischemic encephalopathy ➢ Spinal cord infarction	➢ Headache and migraine ➢ Epilepsy, cramps ➢ Chorea ➢ Movement disorders (parkinsonism, cerebellar ataxia, ballism, etc.) ➢ Transverse myelitis ➢ Opticomyelitis-associated Disorders ➢ Multiple Sclerosis Syndrome ➢ Cognitive Impairment and Dementia ➢ Transient global amnesia ➢ Psychotic and other mental disorders ➢ Peripheral neuropathy ➢ Neuro-ophthalmic Disorders ➢ Disorders of the autonomic nervous system ➢ Idiopathic intracranial hypertension ➢ Sensorineural hearing loss (SNHL), etc.

IS after the occurrence of TIA is 17% for the period of 3 months **[***Fernandez-Nebro A et al., 2015*]. In patients with systemic lupus erythematosus (SLE), it reaches 57% **[***Ward M, 1999*]. Manifestations of TIA may include transient muscle weakness, speech impairment, transient vision loss, dizziness, and transient global ischemia **[***de Amorim L et al., 2017*].

The reasons for the development of IS in APS can be either thrombosis or thromboembolism **[***Roldan J, Brey R, 2007*]. In 50% of patients, the cause of aPL-associated IS is the occlusion or stenosis of the intracranial arteries **[***Babikian V, 1990*], most often the middle cerebral arteries **[***Miesbach W et al., 2006; Peixoto M et al., 2014*], but the lesions of small arteries with the formation of lacunar and subcortical types of IS are also possible **[***Provenzale J et al., 1996*]. In some cases, arteriography reveals a vasculitis-like pattern with multiple areas of narrowing and expansion of the arteries in patients with IS.**[***Provenzale J et al., 1998*]. APL-associated IS can also be caused by damage to extracranial arteries. According to angiography, three possible patterns of lesions were established:

1. stenosis or occlusion of the common carotid or internal carotid arteries;
2. stenosis or occlusion of two or more large vessels (a pattern similar to Takayasu's disease);
3. narrowing of the internal carotid artery (a pattern characteristic of atherosclerosis) [*Provenzale J et al., 1998*].

Cerebral embolism in APS is mainly associated with valve damage, mostly mitral and less often aortic, and only in some cases with intracardiac thrombosis [*Panichpisal K et al., 2012*]. The pathology of the valves can vary from valve thickening to aseptic warty endocarditis [*Rodrigues C et al., 2010*].

The clinical manifestations of aPL-associated IS depend on the localization and nature of the vascular lesion [*Tanne D, Hassin-Baer S, 2001*]. It should be noted that IS manifests with seizures in 19-44% of children [*Abend N et al., 2011; Peixoto M et al., 2014; Saliba E et al., 2017*]. Ischemic changes due to lesions of small vessels may not be clinically accompanied by sensory or motor deficits, and can only be manifested by cognitive impairment or dementia [*Graf J, 2017*]. Neurological deficit due to thrombosis of small vessels may not be detected during MRI, but may be manifested by pathological changes on EEG [*Lampropoulos C et al., 2005*].

Ischemic foci can be localized in any area of the brain. There have also been cases of anti-β2GP1 and LA-associated ischemic cerebellar strokes in children [*Bardella D et al., 2002; Spalice A et al., 2011*].

Apparently, aPLs play an important role in the development of IS: they are detected in more than 20% of patients with IS under the age of 45 [*Hughes G, 2003*], mostly in females [*Rodrigues C et al., 2010*]. According to a meta-review, the presence of aPL in patients under 50 years of age increases the risk of developing cerebrovascular thrombosis 5.48 times [*Sciascia S et al., 2015*]. The risk of IS in patients with SLE and APS is

even higher than in patients with primary APS [*de Amorim L et al., 2017*]. IS develops in 3 to 20% of patients with SLE and APS during the first 5 years after the diagnosis. The most significant predictor of intracranial thrombosis in these patients is the persistence of LA [*Graf J, 2017*].

It has been established that IS in children is not only associated with aCL [*Baca V et al., 1996; Pilarska E, 2001*], LA [*Angelini L et al., 1994; Olson J et al., 1994*] and anti-β2 GP1 [*Katsarou E et al., 2003*], but also with antibodies to phosphatidylcholine and phosphatidylethanolamine, which are known to be the main components of vascular endothelial phospholipids [*Korematsu S et al., 2017*].

Cerebral venous sinus thrombosis (CVST) is a relatively rare manifestation of APS, and, according to Ped-APS [*Avcin T et al., 2008*] it was revealed in 8 out of 121 (7%) children with APS. It has been established that CVST is more often detected in children and young adults and is characterized by more extensive superficial or deep lesions than in dural venous sinus thrombosis which is unassociated with aPL [*Ferro J et al., 2016; Silvis S et al, 2017*].

Clinically, CVST is usually manifested by refractory headaches, nausea, less often cramps, focal neurological symptoms, swelling of the optic nerve head, impaired consciousness, signs of increased intracranial pressure [*Appenzeller S et al., 2005; Algahtani H et al., 2011; Ferro J et al., 2016*]. Additional risk factors for the development of CVST in patients with aPL is the use of high-dose glucocorticoids, and lumbar puncture [*Nishida et al., 2015*]. In most cases, thrombosis of the transverse or superior sagittal sinuses develops [*Alonso-Cánovas A et al., 2009*], quite often the thrombosis of several sinuses can be simultaneously detected [*Algahtani H et al., 2011*]. For the detection of CVST, MRI or CT with a contrast should be performed, since non-contact studies can diagnose CVST in only 30% of cases [*Saposnik G et al., 2011*]. In view of the complexity of CVST detection, it is often diagnosed at late stages in patients with transient neurological deficit and atypical changes in tomograms [*Tsai C et al., 2013*].

The frequency of aCL detection in patients with CVST ranges from 7 to 22% [*Christopher R et al., 1999; Martinelli I et al., 2003*]. So, in a series of 79 patients with CVST between 2 and 82 years of age, APS was diagnosed in 7 patients [*Alonso-Cánovas A et al., 2009*]. A sufficiently high frequency of aPL detection in patients with CVST indicates the need to include them in the list of studies in order to clarify the genesis of the thrombotic complications.

Sneddon's syndrome is a rare non-inflammatory thrombotic vasculopathy with lesions of small and medium dermal and cerebral arteries, which is characterized by a combination of cerebrovascular disorders with generalized Livedo reticularis [*Wu S et al., 2014; Samanta D et al., 2019*]. About 80% of patients with Sneddon's syndrome are young women, but pediatricians should be aware that livedo may precede the neurological symptoms 10 more years earlier, i.e. the first signs of the disease may appear in childhood. There are 3 development stages of neurological disorders. In the prodromal period, headaches and dizziness can occur for several years. Then TIA and IS recur, often in the middle cerebral artery, which leads to contralateral hemiparesis, aphasia and/or visual field defects. In rare cases, stroke of the spinal cord, intracranial or subarachnoid hemorrhages are possible. At the late stage of the disease, memory impairment, personality changes, and a decrease in cognitive functions leading to dementia are often noted. Epileptic seizures, chorea, myelopathy are rarely observed. In addition, patients often have secondary hypertension, damage to the heart valves, eyes and kidneys.

The etiopathogenesis of Sneddon's syndrome has not been established, but autoimmunity, inflammation and thrombophilia probably play a role in the development of the syndrome. The results of a skin biopsy would allow to confirm the diagnosis of Sneddon's syndrome (occlusion of arterioles due to the intimal proliferation of cells). On MRI, changes in the white matter of the brain are usually detected, including infarctions, microbleeds, or atrophy. MRI is more sensitive than CT [*Samanta D et al., 2019*].

APL is detected in 40-60% of patients with Sneddon's syndrome, therefore it is classified as aPL-associated and aPL-unassociated [*Frances C et al., 1999; Samanta D et al., 2019*]. Patients with aPL-associated Sneddon syndrome are more likely to have infarctions in the basin of cerebral vessels such as the middle cerebral artery, while in aPL-unassociated Sneddon's syndrome, leukoaraiosis and small lacunar infarctions are often detected [*Frances C et*

al., 1999]. Livedo is more common in patients without aPL, on the contrary, cramps and mitral regurgitation were more often observed in aPL-positive patients [*Frances C et al., 1999*]. Clinicians presume the possibility of APL emerging in patients over time with the subsequent development of APS or SLE [*de Amorim L et al., 2017*].

The maintenance therapy with the use of antiplatelets and anticoagulants reduces the frequency of repeated IS in patients with Sneddon's syndrome, whereas the recommendations for the use of anti-inflammatory and immunosuppressive drugs are contradictory, and the indications need to be clarified. The prognosis is unfavorable, patients have Attention and concentration deficit disorder, disorders of visual perception and visuospatial abilities[*Samanta D et al., 2019*].

Reversible cerebral vasoconstriction syndrome (RCVS) is a neurological disorder characterized by severe headaches ("thunderclap") and a neurological deficit associated with transient constriction of cerebral arteries due to transient dysregulation of their tone [*Ducros A, 2012; Gupta S et al., 2014*]. RCVS is called "Raynaud's syndrome with cerebrovascular disease", often resulted from APS.

A very severe headache lasting a few seconds is usually the first symptom of CVS, which recurs within 2 weeks. The neurological symptoms emerging later depend on the parts of the brain that have loss of normal blood flow. The most common complications are ischemic or hemorrhagic strokes [*Ducros A, 2012; Article R et al., 2015; Dutra L et al., 2017*].

For the treatment of CVS, it is recommended to use central action calcium channel blockers, which, as experience shows, effectively alleviate headaches and relieve transient neurological symptoms, in particular, Raynaud syndrome, visual disturbances, impaired consciousness, headaches and hearing loss [*Gupta S et al., 2014*].

Acute ischemic encephalopathy is clinically manifested by impaired consciousness, disorientation, hyperreflexia, and asymmetric tetraparesis **[***Briley D et al., 1989*]. Subsequently, on MRI, cerebral atrophy is most often detected in patients with acute ischemic encephalopathy. Acute ischemic encephalopathy is a rare manifestation of APS; according to the EuroPhospholipid Project Group, it was only detected in 1.1% of patients with aPL **[***Cervera R et al., 2002*].

Spinal cord infarction is a possible but very rare manifestation of APS, requiring a complex differential diagnosis with transverse myelitis and multiple sclerosis **[***Hughes G, 2018*]. In the available literature, we have come across only one description of spinal cord infarction case in a 6-year-old boy with primary APS **[***Hasegawa M et al., 1993*].

Treatment and prevention of thrombotic manifestations of APS in children

The prognosis for APS largely depends on the successful prevention of the first and the subsequent thrombotic events in patients. In view of this, several main goals can be distinguished in the treatment of APS:

1. prevention of the first thrombotic episode in patients with aPL (primary prevention);
2. active therapy during thrombosis episode aimed at restoring or improving blood flow in a thrombosed vessel
3. prevention of recurrence of thrombosis (secondary maintenance therapy); identification and, if possible, elimination of various risk factors for thrombosis.

Currently, it is generally accepted that the main treatment of APS is antithrombotic therapy **[***Monagle P et al., 2012; Fleetwood T et al., 2018; Hughes G, 2018*], which includes vitamin K antagonists, mainly warfarin **[***Resseguier A et al., 2017*], unfractionated heparin (UFH) and low molecular weight heparins (LMWH) **[***Hughes G, 2018*]. In recent years, new oral anticoagulants (direct thrombin and X-factor inhibitors) as well as hydroxychloroquine, statins, B-cell inhibitors, inhibitors of complement factor, peptides, etc. have come into pediatric practice **[***Resseguier A et al., 2017*].

Figuring out the tactics of antithrombotic therapy and prevention, the profile of the patient's aPL should be analyzed. "Triple positivity" suggests the simultaneous presence of three types of aPL in a patient (aCL, anti-β2 GP1 and LA) and is considered a more significant risk factor for thrombosis than the presence of two or one type of aPL, although this situation is debatable **[***Erkan D, Lockshin M, 2011; Kalmanti L, Lindhoff-Last E, 2020*]. At the same time, it has been pointed out that LA is a more significant predictor of thrombosis than other APLs **[***Galli M et al., 2003*].

In addition to APL, at least one more risk factor, is detected in almost half of patients with thrombo-

sis [*Aguir C et al., 2015*]. Acquired thrombotic risk factors such as hypercholesterolemia, atherosclerosis, smoking, and oral contraceptives have a less role in children [*Avcin T et al., 2009*]. It should be emphasized that the acquired risk factors can be offset by diet, behavior changes, increased motor activity, drug therapy. The severity of endothelial dysfunction can be decreased by reducing the activity of the underlying disease, if there is any. In contrast, hereditary risk factors for thrombosis in children are more common. So, in 45% (13/29) of children, according to Ped-APS, markers of genetic thrombophilia were detected (The factor V Leiden mutation, protein C or S deficiency, prothrombin gene mutation, etc.). Thrombosis in children is a rather rare event, however, the proportion of patients with aPL-associated thrombosis additionally having genetic prothrombotic risk factors in the pediatric population is greater than in adults [*Tavil B et al., 2007; Kenet G et al., 2011*].

Venous thromboembolism is more often observed in children with congenital heart defects, malignant neoplasms, with central venous catheters and aPL [*Tolbert J, Carpenter S, 2013*].

In order to increase the effectiveness of antithrombotic and maintenance therapy, it is necessary to eliminate additional risk factors as far as possible, and to take into consideration the presence of irreversible factors, particularly genetic ones, while setting up the duration and intensity of the treatment.

Recommendations for the prevention and treatment of thrombosis in children were designed by SHARE experts (The Single Hub and Access point for paediatric Rheumatology in Europe) [*Groot N et al., 2017*]. Due to the small amount of research in children, they are mainly taken from therapeutic practice.

For primary prevention of thrombosis in children with persistent aPL, long-term administration of aspirin is recommended. According to the meta-review [*Arnaud L et al., 2014; Arnaud L et al., 2015*] long-term aspirin use at low doses significantly reduces the risk of thrombosis. In addition, a long-term administration of hydroxychloroquine is also recommended for patients with APL and SLE [*Jung H et al., 2010; Belizna C, 2015*]. This recommendation is due to the fact that this drug has a wide spectrum of action: it inhibits the activation of the complement system [*Bertolaccini M et al., 2016*], partially prevents the development of endothelial dysfunction [*Urbanski G et al., 2018*] and contributes to a decrease in aPL titers [*Nuri E et al., 2017*]. Non-randomized studies have demonstrated a lower rate of thrombosis recurrence in APS patients, who received oral anticoagulants in combination with hydroxychloroquine than in patients who received only oral anticoagulants [*Schmidt-Tanguy A et al., 2013*]. The results of an open pilot randomized trial involving 50 patients with primary APS demonstrated that adding hydroxychloroquine to standard therapy increased the effectiveness of treatment. Long-term treatment with hydroxychloroquine was accompanied by a decrease in aPL titers, except for IgM aCL, though its titer decreased over time regardless of the treatment [*Kravvariti E et al., 2020*]. If the risk of thrombosis in a child with aPL is high (surgery, immobilization, etc.), the use of LMWH is recommended [*Ruiz-Irastorza G et al., 2011*].

The need for primary prevention should be addressed individually, based on the assessment of the aPL profile, the presence of cardiovascular risk factors, autoimmune disease or chronic somatic diseases, concomitant risk factors (genetic thrombophilia, chronic infectious diseases, etc.), metabolic disorders (obesity, diabetes, etc.), physical inactivity, drug therapy, etc. In view of the side effects and risk of bleeding due to injuries during sports, games, etc., long-term preventive therapy for children without any symptoms is not recommended [*Soybilig A, Avcin T, 2020*].

In the active period, in the presence of ischemic thrombovascular disorders, therapy is carried out in accordance with the treatment standards designed for patients without aPL [*Fleetwood T et al., 2018*]. Since the middle of 90's, intravenous thrombolysis [*Julkunen H et al., 1997*] and endovascular thrombectomy [*Camara-Lemarroy C et al., 2016*] have been widely practiced in the treatment of IS in adults [*Bandettini di Poggio M et al., 2019*].

There have been published reports on the successful use of thrombolysis and thrombectomy in cerebral thrombosis in children, presented mainly by the description of individual cases and small series of patients [*Souto Silva R et al., 2019*]. Bigi S and coautors (2018) retrospectively evaluated the

efficacy and safety of intravenous thrombolysis in 5 and endovascular thrombectomy in 11 children with IS and concluded that recanalization therapy is a promising method of treatment and have the same safety as the standard therapy. The results of a meta-analysis of 181 recanalization therapy cases of IS in patients under 18 years of age did not allow to make reliable conclusions about its effectiveness and safety **[***Pacheco J et al., 2018*]. In this regard, to date, conservative therapy with the use of UFH or LMH and with the subsequent transfering to warfarin remains a priority.

Maintenance therapy to prevent recurrence of thrombosis is especially important for children, as, according to several studies, recurrence of thrombosis is more common in children than in adults **[***Aguiar C et al., 2015*]. According to Ped-APS data, after an episode of venous thrombosis, during the monitoring period a relapse was observed in 19% of children, whereas after an episode of arterial thrombosis a relapse was recorded in 21% of children **[***Avcin T et al., 2008*]. The risk of recurrence of thrombosis is especially high during the first 6 months after the withdrawal of treatment (rebound-phenomenon).

According to the SHARE recommendations **[***Groot N et al., 2017*], after a thrombotic event, long-term administration of anticoagulants is indicated for a persistent aPL. It should be borne in mind that thrombosis relapse mainly occurs in the same type of vessels in children: venous thrombosis recurs in 86% of cases and arterial thrombosis is also presented in 75% of patients with arterial thrombosis **[***Avcin T et al., 2008*]. In view of this, after an episode of arterial thrombosis, long-term use of anticoagulants or a combination anticoagulants with antiplatelets (aspirin) is recommended. According to a retrospective study, combination therapy reduces the frequency of recurrence of arterial thrombosis in patients with APS and lengthens the time before it occurs **[***Jackson W et al., 2017*].

To prevent recurrence of venous thrombosis, it is recommended to switch to warfarin with an INR target of 2.0-3.0 (100 Groot) after initial treatment with LMWH or UFH, which is sufficient. More intensive therapy with achievement of higher INR target levels, as indicated, does not reduce the risk of thrombosis recurrence, moreover, it can lead to bleeding **[***Rumsey D et al., 2017*]. If aPL disappears, secondary preventive therapy after an episode of thrombosis is not recommended. It is believed that relapses of thrombosis in APS are most often related to insufficiently intense hypocoagulation **[***Giron-Gonzalez J et al. 2004*]. In patients with persistent aPL having a relapse of thrombosis on the background of oral anticoagulants (INR 2.0-3.0), an increase in dose is indicated to achieve a higher INR (3.0-4.0) or alternative LMWH therapy is recommended **[***Groot N et al., 2017*].

As an alternative to warfarin, new oral anticoagulants might be considered: direct thrombin inhibitors (dabigatran), X-factor inhibitors (apixaban, rivaroxaban). These anticoagulant drugs are assumed to have anti-inflammatory and antiangiogenic effects as well **[***Alberio L, 2014*]. However, to date, the results of the research **[***Dufrost V et al., 2016; Pengo V, Denas G, 2018*], including a randomized RAPS study **[***Cohen H et al., 2016*] did not confirm the benefits of rivaroxaban over warfarin in adult patients with APS.

In the treatment of APS, the possibility of using new class of Antiplatelet therapy with Glycoprotein IIb/IIIa receptor inhibitors GP IIb/IIIa is also being studied. However, so far, abciximab (monoclonal antibodies to GPIIb / IIIa) has not been recommended for the treatment of cerebrovascular disorders due to the negative results of the previous study **[***Ciccone A et al., 2014*].

Patients with secondary APS need adequate therapy for the underlying disease in order to reduce activity and achieve remission. In the active period, patients with SLE and other autoimmune diseases are prescribed glucocorticoids, immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, methotrexate, cyclosporine A, etc.), biological agents (rituximab, belimumab). It was revealed that against the background of belimumab treatment (monoclonal antibodies to B-cell activating BAFF or BLyS) of patients with SLE and APS, the aPL disappeared in some cases **[***Yazici A et al., 2017; Sciascia S et al., 2018*].

CAPS is observed in less than 1% of patients with APS and is considered a “thrombotic storm” **[***Kalmanti L, Lindhoff-Last E, 2020*]. Standard therapy for patients with CAPS includes direct anticoagulants (UFH or LMH) in combination with high-dose therapy with glucocorticoids and intravenous

immunoglobulin **[***Rodriguez-Pinto I et al., 2016*]. SHARE experts recommend plasmapheresis with or without intravenous immunoglobulin **[***Groot N et al., 2017*]. Cases of successful use of rituximab for the treatment of CAPS in children have been reported **[***Nageswara Rao A et al., 2009; Iglesias-Jimenez E et al., 2010*]. Rituximab is a monoclonal antibody against CD20 and causes B cell depletion. The drug is used in the treatment of various autoimmune diseases, including in children. Rituximab has demonstrated its effectiveness in the treatment of microthrombotic angiopathy in adults as well **[***Berman H et al., 2013*]. There have been reports of successful use of eculizumab (monoclonal antibodies inhibiting the activation of complement component C5) **[***Zikos T et al., 2015; Guillot M et al, 2018; Ruffatti A et al., 2019*] for the treatment of severe cases and CAPS relapse in adults.

As "potential" therapeutics, mitochondrial agents such as acetylcestein and coenzyme Q 10, as well as statins are being considered **[***Giannakopoulos B, Krilis SA, 2013*]. Statins, also known as HMG-CoA reductase inhibitors, which have a lipid-lowering effect, can also inhibit the aPL-mediated thrombogenesis and modulate the pro-inflammatory profile in APS, affecting the regulation of the expression of intracellular adhesion molecules 1 (ICAM 1), Vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines, including IL-1β, TNF-α and interferon-α **[***Meroni P et al., 2001; Erkan D et al., 2014*].

Conclusion

APS is an acquired autoimmune thrombophilia with complex multifactorial pathogenesis and a wide range of thrombotic and non-thrombotic manifestations. In the absence of agreed criteria, the diagnosis of APS in children is a difficult task, especially in cases of its non-thrombotic debut manifestations. APS is less common in children than in adults, but can develop at any age, starting from the neonatal period, and its manifestations can significantly affect the life quality of children, their growth and development, causing an unfavorable outcome in some cases. On the whole, thrombosis in children is far less common than in adults, but in the pattern of thrombotic diseases, aPL-associated cases make up a larger proportion of children than adults. These data emphasize the pathogenetic significance of aPL in the genesis of thrombosis in children, while most of them do not have traditional risk factors. And this fact dictates the need for broader measurement of aPL in children with thrombosis and some non-thrombotic neurological and psychiatric syndromes. Recommendations for the diagnosis and treatment of APS in children require further development and testing in wide clinical practice.

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