Spectrum Journal of Innovation, Reforms and Development
Volume 15, May, 2023 | ISSN (E): 2751-1731
Website: www.sjird.journalspark.org

CLINICAL-LABORATORY, IMMUNOLOGICAL, PATHOGENETIC MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME AND IDENTIFICATION OF EFFECTIVE TREATMENT REGIMENS (REVIEWS)

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ABSTRACT:
Antiphospholipid syndrome (APS) is one of the leading causes of thrombosis. According to some estimates, the incidence of APS is about 5 new cases per 100,000 people per year and the prevalence is about 40-50 cases per 100,000 people [1], thus the problem of APS remains one of the most important in medicine.

Keywords: antiphospholipid syndrome (APS), antiphospholipid antibodies, lupus anticoagulant.

Introduction

Antiphospholipid syndrome (APS) is a systemic pathology that can present with one or more clinical signs from different systems and organs. APS is defined by the occurrence of venous and arterial thrombosis and recurrent fetal loss, often accompanied by moderate thrombocytopenia, in the presence of antiphospholipid antibodies (APA), namely lupus anticoagulant (LA), anticardiolipin antibodies (ACA) or anti-B2 glycoprotein-I (B2GPI) antibodies [1;2].

Despite the great interest in the complexities of APS, there are no internationally accepted standards for the treatment of patients with a different clinical picture of APS. This is due to the heterogeneity of the clinical picture, the variety of triggering factors, the different approaches to the diagnosis of APS, and the small number of prospective randomised trials on the prevention and treatment of patients with APS (2).

The first studies on APS date back to the beginning of the 20th century. In 1906,

Wassermann developed a method for diagnosing syphilis, which was based on complement fixation through the interaction of autoantibodies from syphilis patients and "syphilitic antigen" isolated from animal organs [3]. However, it was not until 1941 that J. Pangborn proved that the chemical basis of this reaction was cardiolipin, contained in an alcohol extract of bovine heart and used as an antigen in the Wasserman reaction. Patients with positive results of this test, but without signs of syphilitic infection, had autoimmune, infectious and haematological diseases (false positive Wasserman reaction) [2].

In 1963, W. R. Bowie first described thrombosis in patients with a circulating anticoagulant. In these patients, thrombosis occurred despite the fact that the test results indicated hypocoagulation. For the designation of this non-specific coagulation inhibitor that is not associated with bleeding, in 1970 A. Feinstein and D. Rapaport coined the term "lupus anticoagulant". Despite laboratory test data, Lupus anticoagulant was associated with thrombotic complications and not with haemorrhage [4].

A few years later, D. Alarcon-Segovia described unusual clinical manifestations, such as thromboses of different localisation, reticular liver disease and falsely positive laboratory tests for syphilis, which were associated with manifestations of SLE. These clinical manifestations formed the basis of the antiphospholipid syndrome. Antiphospholipid syndrome was definitively defined in 1983 by the English rheumatologist Graeme R. W. Hughes, who worked at St Thomas' Hospital in London. In 1987 Hughes made the first generalisations about the nature of anti-phospholipid syndrome. It was suggested that it is based on the formation of autoantibodies to phospholipid determinants in endothelial and nervous tissues and platelets [3].

The association between deep vein thrombosis, habitual non-pregnancy and lupus anticoagulant was first described in 1980. The authors of this work were V. Soulier and M. Boffa. In France, the combination was called the Soulier-Boffa syndrome. Subsequently in England, the manifestations of the syndrome expanded to include arterial and venous thrombosis, heart valve disease, neurological disorders (chorea, transverse myelopathy, etc.), and adrenal insufficiency. In 1988, R. Asherson was the first to formulate the definition and diagnostic criteria for primary APS (5). In 1994, at the VI International Symposium on Antiphospholipid Antibodies it was proposed to refer to APS as Hughes syndrome [6]. In 2002, APS was recognized as a systemic pathology, as its manifestations are associated with lesions of various organs and systems, and have a common pathogenesis [1].

Data on the prevalence of APS in the general population are highly variable, probably due to the long-standing lack of accurate laboratory criteria for diagnosing AFS and the statistical criteria used [6]. The number of people with circulating antiphospholipid antibodies is 0.5% of the general population (7). Antiphospholipid antibodies occur in the general population with a reported prevalence of between 1% and 5%, and, like other autoantibodies, increase with age (8). The incidence of APS is about 5 new cases per 100 000 people per year and the prevalence is about 20-50 cases per 100 000 people (depending on ethnic origin) (9).

Women are at greater risk of APS, as the disease occurs more frequently in both the primary

and secondary states in women than in men. In addition, women in their reproductive years may develop ASF (classical or obstetric) and special attention is required for pregnant women diagnosed with ASF (9). The ratio of women to men for primary APS is 3.5: 1, and 7.5: 1 for secondary APS [6]. APS usually develops at the age of 35 years, the predominant age being 20-40 years. The circulation of different types of AHF increases with age, but cases of AHF in children, including newborns, have also been described (7).

The detection of different types of APA, such as antibodies to cardiolipin and lupus anticoagulant, in the blood of healthy individuals, varies up to 14% (mean 1- 5%; high concentration, less than 0.2%) and increases in the elderly and in individuals with underlying diseases, including cancer, severe atherosclerosis, leg ulcers or infection (8).

Clinical manifestations of APS develop in 30% of patients with circulating lupus anticoagulant and in 30-50% of patients with intermediate or high levels of cardiolipin antibodies. AFA frequency among young patients with myocardial infarction history is 21%, among stroke patients - 18-46%, among women with habitual pregnancy failure - 12-15%, among patients with SLE - about one-third of patients. In patients with SLE, the risk of thrombosis increases to 60-70% and decreases to 10-15% in the absence of AFAs (10).

In the general population, the LA phenomenon is detected in 3-4% of cases; in patients with SLE, up to 50%, depending on the method of detection [1]; in other connective tissue diseases, such as rheumatoid arthritis, dermatomyositis, Sjögren's syndrome and systemic sclerosis, it is lower and ranges from 5 to 20% [11].

According to other data, APA is present in about 13% of patients with stroke, in 11% of those with myocardial infarction, and in 9.5% of patients with deep vein thrombosis (11).

Urbanus et al. note an increased risk of thrombosis in smokers with HA [30]. One study identified obesity as a predisposing factor, and one study described diabetes mellitus as a predictor of thrombosis in APS [12].

With regard to prevalence in pregnancy, approximately 1% of women who wish to realise reproductive goals have pregnancies that end in unintended miscarriage (defined as three or more unexplained consecutive fetal losses), and 10-15% of these women are diagnosed with APS [13]. In addition, 11-29% of women with pre-eclampsia and 25% of women with delayed foetal growth test positive for AFS (14).

Two prerequisites are known to be necessary for the development of any autoimmune condition: the presence of a genetic predisposition and the influence of an external factor (11).

The presence of a genetic predisposition to antiphospholipid syndrome is proved by numerous facts, such as the development of the syndrome in identical twins, relatives, and the high incidence of the disease in certain ethnic groups. As early as the early 1980s, the presence of asymptomatic AFA circulation or with the development of clinical manifestations among members of the same family was noted, which determined the beginning of the study of immunogenetic predisposition to the disease, including the major histocompatibility complex (HLA). There is evidence of an association between the circulation of AHF and the carriage of certain HLA genes, as well as genetic alterations in the complement system, which probably explains the incidence of APS in members of the

same family. Data on immunogenetic predisposition to APS are based on the detection of a higher frequency of AFA in families of patients with primary APS: HLADR4, D7, DRw53, DQB1*0302 [12].

It is now known that the most frequent autoantigens for APAs are B2GPI and prothrombin, so most studies have focused on their molecular structure, gene polymorphisms and the biological role of these polymorphisms. The first description of familial cases of APA was made in two pairs of identical twins in whom the presence of lupus anticoagulant was identified. Later, it was possible to describe the development of primary APS in four members of the same family. Close relatives with SLE or primary APS were found to be more likely to have antibodies to cardiolipin, confirming a genetic predisposition to the development of AHF. In 1987, Mackie et al. reported on three families in which one or more members had lupus anticoagulant antibodies (7).

Goel et al. identified clinical and laboratory changes in members of 7 families in which at least one relative had APS (14).

A set of criteria for familial APS has been formulated, and it has been suggested that the gene predisposing to the development of the disease is inherited in an autosomal dominant manner. A high frequency of DR4, DR6 or DR7 HLA haplotypes has been found in many cases of familial APS or circulating APA (14). The genes encoding class II HLA (DP, DQ and DR) are located on chromosome 6. The main function of the molecule is to ensure a specific T-cell immune response. The association of HLA with autoantibodies in SLE has been extensively studied in different ethnic groups. The association of HLA with AFA is of great interest because of the clinically significant prothrombotic effect of autoantibodies.

R. Asherson et al. found a high frequency of DR4 in 13 patients with primary APS in the British population. Similar findings were obtained by E. Camps et al. among residents of southern Spain and Goldstein et al. among Canadians. T. Vargas- Larson et al. found a high frequency of HLA DR5 in 17 Mexicans with primary APS. Studies suggest a possible association of APS with polymorphisms of the HLA class II genes (DPB1*, DMA*0102), complement component C4 and TNF-a (TNF-o 238*A) [14]. The B2GPI gene, by binding to negatively charged phospholipid sites, is involved in the development of phospholipid-dependent coagulation reactions. The gene encoding B2GPI synthesis is located in chromosome 17q32qter. B2GPI undergoes conformational changes upon interaction with phospholipids. Differences in amino acid sequences may lead to disrupted conformational changes in the molecule when interacting with phospholipids [13].

In the European population, low plasma levels of B2GPI have been reported in 6.8-12.5% of cases. Numerous in vitro and in vivo studies have shown no correlation between B2GPI deficiency and the propensity for both thrombosis and haemorrhage [32].

The symptomatology of APS is heterogeneous: some patients present with arterial thrombosis, others with venous thrombosis only; some patients with circulating APS have no clinical manifestations of APS. Such clinical heterogeneity of APS may indicate the presence of additional risk factors for the development of the syndrome (3). In a cohort of patients with APS, genetic thrombophilia, including mutations in factor V Leiden, and prothrombin G20210A, antithrombin, protein C and protein S, is an independent risk factor for recurrent

thrombosis [4].

A study of the effect of thrombophilia predisposing gene polymorphisms on the clinical manifestations of APS found that mutation of factor V Leiden, which is the most common cause of thrombophilia in the European population, and mutation of prothrombin G20210A may increase the incidence of venous thrombosis. Studies by several authors have shown that the presence of the 4G/5G polymorphism of the RAI-1 gene is an additional factor in the development of arterial thrombosis in APS (15). The effects of angiotensin-converting enzyme and factor XIII gene polymorphisms have also been studied, but no effect on the ASF clinic has been found. A genetic predisposition to circulating AHF or to the development of APS is currently being investigated. One of the most likely factors are the genes coding for HLA class II. The main difficulties in determining genetic risk factors for circulating AFAs or the development of APS are related to the high heterogeneity of antigens and the multiple pathophysiological mechanisms of thrombosis (16).

Infection is known to be one of the factors causing autoimmune activation of the immune system.

The leading role in the development of auto-aggression is assigned to various viral infections, given their widespread prevalence in the population [17]. According to some authors, AFS in chronic viral infection occurs in 20-51.5% of cases [18]. Elevated blood levels of AFS are seen against a background of various viral (hepatitis C, HIV, Epstein-Barr virus, cytomegalovirus, parvovirus B19, adenovirus, herpes, measles, rubella viruses etc.), bacterial (leprosy, tuberculosis, salmonellosis, staphylococcal, streptococcal infections, Q-fever etc.), protozoal, fungal, more often mixed infections [19].

Risk factors for APS also include medication (amoxicillin, phenytoin, fanzidar, quinidine, quinine, hydralazine, procainamide, phenothiazine, a-interferon), the presence of malignancies (leukaemia, The presence of malignancies (leukaemia, lymphoproliferative processes, epithelial tumours), various connective tissue diseases, autoimmune diseases (SLE, rheumatoid arthritis, Sjögren's syndrome, autoimmune thrombocytopenic purpura, autoimmune thyroiditis, etc.) and other diseases) [15;20].

Antiphospholipid syndrome is an autoimmune systemic disease with a wide range of clinical signs (symptoms), including thrombosis of various localizations, and adverse pregnancy outcomes, combined with the presence of specific antiphospholipid antibodies according to laboratory tests (21). The non-critical manifestations of APS include thrombocytopenia, various neurological, cardiovascular, haematological and other disorders.

The first clinical and laboratory criteria for APS were proposed by expert scientists in 1999 in Sapporo, Japan, which significantly limited the clinical manifestations, and the laboratory criteria included antibodies to cardiolipin IgG and IgM and lupus anticoagulant (21).

In view of the increasing body of scientific work on the syndrome, APS criteria were revised at the XI International APS Congress in Sydney in 2006, and the clinical manifestations were reinterpreted and antibodies to B2-glycoprotein I were added to the laboratory criteria [22].

Currently, the practical diagnosis of APS is based on the Australian criteria of 2006 [23].

Diagnostic criteria have been summarised in the 2019 EULAR guidelines [21]: common clinical features of APS include venous thromboembolism, stroke, recurrent early miscarriage and late fetal loss.

According to current laboratory criteria for APS, anti-phospholipid antibodies can be one of three types (24): lupus anticoagulant, antibodies to cardiolipin and antibodies to B2-glycoprotein I.

The diagnosis of APS is made when at least one clinical symptom and one laboratory criterion are combined (25).

The diagnosis of APS is confirmed provided that positive laboratory tests and clinical manifestations have been present for at least 12 weeks and not more than 5 years. A history of thrombotic episodes must be confirmed by appropriate diagnostic methods. Superficial venous thrombosis is not included in the clinical criteria (26).

Clinical manifestations not included in the revised APS classification criteria (27): heart disease, reticular liver disease, thrombocytopenia, nephropathy, neurological disorders.

Laboratory parameters not included in the APS diagnosis criteria [28]: cardiolipin IgA antibodies, B2-glycoprotein I IgA antibodies, phosphatidylserine antibodies, phosphatidylethanolamine antibodies, phosphatidylserine-prothrombin antibodies, annexin V antibodies.

The diagnosis of APS is not a routine method and requires strict standardisation. APS is detected by immunological methods (ELISA) and using phospholipid-dependent coagulation tests aimed at the detection of lupus anticoagulant (29).

The determination of antibodies to cardiolipin and to b2-glycoprotein I is performed by enzyme-linked immunosorbent assay (ELISA), in which IgG and IgM iso-forms are determined. ELISA is defined by IgG- and IgM-labelled antibodies [24]. The unit of APA is expressed as mpl or GPI. The antibody titer is divided into "high" (more than 60 mpl or GPL), "medium" (40-60 GPL or mpl) or "low" (20-40 GPL or mpl). Results below 20 GPL or mpl are negative.

Regarding specific immunoglobulin types, there is evidence that carriage of IgG antibodies is associated with a higher risk of adverse pregnancy outcomes compared with circulating IgM antibodies (30).

Researchers distinguish between primary and secondary forms of APS (31).

APS is primary in the presence of clinical signs and in the absence of autoimmune diseases, such as SLE, rheumatoid arthritis, autoimmune thrombocytopenic purpura, etc. A distinction is made between thrombotic and obstetric primary ASF (27).

Secondary APS is considered to be against a background of various autoimmune diseases, malignancies, infections, as well as drug-induced [28].

The controversial variant is seronegative APS, in which there are clinical signs but no laboratory confirmation of the diagnosis.

Less than 1% of patients develop catastrophic antiphospholipid syndrome (CAPS), defined as small vessel thrombosis in three or more organs in less than 1 week in the presence of AFS, with histopathological confirmation of small vessel thrombosis in the absence of inflammation. CAFS is associated with a high (50%) mortality rate, mainly due to cerebral

and cardiac thrombosis, infections and multi-organ failure (29;30).

Venous thrombosis is the most common thrombotic manifestation of APS, with deep vein thrombosis (DVT) up to and including pulmonary embolism (31;32). APS is also associated with thrombosis of various localisations: axillary, retinal, glomerular and adrenal veins. APS is the most common cause of Bad Da-Chiari syndrome, in which hepatic vein thrombosis occurs (33;34). In the arterial arm, cerebral infarcts and transient ischaemic attacks are characteristic of APS, which significantly increase the risk of ischaemic stroke, and are associated with involvement of the intracranial arteries (35). Coronary heart disease, peripheral arterial occlusion, acute abdomen, and ischaemic colitis due to mesenteric thrombosis are also manifestations of arterial thrombosis in APS. Recurrent thrombosis and thromboembolism or multiple localised lesions are possible with AFS (36).

The pathogenesis of APS is thought to be multifactorial, as there are many different mechanisms explaining the cause of hypercoagulability and thrombotic complications in APS. Despite the variety of mechanisms, what is clear is that APS disrupts the balance between clotting factors, fibrinolysis, platelets and endothelial tissue, reducing the body's antiaggregant and anticoagulant potentials. This creates conditions for the development of thromboses of various localisations. Besides thrombotic effect, a great role in pathogenesis of APS is played by nonthrombotic effects of AFAs [37].

Antiphospholipid antibodies are a family of auto- and alloimmune immunoglobulins (IgG, IgM and IgA) that bind phospholipid protein complexes. In addition to ACA and LA, other AFAs belong to this family: anti-phosphatidylserine antibodies, anti-phosphatidylinositol, anti-phosphatidylglycerol, anti-phosphatidylethanolamine antibodies (38).

When highly sensitive tests are used, the presence of antibodies to these phospholipids can also be detected in healthy individuals. It is assumed that the circulation of AFAs is a universal response of the organism to various conditions caused by infection, autoimmune and malignant diseases, the use of medications, as well as environmental factors (allergic, radiation, etc.).

However, in most people, the presence of APA is transient and does not manifest clinically (39).

Cell membranes are known to be composed of two types of phospholipids:

1) phosphoglycerides (the main constituent of cell membranes), with phosphatidylcholine and phosphatidylethanolamine being more common in the body;

2) sphingophospholipids (present mainly in nervous tissue). Thanks to numerous APS studies, it has been shown that thrombosis is not caused by a direct interaction between AFAs and phospholipids, as previously thought, but rather by protein-mediated interactions. Blood plasma protein B2-glycoprotein I (apolipoprotein H), which binds to phospholipids to form a true antigen for APA, and prothrombin are such cofactor proteins [40]. In addition to B2-GPI and prothrombin, other cofactor proteins that are targets for AFAs (protein C, protein S, tissue plasminogen activator (t-PA), annexins, thrombomodulin, oxidised low-density lipoproteins, coagulation factors XII, X, XI, VII/VIIa, precallikrein, high and low molecular weight kininogen, H and C4b components of complement, endothelial protein C receptor (EPCR) [31].

AFAs are therefore defined as antibodies against prothrombin or B2GPI. AFAs are often described as lupus anticoagulants or anticardiolipin antibodies, depending on the method of investigation that detects the APA. In some cases, e.g. in an infective process, direct interaction of the AFA with phospholipids is also possible, with the AFA being represented by IgM (32).

The treatment of APS has long been the subject of intensive research, because the understanding of the syndrome has increased considerably over the years, and various therapeutic options have been proposed. An international consensus has created a document in the context of the APS treatment trends task force. This document was created as part of the 14th International Congress on APS (Rio de Janeiro, September 2013). The main aim of the task force was to systematically review current and potential future treatment strategies for APS-positive patients. The British Haematology Society also developed guidelines for the management of patients.

It is important to note that lifestyle modification to reduce cardiovascular risk factors (regular exercise, smoking cessation, weight loss, correction of hypertension, dyslipidaemia and diabetes) will be beneficial for the overall health and prevention of thrombotic complications in patients with APS (33).

The main drugs for the treatment of thrombotic manifestations of APS are anticoagulant drugs, including a vitamin K antagonist (Warfarin) or heparin, and antiplatelet therapy, such as low-dose aspirin (34).

Preliminary evidence supporting the use of direct oral anticoagulants (POACs) for APS in patients with previous venous thromboembolism is available and known, and other studies are ongoing, while the evidence base is not yet sufficient to fully support the use of POACs for APS [35]. According to EULAR (2019), the use of POACs (particularly rivoroxaban) in APS and arterial thrombosis leads to an increased rate of recurrent thrombotic complications [40].

In rare cases, immunomodulatory agents as well as anticomplement therapy are used in patients who do not respond to antithrombotic drugs.

In pregnancy, therapeutic doses of LMWH are used as therapy for venous thromboembolic complications.

Conclusion

More than three decades have passed since the study of APS began, and researchers are still uncovering new details of the complex pathogenesis and treatment features of the disease.

To date, there are no generally accepted international standards for the treatment of patients with different clinical features of APS, because of the small number of prospective randomized trials, heterogeneity of clinical presentation, and different approaches to the diagnosis of APS.

Despite current treatments for APS, unfortunately, existing treatments do not prevent all complications of the disease, as in 20-30% of cases with APS this tactic is ineffective. These findings highlight the need to seek alternative treatments to improve the quality of life of patients with APS.

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