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NERVOUS SYSTEM INVOLVEMENT IN CHILDREN WITH ANTIPHOSPHOLIPID SYNDROME. NON-THROMBOTIC NEUROLOGICAL MANIFESTATIONS AND THEIR TREATMENT

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Abstract

Antiphospholipid syndrome, according to the generally accepted definition, is an autoimmune disease characterized by recurrent arterial and/or venous thrombosis and/or fetal loss occurring due to the presence of antiphospholipid antibodies. However, patients with antiphospholipid syndrome often have various non-thrombotic manifestations, including those indicating nervous system involvement. Their spectrum is quite wide and includes epilepsy, migraine, chorea, a syndrome mimicing multiple sclerosis, opticomyelitis-associated disorders, transverse myelitis, cognitive dysfunction, etc. Antiphospholipid syndrome is far less common in children than in adults, however, taking into account the significant impact on a child's quality of life and its social prognosis, it is an important problem of pediatrics. It is known that the hemostatic system in different periods of a child's life is characterized by a number of significant features, thus determining different rates of development of antiphospholipid syndrome thrombotic manifestations with peaks in the neonatal period and in adolescence. However, the prevalence and clinical features of various non-thrombotic neuropsychiatric manifestations in children have not been thus far adequately addressed. The issue of their possible inclusion in the antiphospholipid syndrome classification criteria still remains unresolved, there are no agreed recommendations for treatment. Recommendations for the treatment of non-thrombotic manifestations of antiphospholipid syndrome are mainly based on the results of a few non-randomized retrospective studies and descriptions of individual cases, therefore they are quite subjective. Autoimmunity and inflammation are believed to have a large role in the development of non-thrombotic neurological disorders but the contribution of ischemia is not excluded. In view of this, immunosuppressive drugs, glucocorticoids, as well as anticoagulants and antiplatelets are used for treatment, in addition to symptomatic medications (anticonvulsants, psychotropic drugs, analgesics, etc.).

This review summarizes current data on the pathogenesis, clinical manifestations and treatment of neuropsychiatric manifestations of antiphospholipid syndrome with an emphasis on their features in children.

Keywords: *antiphospholipid syndrome, antiphospholipid antibodies, central nervous system disorders, non-thrombotic neurological manifestations, children.*

Introduction

Antiphospholipid syndrome (APS), according to the generally accepted definition, is an autoimmune disease characterized by recurrent arterial and/or venous thrombosis and/or fetal loss occurring due to the presence of antiphospholipid antibodies (aPL) [*Avcin T et al., 2008*]. Since thrombosis can develop in a vessel of any caliber and localization, the spectrum of clinical manifestations of APS is very wide. Nervous system (NS) involvement is the second most common impairment after obstetric pathology in adults with APS [*Hughes G, 2018*], and often occurs in children with APS [*Avcin T et al., 2009*].

Thrombotic neurological manifestations of APS, such as ischemic stroke, transient ischemic attacks and cerebral sinus thrombosis are well known to neurologists, rheumatologists, and pediatricians. At the same time other neurological

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symptoms and syndromes can occur in patients with aPL. The pathogenetic mechanisms of their development are complex and have not yet been fully studied, and probably are not limited to ischemia. They are somewhat conditionally called "non-thrombotic" manifestations of APS.

Non-thrombotic manifestations, including neurological ones, are not included in the list of classification criteria for the APS in both adults and children [*Aguiar C et al., 2015*], despite the fact that they are often detected in patients. Thus, according to the Ped-APS Registry, during the first thrombotic episode, non-thrombotic neurological manifestations were detected in 16% of children with APS: 7% of the patients had migraine, 4% chorea, 3% epilepsy, 1% mood disorders and 1 % showed pseudotumor cerebri syndrome [*Avcin T et al., 2009*]. Judging by the available data, on the whole, migraine, epilepsy, and chorea in children with APS are significantly more common than in adults [*Aguiar C et al., 2015*]. With the increasing number of studies and the newly-available data on APS, the range of aPL-associated neurological disorders is continually expanding, and the issue of including some of them in the list of diagnostic criteria is a subject of active discussions.

When non-thrombotic neurological manifestations occur in a child after a thrombotic episode, the detection of aPL, the establishment of diagnosis, their association with the APS is beyond doubt. However, it was concluded that various neurological symptoms and syndromes, such as epilepsy or migraine, can appear in patients long before a thrombotic event. In this case, their association with aPL can be confirmed only after an additional examination. The identification of aPL persistence is of great importance for setting up patient management tactics.

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

This review summarizes the information on APS. Since there are few publications on the problem of APS in children, the results of adult studies are included. The objective of review: to provide current data on pathogenetic mechanisms of development, clinical manifestations, diagnosis and treatment of non-thrombotic aPL-associated neurological disorders in children.

NON-THROMBOTIC NEUROLOGICAL MANIFESTATIONS OF NTIPHOSPHOLIPID SYNDROME

Headache, especially migraine, is a common and characteristic manifestation of APS, which is observed in 20.2% of patients, according to the EuroPhospholipid Project Group Study [*Cervera R et al., 2002*]. Often migraine seizures first appear in adolescence and are characterized by a high frequency and severity of manifestations. Attacks may disappear in their 20s, and then have a new onset at the age of 30 and 40 [*Hughes G, 2018*]. Apparently, migraine seizures can appear years before the onset of other symptoms and the diagnosis of APS [*Noureldine M et al., 2017*], which makes them be regarded as precursors of more severe ischemic disorders [*Graf J, 2017*].

Migraine is currently postulated to be an autoimmune-mediated neurological disease. This is indicated by a significantly more frequent detection of aPL in patients with migraine than in their peers [*Cavestro C et al., 2011*]. According to the results of a meta-analysis of some authors [*Islam M et al., 2017*]a, and summarizing data from 1995 publications, the incidence of aCL was 8.59%, anti-β2GP1 - 15.21% and LA - 4.11% in patients with migraine, which was respectiviely 4.83, 1.63 and 3.03 times more frequent than in healthy ones. The presence of aCL and anti-β2GP1 was significantly associated with the development of migraine attacks. Although Avčin T. And co-authors also reported a similar incidence of aPL in otherwise healthy children with migraines and tension headaches, however, the authors did not exclude the possible role of aPL in migraine development in specific patients [*Avčin T et al., 2004*]. Perhaps their results can be explained by the relatively small number of the surveyed patients and, on the other hand, by the very high prevalence of headaches in the population.

It is postulated that the association of migraine with APS is due to platelet activation and impaired serotonin metabolism [*Noureldine M et al., 2017*], which leads to an imbalance of these neurotransmitters. However, no convincing evidence of this hypothesis has been presented [*Abreu M et al., 2015*].

Migraine attacks associated with aPL are practically not controlled by non-narcotic analgesics [*Sanna G et al., 2006; Rodrigues C et al., 2010*]. At the same time, there is evidence of migraine disappearance during anticoagulant therapy in pregnant women who received heparin [*Hughes G, 2018; Hughes G, 2003*], which shapes prospects for therapy.

Epilepsy and seizures. Convulsive syndrome is recorded in 3.2-10.0% of patients with APS [*Shoenfeld Y et al., 2004; Cervera R et al., 2009a; De Carvalho J et al., 2012*], which is approximately 10 times higher than the incidence in population [*Noureldine M et al., 2016*]. In patients with secondary APS, seizures are even more common, their incidence reaches 13.7% [*Shoenfeld Y et al., 2004*]. Seizures occur in 7-40% of patients with systemic lupus erythematosus (SLE) [*West S, 2004; Andrade R et al., 2008*]. They were previously considered a manifestation of cerebrovasculitis, and glucocorticoids and immunosuppressive drugs were used for the treatment. Meanwhile, it was reported that in SLE cases, convulsions more often occur in patients with aPL, particularly, in those with IgG aCL [*Appenzeller S et al., 2004; Cimaz R et al., 2006*]. The incidence of aCL in SLE patients with seizures reaches 76%. Liou H. (1996), Mikdashi J. (2005) and co-authors recorded convulsions in 28 (14%) of 195 SLE patients (21 generalized, 7 partial), epilepsy was diagnosed in 12 (43%) of 28 patients. According to these authors, three factors increase the risk of seizures and epilepsy in SLE: high disease activity, previous neuropsychiatric manifestations of SLE, the presence of aCL.

A number of publications have reported a high incidence of APL in patients with epilepsy, which makes 19-43% [*Verrot D et al., 1997; Peltola J et al., 2000; Chapman J et al., 2003*], with the highest incidence of aCL detection, less often anti-β2 GP1 and LA [*Inzelberg R, Korczyn A, 1989; Verrot D et al., 1997; Eriksson K et al., 2001*]. However, there are studies not reflecting this association [*Debourdeau P et al., 2004; Ranua J et al., 2004*]. Nevertheless, it was demonstrated that in patients suffering from partial epilepsy for more than 30 years and having poor control, the frequency of aCL detection was 3 times higher than in patients with a disease duration of up to 10 years. The risk of aPL persistence in patients with frequent seizures (more than once per month) is 2.2 times higher than that in patients with rare seizures [*Noureldine M et al., 2016*].

Data about the association of epilepsy with aPL-positivity in children are also uncertain. According to Cimaz R et al. [*Cimaz R et al., 2006*] 20% of idiopathic juvenile epilepsy cases can be associated with aPL, while patients most often have temporal lobe epilepsy, which is not easily recognized. ACL persistence was recorded in 10%, and anti-β2GP1 in 17% of young patients with epilepsy (142 patients were examined, the average age is 10 years) [*Cimaz R et al., 2002*]. Eriksson et al. [*Eriksson K et al., 2001*] found aCL in 44% of cases in 50 children with epilepsy and only 10% in the controls, with the highest incidence of aCL (80%) in patients with symptomatic or cryptogenic epilepsy, as well as in patients with a mixed form. Meanwhile, Constanti T. and co-authors (2009) revealed aCL in only one of 60 children with epilepsy; 6 of 43 patients were LA-positive, anti-β2GP1 was not found in any patient. According to Angelini L. and co-authors (1998) aPL were detected in 3 of 23 children with partial seizures without signs of ischemic changes on the MRI and CT.

It has been established that previous thromboembolic events in the central nervous system are the most significant risk factor for seizures [*Shoenfeld Y et al., 2004*]. This is particularly indicated by the fact that in almost half of patients, convulsions appear after the diagnosis of APS is established [*Cervera R et al., 2009b*]. The most likely pathogenetic mechanism for the development of epilepsy in APS is ischemic damage to brain tissue with the formation of a cortical epileptogenic focus [*Yelnik C et al., 2016*]. In addition, the role of immune disorders in the formation of ischemic stroke and its consequences may be indicated by a lower incidence of epileptic seizures after stroke in the population (10%) and a greater incidence (17%) in similar patients with APS [*Silverman I et al., 2002*]. Smoking is an additional risk factor for seizures in APS [*de Carvalho J et al., 2012*].

Despite the fact that aPL-associated ischemia has a leading role in the development of epilepsy, not every case is resulted from it. In a number of studies, a higher aPL incidence was recorded in patients with epilepsy, as compared with the controls, in the absence of ischemic or thrombotic changes during neuroimaging [*Peltola J et al., 2000; Chapman J et al., 2003*]. The development of seizures in a structurally normal brain suggests a possible antibody-mediated mechanism of its damage [*de Carvalho et al., 2012*]. The possible role of autoimmunity in the pathogenesis is indirectly indicated by the high risk of developing epilepsy in patients with autoimmune diseases, especially children [*Ong M et al., 2014*]. It was found that aPL can directly bind to ependymal tissue, myelin, and other brain tissues, which is a potential immunological basis for aPL-associated epilepsy [*Roldan J, Brey R, 2007*]. Direct effects of antibodies can result in depolarization disorder and membrane permeability, as well as decreased GABA response and binding to neurotransmitters [*Liou H et al., 1994; Chapman J et al., 2005; Cimaz R et al., 2006*].

The role of antiepileptic drugs in the induction of aPLs has been actively discussed earlier since they have often been detected during treatment with anticonvulsants. So, Pardo A. and other authors [*Pardo A et al., 2001*] found aPL in 43% of patients with seizures who received phenytoin and valproate, although most of them had IgM type of aCL. However, most of the recent studies have found no association between anticonvulsant therapy and the presence of various types of aPL, including aCL, either in adults [*Verrot D et al., 1997; Peltola J et al., 2000; Eriksson K et al., 2004*] or in children [*Attilakos A et al., 2020*]. Currently, the predominant point of view is that a high incidence of autoantibodies in patients with idiopathic epilepsy is associated with the disease itself.

Patients with aPL can have all forms of epilepsy, including subclinical, which is confirmed by the changes on the EEG [*Hughes D, 2003*]. Half of the patients with aPL-associated seizures usually have two or more non-thrombotic manifestations of APS [*Herranz M et al., 1994*]. It was established that there is a significant association of epilepsy with thrombocytopenia [*Krause I et al., 2005*], livedo, heart valve damage [*Shoenfeld Y et al., 2004; Yelnik C et al., 2016*], as well as with high levels of anti-β2GP1 IgG in a secondary APS and anti-β2GP1 IgM in a primary APS [*Stojanovich L et al., 2013*].

There is no evidence that isolated aPL carriage is associated with MRI changes [*Noureldine M et al., 2016*]. The presence of SLE and other neurological symptoms in patients significantly correlates with the presence of changes in the white matter according to MRI. In contrast, the correlation between aPL and changes in the white matter is weak [*Noureldine M et al., 2016*]. Moreover, MRI does not detect changes in the brain in more than 30-40% of SLE patients with neuropsychiatric disorders, both with and without aPL [*Castellino G et al., 2008; Sarbu N et al., 2015*].

APL-associated epilepsy is a rule out diagnosis. However, the aPL identification should be recommended for young patients with atypical seizures and multiple hyperintense foci according to MRI data, in the absence of other possible causes [*Noureldine M et al., 2016*].

The treatment of patients with epilepsy and APS is based on the use of antiepileptic drugs and anticoagulants in the presence of thrombosis. Antiepileptic therapy is recommended for patients who have had two or more seizures [*Noureldine M et al., 2016*]. In cases where neuroimaging has confirmed the presence of an ischemic lesion, it is necessary to immediately begin anticoagulant therapy [*Espinosa G, Cervera R, 2015*]. Anticoagulant treatment and preventive therapy should be carried out according to the recommendations of SHARE experts [*Groot N et al., 2017*]. Therapy of patients with epilepsy in the presence of a systemic autoimmune disease involves the administration of glucocorticoids, intravenous immunoglobulin and other immunomodulatory drugs [*Valencia I, 2014*].

Chorea occurs in 1.3-4.5% of patients with APS [*Cervera R et al., 2002; Appenzeller S et al., 2012a*] and may be its first manifestation [*Safarpour D et al., 2015*]. Significantly more often, chorea occurs in children and pregnant women with APS [*Cervera R et al., 2002*]. In SLE patients chorea is detected in 9% of children and 1-3% of adults with APS and might often precede the diagnosis of SLE or occur within 1 year after its onset [*Baizabal-Carvallo J et al., 2011*].

Clinically, aPL-associated chorea is not different from chorea in other systemic or hereditary diseases. Involuntary movements can occur in different parts of the body [*Peluso S et al., 2012*]. Chorea can be bilateral or unilateral, segmental, multifocal or generalized [*Orzechowski N et al., 2008; Reiner P et al., 2012*]. Choreic hyperkinesis may be the only episode and resove spontaneously or due to the treatment. According to Reiner P. and others (2011), average duration of chorea was 7.44 weeks.

APL-associated chorea is often accompanied by other neurological manifestations, such as cognitive dysfunction, ataxia, epilepsy, mental disorders, migraine and dystonia [*Orzechowski N et al., 2008*]. More than half of patients with aPL-associated chorea have a mitral or aortic valve disease [*Reiner P et al., 2012*].

The pathogenetic mechanisms of the development of chorea in APS are not completely clear. It is postulated that there is a direct interaction of aPL with the epitopes of the cells of the basal ganglia, which leads to their dysfunction [*Katzav A et al., 2003*]. In addition, chorea can result from ischemic damage to the caudate nucleus and/or shell (putamen) [*Tanne D, Hassin-Baer S, 2001*]. Ischemic lesion of the basal ganglia is detected on neuroimaging in 6-16% of patients with aPL-associated chorea [*Peluso S et al., 2012*]. Currently, PET scan is used to assess the condition of the basal ganglia. The presence of inflammatory changes in patients with aPL-associated chorea can be indicated by an increase in the metabolic activity of the basal ganglia during PET scanning [*Yelnik S et al., 2016*]. Lupus anticoagulant (LA) is detected in

the vast majority (84-92%) of patients with aPL-associated chorea [*Cervera R et al., 1997; Reiner P et al., 2011*]. Persistence of LA in chorea is also present in children [*Avcin T et al., 2008 a*].

Symptomatic treatment of chorea involves a use of dopamine receptor antagonists [*Tanne D, Hassin-Baer S, 2001]*. However, it has been demonstrated that chorea can resolve due to anticoagulant therapy [*Hughes G, 2018*]. Patients with bilateral chorea have an increased risk of thrombosis, and therefore, antithrombotic therapy is especially indicated for these patients [*Peluso S et al., 2012*]. EULAR experts recommend using a combination of glucocorticoids and immunosuppressants to treat SLE patients with chorea and aPL [*Bertsias G et al., 2010*]. For resistance, intravenous immunoglobulin, (IVIg), plasmapheresis, and biological agents (rituximab) are added [*Peluso S et al., 2012*].

Movement disorders rarely seen in patients with APS include dystonia, ballism, paroxysmal dyskinesia, tremors, tics, myoclonus, cerebellar ataxia, parkinsonism (degenerative corticobasal-like syndrome and progressive supranuclear palsy, both syndromes with poor response to treatment with levodopa) [*Reitblat T et al., 2003; Martino D et al., 2006; Orzech N et al., 2008*]. The cumulative incidence of movement disorders in APS is 0.3-0.7% [*Cervera R et al., 2002*].

The pathogenesis of movement disorders, as with chorea, includes two main mechanisms. The presence of cerebral infarctions and the white matter damage on MRI indicates a mechanism of occlusive thrombus [*Tanne D, Hassin-Baer S, 2001; Ricarte I et al., 2018*], but there is evidence of immune-mediated damage to the basal ganglia [*Carecchio M et al., 2014*]. In view of the uncommonness of these disorders, the correlation between the aPL type and the clinical manifestations has not been established [*Carecchio M et al., 2014*]. Recommendations for the treatment of patients with aPL-associated movement disorders have not been drawn up.

Transverse myelitis are a rare manifestation of APS, its prevalence is 0.4-4.0% [*Cervera R et al., 2002*]. Transverse myelitis is characterized by acute inflammation of the white and gray matter of the spinal cord [*Campi A et al., 1998; Rodrigues C, de Carvalho J, 2011*]. The thoracic region is commonly affected [*Tanne D, Hassin-Baer S, 2001; Espinosa G, Cervera R, 2015*]. Clinically, transverse myelitis is manifested by acute or subacute sensory impairment, the development of paraparesis or tetraparesis and pelvic dysfunctions [*Rodrigues C, de Carvalho J, 2011*]. The mechanisms of transverse myelitis are not completely understood, and probably include vasculitis and/or arterial thrombosis, resulting in ischemic necrosis [*Arnson Y et al., 2010*].

Transverse myelitis more often occurs in patients with primary APS. At the same time there was a significant association of transverse myelitis with aPL in SLE patients; the frequency of detection in two cohorts of patients was 43% and 64% [*Graf J, 2017*]. In most cases, patients with transverse myelitis responded to treatment with glucocorticoids in combination with or without anticoagulants and cyclophosphamide [*Aziz A et al., 2000; Tanne D, Hassin-Baer S, 2001*]. Plasmapheresis and rituximab are also used [*Rodrigues C, de Carvalho J, 2011*].

Opticomyelitis-associated disorders. The term "spectrum of optoneuromyelitis-associated disorders" (neuromyelitis optica spectrum disorders, or NMOSD) was proposed in 2007 to refer to the demyelinating disorders of the central nervous system which are clinically characterized by predominant involvement of the optic nerves and spinal cord (three or more segments) and a detection of highly specific autoantibodies to the protein of water channels, aquaporin-4 (AQP4) or anti-myelin oligodendrocyte glycoprotein (anti-MOG) in blood [*Tobin W et al., 2014*]. Currently, the range of these disorders is expanded to include not only seropositive (antibodies to aquaporin-4), but also seronegative cases [*Lennon P et al., 2004].* The disease has a chronic course, characterized by recurrent episodes of optic neuritis in combination with progressive transverse myelitis. Since it was found that these disorders and APS can occur in one patient, forming an overlap, APS patients with myelitis or optic neuritis should be tested for the presence of antibodies to aquaporin [*Recarte I et al., 2018*].

A syndrome similar to multiple sclerosis [MS-like syndrome] is described as a rather rare neurological manifestation in APS and its prevalence is not precisely specified [*Fernandez-Fernandez F et al., 2006; Yelnik C et al., 2016*]. Meanwhile, the debate regarding the nosological nature and differential diagnosis of MS-like syndrome and MS actively continues.

Many years ago, some similar clinical and laboratory symptoms were recorded in patients with MS and a systemic autoimmune disease such as SLE, which gave rise to the hybrid term "lupoid sclerosis" [*Fleetwood T et al., 2018*]. This encouraged to study the pathogenetic role of antinuclear antibodies and

aPL in the development of neurological symptoms in these diseases [*Keiserman B et al., 2010*].

Many clinical observations have been published, reporting about aPL patients with coordination disorders, loss of hearing or vision, as well as movement and sensory disorders with a wave-like course characterized by exacerbations and remissions. These changes were identical with the manifestations of multiple sclerosis detected on the MRI in T2 mode [*Cuadrado M et al., 2000; Fernandez-Fernandez F et al., 2006; Lima I et al., 2007; Mayer M et al., 2010*]. At the same time, research on exploring the association of aPL with a specific MS have shown very contradictory results. The frequency of aPL detection in these patients ranged from 2% to 88% [*Uthman I et al., 2015*]; higher aPL titers were recorded during exacerbations of the disease [*Bidot C et al., 2007*]. ACL and anti-β2HP1 in MS patients seem to have a higher incidence than LA [*Uthman I et al., 2015*]. The prevalence of aCL has been studied in a greater amount of research. According to the summarized data, aCL of IgG isotype were revealed in 6% of the MS patients, and the frequency of detection of aCL of IgM isotype varied in a wide range from 2% to 69% [*Heinzlef O et al., 2002; Liedorp M et al., 2007; Yelnik C et al., 2016*]. According to Roussell et al. [*Roussell V et al., 2000*] the frequency of aPL detection in MS patients was 21.4% for aCL carriage and 15.7% for anti-β2 GP1 carriage versus 10.3% and 7.1%, respectively, in the control group of patients with other neurological diseases, except for ischemic stroke and other manifestations characteristic of APS. LAs were not found in any group. However, some authors [*Karussis D et al., 1998*] demonstrated that aCL are more often detected in MS-like syndrome than in MS, especially in patients with headaches. Finally, in 2019, it was reported [*Sahebari M et al., 2019*] that they had detected aCL (IgM and IgG) and LA in all three MS patients examined by them. The role of aPL in the genesis of MS and MS-like syndrome has not been finally concluded. It is believed that aPL can disrupt the integrity of the blood-brain barrier and promote the penetration of immune cells into the central nervous system [*Bidot C et al., 2007*].

It is very difficult to make a differential diagnosis between a specific MS and a PC-like syndrome. The sudden onset and rapid resolution of symptoms, the presence of other neurological manifestations typical of APS at the same time, such as headache or epilepsy, and/or signs associated with systemic diseases of connective tissue, an indication of a history of thrombosis, a pathology of pregnancy can help establish a diagnosis of APS with MS-like syndrome [*IJdo J et al., 1999; Arnson Y et al., 2010*]. Apparently, 30% of patients with MS-like syndrome have optical neuropathy, therefore, its detection can help establish a diagnosis [*Tourbah A et al., 1998*].

In APS patients, brain MRI in T2 mode can help reveal hyperintense foci, which are difficult to differentiate with those in multiple sclerosis [*Mayer M et al., 2010*]. There is evidence that lesions detected on neuroimaging in APS are smaller, often localized in the subcortical region, stable in time, and positive dynamics can be achieve due to anticoagulant therapy [*Stosic M et al., 2010; Uthman I et al., 2015*]. The absence of cytosis and oligoclonal bands in the cerebrospinal fluid also suggests APS [*Ferreira S et al., 2005*]. In addition, it is known that MRI might reveal periventricular changes (the "central vein sign") in MS patients with a high prevalence (88%). However, they are far less common in patients with inflammatory vasculopathies and APS. The presence of this symptom makes it possible to differentiate MS from similar diseases with very high accuracy [*Maggi P et al., 2018*].

Immunosuppressive therapy is widely common for MS. Meanwhile, there are reports of effective anticoagulant therapy in patients with MS-like syndrome [*Cuadrado M et al., 2000*], which, according to Graf G. (2017), leads to the suggestion that MS and MS-like syndrome have different mechanisms of development, despite their clinical similarity.

Coordination disorders, according to Hughes G. (2018), often occur in patients with APS, ranging from mild to severe. Adult patients with the development of such symptoms, have often been misdiagnosed as having Meniere's disease.

Cognitive dysfunction and dementia. In primary APS, cognitive dysfunction is detected in 42-80% of patients; usually it is a subcortical pattern characterized by disorders of attention, difficulty in concentrating, information transfer rate, verbal learning skills, ingenuity, visual spatial orientation, executive functions and poor memory [*Brey R et al., 2011; Kozora E et al., 2014; Yelnik C et al., 2016 a, b*]. The severity of cognitive dysfunction can vary from mild impairment to dementia [*Tektonidou M et al., 2006*].

Cognitive deficits may precede the diagnosis of APS. So, one of the studies showed that cognitive impairment was detected in a third of non-elderly aPL patients in the absence of any other symptoms

[*Jacobson M et al., 1999*]. Signs of cognitive deficits can occur in patients not only after thrombotic events, but also after the patient has been diagnosed with APS. After all, the association of cognitive dysfunction with ischemic changes has not been demonstrated in some studies [*Appenzeller S et al., 2012b*]. Cognitive deficits can occur in patients with aPL, regardless of previous neurological symptoms, and its occurrence cannot be solely explained by vascular pathology [*Tektonidou M et al., 2006*]

Several surveys of patients with or without SLE helped to reveal a correlation of cognitive dysfunction with aCL levels and persistence [*Hanly J et al., 1999; Jacobson M et al., 1999; Menon S et al., 1999; Roldan J, Brey R, 2007*]. It has been reported that in APS there is an association of cognitive dysfunction with livedo reticularis, but not with ischemic stroke [*Tektonidou M et al., 2006; Yelnik C et al., 2016*].

Cognitive dysfunction is detected in children with APS as well. They can be easily viewed, as children just start developing their cognitive skills, or, conversely, can be misdiagnosed in patients having difficulty learning due to non-organic causes. In the pediatric population, the identification of aPL should be carried out in patients with learning difficulties. And of course, large cohort studies are needed to establish a possible connection between cognitive dysfunction and aPL.

A pilot study has demonstrated that cognitive dysfunction correlates with abnormal activity of the brain, especially the frontal lobes, in patients with APS, which was detected during the performance of functional tests [*Kozora E et al., 2016*].

On MRI, patients with APS and neurological impairment often present with infarctions in the cortical, subcortical and basal ganglia, some of which are asymptomatic, but there is no evidence of a high prevalence of infarctions in patients with cognitive dysfunction [*Tektonidou M et al., 2006; Zhu D-S et al., 2014; Yelnik C et al., 2016 a*]. At the same time, MRI reveals lesions in the white matter of the brain in patients with APS and cognitive impairment with a higher frequency than in patients without cognitive impairment [*Tektonidou M et al., 2006*]. The size and number of these lesions may be different and their nature has not been finally identified. It is not clear whether they are caused by ischemia or inflammatory demyelinating processes [*Yelnik C et al., 2016 b; Zhu D-S et al., 2014*].

Using experimental models, it was demonstrated the possibility of direct interaction between the IgG of APS patients and the neuronal structures of the hippocampus and cerebral cortex of mice, which significantly affected their behavior and learning skills [*Shoenfeld Y et al., 2003*]. The results of these studies support the idea of direct effects of aPL on cognitive functions. It is also postulated that aPL-mediated dysregulation of the dopaminergic system has a certain role in the development of cognitive dysfunction [*Abreu M et al., 2015*].

Based on the available data, the multifactorial nature of cognitive dysfunction in APS has been conceptualized. Apparently, the occurrence of cognitive deficit is due to several factors, each of which plays a specific role: ischemic disorders, genetic predisposition, the specificity of antibodies and the duration of their exposure, increased permeability of the blood-brain barrier, allowing direct interaction of aPL with brain cells, etc. [*Appenzeller S et al., 2012a*]. The complex genesis of cognitive dysfunction indicates the need for a personalized approach in the choice of therapy.

Dementia in APS is less common than cognitive dysfunction. The prevalence of dementia in patients with APS varies from 0 to 6% [*Cervera R et al., 2002; Yelnik C et al., 2016*]. Patients with dementia are older and more likely to have changes on the brain CT and EEG [*Chapman J et al., 2002*]. Meta-analysis data set up a significant association of dementia with aCL [*Islam M et al., 2017b*].

It has been postulated that dementia in APS is primarily caused by multiple infarctions of small vessels, similar to multi-infarction dementia [*Tanne D, Hassin-Baer S, 2001*]. However, publications on the successful use of immunosuppressive therapy indicate that other mechanisms are involved in the development of dementia, at least in some patients [*Graf J, 2017*].

Patients with APS often present with memory impairment. Memory problems can be presented by a variety of manifestations, including transient complete amnesia. However, as Hughes G. points out [*Hughes G, 2018*], memory loss is one of the symptoms and its severity can be reduced very quickly and significantly after the start of anticoagulant therapy.

Psychiatric disorders. Patients with APS have a variety of psychatric disorders, including psychosis, acute depression, delirium, manic states, bipolar and obsessive-compulsive disorders, schizophrenia, etc. [*Raza H et al., 2008; Yelnik C et al., 2016*].

Psychiatric disorders may precede the onset of somatic symptoms of APS for several years [*Kurtz G, Muller N, 1994*]. So, Shabana M. and co-authors

(2009) presented a clinical follow-up of a 9-year-old girl with psychosis, no thrombotic manifestations, persistent aCL in a high titer in the absence of antinuclear antibodies, DNA antibodies, with no changes on the CT, MRI and angiography. The psychotropic drugs were ineffective, positive dynamic was achieved only due to complex therapy, which included antidepressants, aspirin and hydroxychloroquine. On cessation of aspirin, axillary vein thrombosis occurred. Thus, psychosis was the first manifestation of primary APS, and the presence of aPL indicated the patient management tactics.

Clinical observations provide evidence that depression and aggressive behavior may be associated with aPL [*Raza H et al., 2008*]. In a retrospective analysis of 100 patients with APS, depression was detected in more than 10% of cases [*Etemadifar M et al., 2013*]. The risk of depression and anxiety in patients with APS ranges from 1.57 to 1.64 [*Gris J et al., 2017*]. There has been a report of development of fulminant encephalopathy in a CAPS patient with multi-organ thrombosis [*Chinnery P et al., 1997*].

The frequency of aPL detection in patients with psychiatric disorders varies from 4% to 24% [*Yelnik C et al., 2016*]. However, in view of the fact that psychotropic drugs can induce the synthesis of aPL, in particular, IgM aCL and LA, this should be taken into account when interpreting these data [*Graf J, 2016*]. However, Schwartz M. and the other authors (1998) who examined 34 patients with psychiatric disorders before these patients began to receive psychotropic drugs, found elevated aPL levels (in most of the cases IgL aCL and LA) in 32% of them and none in the control group. None of these patients with psychiatric disorders had SLE, any other autoimmune diseases or thrombotic manifestations of APS. Similar results were obtained in another study involving 100 patients with hallucinations and/or delirium. APL were detected in 25% of the cases, and not only aCLs of all the three isotypes, but also antibodies to phosphatidylethanolamine, phosphatidylserine and phosphatidylcholine [*Sokol D et al., 2007*]. In a series of 7 patients with impaired behavior (irritability, emotional lability, suicidal mood, lethargy, akathisia and movement disorders), elevated levels of aPL and/or APS were found in all of them [*Gorman D, Cummings J, 1993*] There has been an account of one case of a 31-year-old man with APS who developed a manic episode [*Raza H et al., 2009*]. Elevated levels of aCL and LA were found in patients with schizophrenia [*Ricarte I et al. 2018*]. One of the surveys revealed a higher statistically significant incidence of anti-β2-GP1 in children with SLE and neuropsychiatric disorders [*Avcin T et al., 2008 b*].

The risk factors associated with psychiatric disorders in APS are older age, cerebral ischemia and the presence of all three types of aPL (aCL, LA and anti-β2GP1) [*Yelnik C et al., 2016 b; Gris J et al., 2017*].

The development of psychiatric disorders in patients with aPL without clinical and instrumental signs of thrombotic changes suggests the possibility of a direct effect of aPL on the central nervous system. In particular, an experiment helped to establish that hyperactivity and anxiety were detected in laboratory animals after prolonged aPL exposure [*Chapman J et al., 2003*]. It is likely that the aPL-mediated effect on neurons and glia cells disrupts their functions and inhibits the proliferation of astrocytes [*Brey R, Escalante A, 1998; Sanna G et al., 2003*].

Peripheral neuropathy is often recorded in APS patients, in contrast to SLE cases, for which it is not characteristic [*Hughes G, 2018*]. According to Santos et al. [*Santos M et al., 2010*] in most cases, patients have sensory-motor neuropathy and carpal tunnel compression syndrome. Patients may complain of a sensory impairments of the lower limbs, but often they do not show complaints, and no pathological changes are detected during a physical examination. Perhaps these changes occur due to thrombosis of the vasa nervorum, vasculitis, or the interaction of aPL with the lipid components of myelin [*Fleetwood T et al., 2018*].

Perhaps the same pathogenetic mechanisms play a role in the development of Guillain – Barré syndrome (acute autoimmune inflammatory polyradiculoneuropathy, manifested by flaccid paresis, sensory disturbances, autonomic disorders) in patients with APS [*Sanna G et al., 2003*]. Among the aPLs in these patients, anti-β2GP1 of IgM isotype prevail [*Sahebari M et al., 2019*].

Neuroophthalmic disorders. There have been reports of many visual loss patterns in APS [*Hughes G, 2018*]. Transient blindness of one or both eyes, which is regarded to be a consequence of cerebral ischemia, according to the EuroPhospholipid Project Group Study was detected in 5.4% of patients with APS, optic neuritis was revealed significantly less often (in 1% of patients) [*Cervera R et al., 2002*].

Optic nerve damage in APS, is usually represented by either Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) resulted from ciliary vascular thrombosis, or retrobulbar optic neuropa-

thy, which may be caused by both thrombosis and inflammation [*Suvajac G et al, 2007; Giorgi D, Balacco Gabrieli C, 1999*]. Both disorders are characterized by a sudden decrease in vision and a unilateral color blindness. Papillary edema with linear hemorrhages is considered a typical manifestation of anterior optic neuropathy [*Suvajac G et al., 2007*]. Retrobulbar optic neuropathy is more often detected in secondary APS, but also in primary APS [*Suvajac G et al., 2007*]. A very significant association of optic neuritis with anti-β2GP1 IgM and other neurological disorders has been reported [*Sahebari M et al., 2019*].

Optic neuritis is very rare in children. The researchers [*Patra S et al., 2011*] described a 11-year-old girl with SLE and APS, who developed acute bilateral optic neuritis with blindness due to a high activity of the pathological process. The MRI detected thrombosis of several cerebral sinuses. Despite the complex therapy, which included anticoagulants, the patient ended up developing bilateral optic atrophy, and did not recover the vision. Three cases of optic neuritis in children with SLE have been reported by Suri D. and others (2016). In the first two cases this syndrome was the first manifestation of the disease, and in the third, ischemic neuropathy occurred due to the underlying SLE and secondary APS.

Occasionally, orbital ischemic syndrome is characterized by bilateral ophthalmoparesis, ptosis, increased intraocular pressure and necrosis of orbital tissue, which can be detected in patients with CAPS [*Vaphiades M et al., 2001*]

Autonomic nervous system disorders can also be a manifestation of APS, sometimes initial [*Hughes G, 2018*]. According to JR Schofield [*Schofield J, 2017*], who examined 22 patients, the clinical manifestations of autonomic nervous system disorders included postural orthostatic tachycardia syndrome with fainting and tachycardia after standing up, neurocardiogenic syncope, sinus tachycardia, labile arterial hypertension, local pains, pronounced gastrointestinal motility disorders, a neurogenic bladder, with 45% of patients having more than one disorder. Despite the fact that most patients had low-titre IgM aCL, 13 patients of 22 (59%) presented with one or more thrombotic episodes. Thus, autonomic nervous system disorders in these patients was associated with significant thrombotic risk and high degree of disability, which was indicated by a high incidence of arterial thrombosis (45%), including ischemic stroke (36%), transient ischemic attacks, and amaurosis. The reduction of small vegetative and sensitive fibers due to microthrombosis or direct interaction of aPL with neuron-associated epitopes is considered to be a possible cause of autonomic nervous system disorders.

A number of studies have reported a positive dynamic in patients with autonomic nervous system disorders due to antithrombotic therapy and the intravenous immunoglobulin administration [*Schofield J et al., 2014; Hughes G, 2014; Schofield J, 2017*].

Sleep deprivation is a complaint of patients with APS. Patients with primary APS are significantly more likely to have sleep problems: inadequate sleep duration, sleep disturbances, patients do not get enough sleep, daytime sleepiness, constant intake of sleeping pills [*de Oliveira L et al., 2018*] Cases of narcolepsy and catalepsy have been reported. Sleep deprivation is likely to result from cerebral ischemia [*Hughes G, 2018*].

Moyamoya disease. There have been published data on the association of aPL with Moyamoya disease which is a vasculopathy of unknown etiology, characterized by progressive narrowing of the anterior brain arteries with the formation of collaterals. According to Wang Z. and co-authors (2014), in a series of 16 patients with Moyamoya disease and aPL, APS was diagnosed in 21% of cases. A sufficiently high frequency of detection of aPLs probably indicates their role in the pathogenesis of vascular disorders in this pathology.

Autism spectrum disorders in children may also be associated with aPL [*Lageix F et al., 2015*]. It was revealed that children with autism spectrum disorders have elevated anti-β-2HP1 titers as compared to a group of patients with developmental delay and the control group; and elevated aCL levels as compared to the controls. In view of the significant increase in the prevalence of autism in children, the research of the possible correlation of this pathology with aPL should be continued [*Careaga M et al., 2013*].

Idiopathic intracranial hypertension (pseudotumor cerebri syndrome) is another form of the central nervous system pathology and its development may be associated with aPL. It is characterized by a rapid increase of intracranial pressure, not associated with the presence of a "volume" in the cranium, obstruction of the cerebrospinal fluid passageaways or local structural disorders in active and oriented patients. The term "idiopathic" requires exclusion of cerebral sinus thrombosis. According to the literature, the frequency of aPL detection in patients of several small series with idiopathic intracranial hyperten-

sion ranged from 8.1% to 43%, and this makes it be regarded as a possible manifestation of APS [*Khamashta M, 2006*].

Sensorineural hearing loss is currently considered a possible manifestation of APS, since its development has been detected in patients with various autoimmune diseases and aPL carriage [*Khamashta M, 2006*].

Neuroimaging

Various pathological changes are detected in 35-90% of patients with APS due to neuroimaging [*Rovaris M et al., 2001*]. Hyperintense signal foci of various sizes, from small focal to diffuse, are most often detected in the subcortical white matter of the brain [*Roldan J, Brey R, 2007; Erkan D et al., 2011; Kaichi Y et al., 2014; Zhu D et al., 2014*]. Their prevalence in primary APS is 17-45% [*Ricarte IF et al., 2018*]. The genesis of these changes is unclear, they can be caused by both ischemia and inflammation, or possibly both [*Zhu D et al., 2014*].

In APS, changes in the white matter are found in patients with various neurological disorders: focal neurological deficits, cognitive dysfunction, seizures, etc. Changes in the white matter are non-specific and similar to those found in patients with inflammatory demyelinating diseases of nervous system and vascular pathology [*Rovaris M et al., 2001; Graf J, 2017*]. At the same time, multiple infarctions and encephalomalacia are detected in young patients with neuropsychiatric disorders and generalized movement disorders [*Li C et al., 2013*].

Using diffusor tensor imaging, it has become possible to detect early microstructural changes in the white matter in APS, for example, diffuse hypoperfusion foci in the cerebral cortex compatible with axonal damage and myelin sheath [*Pereira F et al., 2016*]. Radioisotope scanning (Tc-99m ECD SPECT) allows early detection of a pronounced heterogeneity of cerebral perfusion in patients with APS, which correlates with the number of different types of aPL [*Lin T et al., 2017*].

Cerebral atrophy is detected in 12-36% of patients with APS, which can be an isolated find or be matched with changes in the parenchyma [*Recarte J et al., 2018*]. A significant association between cerebral atrophy and the presence of LA has been identified [*Hachulla E et al., 1998*].

Treatment

Recommendations for the treatment of non-thrombotic manifestations of APS are mainly based on the results of a few non-randomized retrospective studies and descriptions of individual cases, therefore they are quite subjective. Autoimmunity and inflammation are believed to have a large role in the development of non-thrombotic neurological disorders but the contribution of ischemia is not excluded. In view of this, immunosuppressive drugs, glucocorticoids, as well as anticoagulants and antiplatelets are used for treatment, in addition to symptomatic medications (anticonvulsants, psychotropic drugs, analgesics, etc.).

Anticoagulant therapy has proved to be effective in treating neurological disorders in APS that are not considered initially thrombotic. Moreover, positive dynamics due to the anticoagulant therapy can help in making differential diagnosis of APS and autoimmune diseases of the central nervous system [*Uthman I et al., 2015*]. However, the potential role of aPL-mediated impairment substantiates the use of immunosuppressive therapy [*Espinosa G, Cervera R, 2015*].

A combination of glucocorticoids and antipsychotics is presented as An effective therapy in most patients with APS and chorea [*Demonty J et al., 2010; Ayalew Y, Khattak F, 2012; Safarpour D et al., 2015*]. In addition, the efficacy of intravenous globulin [*Brogna C et al., 2014*], as well as the immunosuppressive drug mycophenolate mofetil [*Yokoyama K et al., 2018*] has been demonstrated in the treatment of chorea in children.

Meanwhile, there have been reports of positive dynamics in the condition of patients with severe migraine attacks, but without signs of cerebral infarctions [*Cuadrado M et al., 2001; Asherson R et al, 2007*], with psychiatric disorders, such as obsessive-compulsive behavior [*Roie E et al, 2013*] and movement disorders [*Carecchio M et al., 2009*] due to anticoagulant therapy. At the same time, there is evidence that an early use of glucocorticoids is very beneficial for the treatment of young patients with psychiatric disorders associated with aPL [*Lai J et al., 2012*]. It is worth mentioning the reports of significant positive dynamics in the status of patients with cognitive dysfunction who received anticoagulants for other manifestations of APS [*Hughes G, 2003*]. The alternative therapy, also recommended for patients with cognitive dysfunction, involves a combination of low-dose aspirin with hydroxychloroquine [*Mayer M et al., 2010*].

For the treatment of patients with atypical demyelinating syndromes and transverse myelitis, the entire spectrum of drugs is used: glucocorticoids in combination with immunosuppressive agents, anticoagulants and/or antiplatelets [*Espinosa G, Cervera R, 2015*].

A pilot study evaluating the efficacy and safety of rituximab in the treatment of non-thrombotic manifestations in primary APS, along with others, included 6 patients with cognitive dysfunction. In view of the small number of observations, it is too early to make definite conclusions, but the results are encouraging. There has been an improvement in attention, visuomotor speed and flexibility [*Erkan D et al., 2013*].

Conclusion

Non-thrombotic neurological manifestations are often detected in patients with APS. It is known that non-thrombotic neurological manifestations such as chorea, migraine, epilepsy, psychosis can be the initial manifestation of APS and precede the thrombotic symptoms many months and even years before. Since non-thrombotic manifestations are not included in the list of the existing diagnostic criteria, even with persistent aPL in high titers, the diagnosis of APS in such cases is not established. Meanwhile, these manifestations can be considered as possible predictors of thrombosis and the risk of the latter can be reduced due to adequate primary antithrombotic prophylaxis. Children with atypical manifestations of classical neuropsychiatric diseases such as epilepsy, migraine, etc., patients with autoimmune diseases, such as SLE, as well patients with an unclear diagnosis but with the identified multiple hyperintensive foci in the brain on the MRI should undergo examination and testing for aPL.

We need fundamental research to clarify the genesis of non-thrombotic neurological disorders, large cohort studies to find out their prevalence, clinical and course characteristics in children, as well as randomized studies to evaluate the effectiveness and safety of the use of new immunosuppressive drugs, including biological agents, new oral anticoagulants, etc.

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