

Antiphospholipid Syndrome

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Antiphospholipid syndrome · Hughes' syndrome ·
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Abstract

Antiphospholipid syndrome (APS) is a disease characterized by venous and arterial thromboses or spontaneous abortions and the repeated detection of antiphospholipid antibodies (aPL). APS may be associated with another autoimmune disease (secondary APS), particularly systemic lupus erythematosus (SLE), or unrelated to an underlying disease (primary APS). APS affects almost all organs. In addition to the clinical criteria, lupus anticoagulant testing and immunological aPL determinations are required to establish the diagnosis of APS.

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Antiphospholipid syndrome (APS) is characterized by venous/arterial thrombosis and/or recurrent fetal loss and the repeated detection of antiphospholipid antibodies (aPL) directed against phospholipid-protein complexes. APS may be associated with another autoimmune disease (secondary APS), particularly systemic lupus erythematosus (SLE), or unrelated to an underlying disease (primary

APS/PAPS). The clinical syndrome of thrombosis, recurrent abortions and neurological symptoms in conjunction with the detection of aPL was first described by Hughes [1] in 1983. It was therefore proposed that the syndrome be named after him [2]. The history of this syndrome (table 1) dates back to William Osler, who described stroke as a symptom of lupus.

Epidemiology and Classification

APS may be one of the most common autoimmune diseases, i.e., one of the major causes of organ damage in autoimmune diseases. A clear classification system is needed to properly assess the frequency of occurrence of a syndrome. The most common criteria for classification of APS (table 2) differ from other classification criteria in rheumatology because they have not been tested in large numbers of patients. Hence, no data on their specificity and sensitivity are available.

New preliminary criteria for the classification of APS (table 3) have recently been proposed. They clearly define the obstetric complications of APS and provide clear-cut data on aPL and their isotypes. After the manuscript had been accepted the preliminary criteria for the classification of the APS were published in a modified form [48]. Many subsets of APS are encountered in practice (ta-

Table 1. History of antiphospholipid syndrome (Hughes' syndrome)

Authors	Year	Discovery
Conley and Hartmann [3]	1952	circulating anticoagulant in SLE
Moore and Mohre [4]	1952	BFP-STs especially in SLE
Bowie et al. [5]	1963	thrombosis in SLE despite circulating anticoagulant
Feinstein and Rapaport [6]	1972	introduction of the term 'lupus anticoagulant'
Nilsson et al. [7]	1975	SLE associated with lupus anticoagulant and intrauterine death
Thiagarajan et al. [8]	1980	nature of lupus anticoagulant: aPL
Hughes [1]	1983	anticardiolipin syndrome
Harris et al. [9]	1983	aCL – detection by radioimmunoassay
Loizou et al. [10]	1985	aCL – detected by ELISA
Galli et al. [11]	1990	β ₂ -GPI-cofactor
McNeil et al. [12]	1990	
Matsuura et al. [13]	1990	
Gharavi et al. [14]	1998	classification criteria of workshop on APS

Table 2. Suggested criteria for the APS [15]

Clinical	Laboratory
Venous thrombosis	lupus anticoagulant
Arterial thrombosis	IgG anticardiolipin (>20 GPL units)
Pregnancy loss (unexplained)	IgM anticardiolipin (>20 MPL units)
Thrombocytopenia	

Patients should have at least one clinical and one laboratory feature to make the diagnosis. The laboratory test should be positive on at least two occasions, 8 weeks apart.

Table 3. Preliminary international criteria for the classification of APS [14]

1	aPL documented on at least two occasions 6 weeks apart and occurring at the same time as:
2	One or more clinical features that have previously been associated with aPL in serum
ad 1.	aPL: aCL IgG, IgM or IgA or LA
ad 2:	Thrombosis criteria
a	One or more episodes of arterial or venous thrombosis, confirmed by imaging or Doppler studies or histopathology.
b	Three or more unexplained consecutive miscarriages or one or more unexplained deaths of a morphologically normal fetus at or after the 10th week of gestation or one or more premature births at or before the 34th week of gestation, associated with severe preeclampsia or placental insufficiency
c	Two or more episodes of reversible cerebral ischemia
d	Multiple sclerosis-like syndrome or focal neurologic deficit, otherwise unexplained
Associated features – not criteria	
1	Thrombocytopenia <100,000/mm ³
2	Hemolytic anemia with reticulocytosis and positive Coombs test, not induced by drugs
3	Transverse myelopathy, otherwise unexplained
4	Livedo reticularis
5	Unexplained mitral or aortic valve thickening and/or regurgitation of blood, demonstrated by echocardiography
6	Unexplained chorea, observed by a physician
7	Migraine, onset within 1 year of a positive test for aPL in blood

ble 4). There seems to be a genetic basis for APS since a familial occurrence of primary APS is observed in 10% of the cases. The HLA loci DR4, DR7 and DRw53 were also found to be associated with APS.

Etiology and Pathogenesis

aPL are a group of heterogeneous antibodies directed against phospholipid-binding proteins such as β₂-glycoprotein I (β₂-GPI) (or apolipoprotein H), prothrombin, protein C, protein S, thrombomodulin, annexin V and kininogen. The term 'antiphospholipid antibody' is therefore incorrect, since the antibody is actually directed against a phospholipid-protein complex, but the name has been kept for historical reasons. Although the negatively charged phospholipid cardiolipin plays the most impor-

Table 4. Classification of APS into various subsets [16]

'Primary' vs. 'secondary' APS
Other clinical subsets
Patients characteristics
Sex
Age
Sporadic vs. familial forms
Nature of the vessels involved
Veins vs. arteries
Macro- vs. microvasculature
Preferential clustering of symptoms
Cerebral ischemia/left-sided heart valve lesions
Cerebral ischemia/livedo reticularis (Sneddon's syndrome)
Disease course
One-shot vs. multiple-shot
Timing of events
Catastrophic APS
Purely obstetrical APS

tant role, phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine may also form part of the complex. The target epitope is still not fully explained. The reactions between cardiolipin and β_2 -GPI are the best known. β_2 -GPI was first described in 1961, and its amino acid sequence has been decoded. This glycoprotein acts as a natural inhibitor of blood coagulation at various sites of the coagulation cascade. The binding site for cardiolipin on β_2 -GPI is also known [reviewed in ref. 17].

aPL have an effect on all phospholipid-dependent hemostasis processes. Phospholipid-dependent hemostasis tests are delayed in vitro due to the inhibition of prothrombin activation. Thrombophilia in these patients can be attributed to the interactions between aPL and natural inhibitors of blood clotting such as activated protein C, protein S, and thrombomodulin. This suggests that aPL are of pathogenetic importance for the development of thrombosis. This pathogenetic role is supported by evidence from animal experiments. During their passive transmission or active immunization, aPL induce thrombocytopenia, fetal resorption (equates to spontaneous abortion in humans), and increased coagulation.

Thrombosis does not develop in all patients with aPL. Additional pathogenetic mechanisms must contribute to the development of thrombosis (secondary 'hit'). Endothelial vessel damage (infection?) is a very important developmental factor. Thrombosis is the primary symp-

tom of both primary and secondary APS. Veins and arteries of all calibers located throughout the entire body may be involved.

Clinical Manifestations

Thromboses

Recurrent thromboses are the major clinical manifestation of APS. 2.5–3.5% of all patients with APS – whether primary or secondary – are affected by thrombosis each year. Venous thrombosis (65–70%) is more common than arterial thrombosis. aPL can be detected in 8–10% of all patients with venous thrombosis. Based on data from retrospective studies, the risk of phlebothrombosis in patients who test positive for aPL was estimated to be 2.7–11.9 [see review in ref. 18]. Venous thromboses are usually localized in the lower extremities and are frequently multiple and bilateral. Around one third of the cases are complicated by pulmonary embolism, which can lead to pulmonary hypertension and right heart failure. Primary thromboses in the pulmonary circulation can also result in pulmonary hypertension. aPL are detected in around 10% of all patients with pulmonary hypertension. Postthrombotic symptoms associated with ulcers, frequently on the medial malleolus, are further complications of leg and pelvic vein thrombosis. Thromboses of the axillary veins, subclavian vein, inferior vena cava, superior vena cava and veins of various organs may also occur together with the corresponding clinical symptoms (table 5).

Among the great vessels, arterial thrombosis most commonly involves the cerebral arteries, but may also affect the coronary arteries and those in the extremities and other organs (table 5). aPL can be detected in 18–20% of all stroke patients under 50 years of age. The risk of stroke development in aPL-positive patients was determined to be 2.33–10.6. General risk factors such as smoking, hypertension, metabolic disease, heart disease and the use of oral contraceptives increase the risk of thrombosis.

One third of all APS patients experience only one thrombotic event; the other two thirds have recurrent thromboses. A history of thrombosis is the greatest risk factor for future occlusions. Eighty percent of the patients have either recurrent venous thromboses or recurrent arterial thromboses, whereas only 20% have both arterial and venous thromboses [19]. The time between the initial occurrence and the recurrence may be several days to several years. The reason why some patients develop venous thrombosis (approximately 48%), whereas others develop

Table 5. Thromboses and clinical manifestations of APS

Venous		Arterial	
vessel	clinical finding	vessel	clinical finding
Extremities	phlebothrombosis thrombophlebitis	Brain	stroke, transient ischemic attack multi-infarction dementia
Skin	livedo reticularis, ulcers pulmonary embolism		valvular vegetations myocardial infarction
Lungs	pulmonary hypertension	Heart	thrombus, cardiomyopathy
Liver	Budd-Chiari syndrome	Kidney	renal infarction microangiopathy
Adrenal glands	Addison's disease	Liver	hepatic infarction
CNS	sinus vein thrombosis sinus cavernosus thrombosis	Skin	finger gangrene
		Eyes	retinal artery occlusion

arterial thrombosis (approximately 38%) or recurrent abortions is still unexplained.

Disseminated clot formation in numerous vessels associated with multiple organ failure and thrombocytopenia is called 'catastrophic antiphospholipid syndrome' [20]. This form of the disease can be lethal.

Complications during Pregnancy and the Puerperium

Over half of all thromboses in women with APS occur during pregnancy, the puerperium, and during oral contraceptive use. Two prospective studies found that 5 and 12% of pregnant women with APS developed thrombosis or stroke, despite prophylactic heparin administration in a portion of cases [21, 22]. Furthermore, the occurrence of preeclampsia and gestational hypertension is higher in women with APS.

The complications of APS that may involve the fetus are recurrent miscarriage, intrauterine fetal death, premature delivery (30%) and fetal growth impairment (30%). In patients with APS, fetal loss is more common after the 10th gestational week than in early pregnancy. Some investigators even doubt whether early abortion should be considered as the sole clinical criterion for APS [23]. It is difficult to assess the risk of fetal loss in healthy women with aPL. Additional factors that increase the risk of spontaneous abortion in healthy aPL-positive pregnant females have not yet been identified. Genetic factors, infections, medications, and subclinical autoimmune disease or environmental factors have been discussed as possible factors. High aPL titers in pregnant women with SLE are predictive of spontaneous abortion, with rates of 50–85% reported in the literature. Eighty percent of all untreated healthy women with high aPL titers and previous fetal loss have another miscarriage in a subsequent pregnancy.

Thrombosis and infarction of the placental vessels are considered to be responsible for the complications in pregnancy but, since these placental pathologies do not occur in all cases, other mechanisms have also been proposed [see review in ref. 24].

Hemocytopenia

Thrombocytopenia, hemolytic anemia and, less frequently, leukocytopenia are observed in patients with APS, whereas thrombocytopenia is usually mild and does not cause severe bleeding. The prevalence was estimated to be 30–50% for mild thrombocytopenia ($50-100 \times 10^9/l$) and 5–10% for severe thrombocytopenia ($<50 \times 10^9/l$) [25]. The cause of thrombocytopenia is complex and the details are not fully understood. Binding of aPL to the platelet membrane apparently occurs in the presence of β_2 -GPI.

Thirty percent of patients with idiopathic thrombocytopenic purpura are aPL-positive, and they probably form a special subset.

Hemolytic anemia in APS may occur as isolated hemocytopenia or in conjunction with thrombocytopenia. Hemolytic anemia is frequently associated with anticardiolipin antibodies (aCL) of the IgM isotype.

A connection between APS and thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome is assumed as well.

Neurological Manifestations

The most common neurological manifestations of APS are ischemic stroke and transitory ischemic attack. aPL-positive stroke patients are usually younger than 50 years of age and have a very high rate of recurrence. The recurrence usually takes place within 1 year after the initial

event. aPL are also an independent risk factor for development of cerebral infarction in the elderly.

Cardiac etiologies such as valvular defects, intracardiac thrombus and other risk factors must also be taken into consideration. Multiple infarction events can result in dementia.

A number of other neurological symptoms are associated with aPL detection, but a causal relationship cannot be identified in every case (table 6). A possible connection between APS and Sneddon's syndrome, which is characterized by symptoms of cerebrovascular disease, hypertension and livedo racemosa, has been suggested. aPL can be detected in at least a portion of patients with Sneddon's syndrome.

There is also a significant correlation between aPL positivity and CNS manifestations in patients with SLE. It therefore seems justified to perform aPL testing as well as magnetic resonance imaging and single-photon computed emission tomography (SPECT) in addition to the conventional neurological work-up in all SLE patients with suspected neurolupus. These are currently the best studies for identifying clinically silent CNS manifestations of APS.

Cardiac Manifestations

The potential cardiac manifestations of APS are valvular heart disease (usually involving the mitral valve), coronary artery occlusion, intracardiac thrombus, pericardial effusion, dilatative cardiomyopathy due to occlusion of smaller vessels, and early bypass occlusion after coronary surgery.

High aPL titers are an independent risk factor for myocardial infarction and sudden cardiac death. The risk is even higher in patients who also have antibodies against oxidized low-density lipoproteins (ox LDL). aPL and antibodies to ox LDL were found to cross-react [27]. Since the latter antibodies play a role in the progression of arteriosclerosis, a connection with arteriosclerotic complications is being debated.

Morphological studies of pathological changes in the heart valves in patients with APS have revealed fibrin deposits and subsequent valvular damage in the absence of an inflammatory process. Hence, the way in which aPL antibodies are involved in the pathogenesis of endocardial lesions remains unclear.

Skin Manifestations

The skin manifestations of APS are multifarious. Thrombotic occlusions of the cutaneous vessels are not always the underlying cause. Livedo reticularis, a reticular

Table 6. Neurologic syndromes associated with aPL [26]

Cerebrovascular ischemia
Stroke
Transient ischemic attack
Sinus thrombosis
Ocular ischemia
Dementia
Acute ischemic encephalopathy with Sneddon's syndrome
without Sneddon's syndrome
Atypical migraine-like events
Seizures
Chorea
Transverse myelopathy
Guillain-Barré syndrome
Transient global amnesia
Psychiatric disorders
Orthostatic hypotension

and cyanotic circular discoloration of the skin with a pale central area, and skin ulcers are the most common skin manifestations of APS. Livedo reticularis may form a fine, closed pattern caused by anastomoses between the very small skin vessels that result in reduced blood flow, or it may have a larger, lightning-like shape with small areas of necrosis. The latter type is classified as livedo racemosa in the European literature. Livedo reticularis is observed in 20–50% of patients with APS.

The skin ulcers most commonly associated with APS are small ulcers secondary to necrotizing purpura. They are usually 0.5–3 cm in diameter and occur on the ankles, feet, calves and leave a white atrophic scar (atrophie blanche) after healing. Other large ulcers are reminiscent of pyoderma gangrenosum. Postthrombotic ulcers may also occur.

Large areas of skin necrosis, finger and toe gangrene, malignant atrophic papulosis-like lesions, multiple subungual splinter hemorrhages, anetoderma and melanoderma are also associated with APS.

Renal Manifestations

In APS clots may form in the arteries and veins as well as in the glomerular capillaries, which can result in proteinuria, hypertension, renal cortical infarction, and renal failure. A correlation between vessel transplant thrombosis in chronic dialysis patients and aPL has also been reported.

Various Other Organ Manifestations

Addison's disease due to thrombosis of the adrenal vessels, intestinal vessel occlusion with intestinal necrosis, and Budd-Chiari syndrome with hepatic vein thrombosis may also occur in APS. Hepatic artery occlusion with liver infarction, fibrin thrombi in the lesser liver vessels with hepatomegaly and increased enzyme activity, splenic infarction and occlusion of other organ vessels are less common.

aPL in Infectious Diseases

There is a strong correlation between aPL and infectious diseases. Syphilis was the first infectious disease in which anticardiolipin antibodies were identified as the 'reagin'. AIDS, malaria, borreliosis, leprosy, tuberculosis, and streptococcal, mycoplasmal, salmonella and coli infections as well as measles, mumps and infectious mononucleosis are associated with aPL at various rates of frequency. In infectious diseases, aPL do not need β_2 -GPI for binding in enzyme-linked immunosorbent assays (ELISA), nor are they associated with the development of the clinical symptoms of APS. Hence, the pathogenetic importance of aPL associated with infectious diseases is fundamentally different from that in SLE and PAPS.

Laboratory Diagnosis

aPL can be detected using the lupus anticoagulant (LA) test or immunological tests.

Lupus Anticoagulant

The LA test was originally used in patients with SLE [3]. By definition, LA consists of immunoglobulins that interfere with one or more in vitro phospholipid-dependent coagulation tests. Several methods of LA testing have been developed because of the heterogeneity of LA, among other things. Since none of these methods cover all variants of LA, the SSC Subcommittee for Standardization of Lupus Anticoagulants published a set of guidelines and revised criteria for testing [28, 29]. In accordance with these guidelines, multi-step LA testing is recommended according to the following scheme:

- (1) abnormal screening test;
- (2) demonstration that the abnormality of the screening test is due to an inhibitor;
- (3) demonstration that the inhibitor is PL dependent, and
- (4) confounding coagulopathies (e.g., FVIII, FIX) ruled out.

LA Screening Tests. The most commonly used screening tests for the detection of LA are the activated partial thromboplastin time (APTT), kaolin clotting time (KCT), and diluted Russell viper venom time (dRVVT) tests. These tests may exhibit extremely variable differences in sensitivity and specificity depending on the manufacturer. It is therefore recommended to perform two independent screening tests in doubtful cases. Additional screening tests include the tissue thromboplastin inhibition (TTI) test, plasma clotting time (PCT) test, and the textarin clotting time test [review in ref. 29, 30].

Identification of LA as Inhibitor. The identification of LA as the inhibitor is achieved using a plasma exchange technique. In the presence of LA, the extended clotting time cannot be corrected by addition of normal plasma. These plasma exchange techniques are poorly standardized, and they are affected by a number of variables.

Confirmation Tests. The most commonly used confirmation tests include the platelet neutralization test and various modifications of the dRVVT, TTI and APTT tests [review in ref. 29, 30].

Immunological Tests

In addition to the aforementioned coagulation tests, aPL diagnosis should always include immunological determination of aPL. Since the introduction of the radioimmunoassay by Harris et al. [9] and the introduction of the ELISA shortly thereafter [10], immunological determination of aPL is almost always performed using the ELISA (table 1).

For the sake of completeness, we also mention the use of FACS analysis for the determination of aCL [31].

The principle of the ELISA is based on the binding of cardiolipin or other phospholipids (e.g., phosphatidylserine, phosphatidic acid, phosphatidylethanolamine) to the ELISA plate and subsequent binding of aPL and detection of the bound antibodies with an enzyme-labeled isotype-specific anti-human antibody.

Although the principles of these tests are the same as those of any ELISA test, many modifications specific to anticardiolipin tests have been introduced. The sensitivity and specificity of the anticardiolipin test and other antiphospholipid tests depend on a few factors enumerated below and the experience of the tester.

Pre-Analytical Considerations. Immunological aPL tests can be performed in serum as well as in plasma. Lipemic sera should not be used in testing. Repeated freezing and thawing of the sera can lead to false-positive test results.

Purity of the Antigen. The purity of the antigen (>98%) is of immense significance for the specificity of the test.

Antigen Presentation. Besides the phosphodiester groups, the glyceride portion including the fatty acid chains is important for antibody binding [32–34]. ELISA plates are often coated with cardiolipin or phosphatidylserine in ethanol, then evaporating the ethanol to dryness (either by exposure to air or nitrogen).

As Rauch and Janoff [35] showed using the example of phosphatidylethanolamine, the phospholipid bilayer that forms in these methods has only limited reactivity with aPL. Only the hexagonal structure (H_{II}) of phospholipid generates epitopes that react with aPL.

Blocking Medium. As already mentioned, the anticardiolipin test originally had many shortcomings. The use of fetal calf serum (FCS) or adult bovine serum instead of gelatin to block the plates increased the sensitivity of the ELISA.

Dilution Buffer. In 1984 and 1985, some investigators [10, 36] observed a sharp increase in the readings of positive samples relative to negative controls when about 10% (v/v) FCS or adult bovine serum in phosphate-buffered saline was used as the serum diluent. aPL require a cofactor for phospholipid binding. In 1990, several groups [11–13] reported that β_2 -GPI is such a cofactor, and that the aPL are directed against a complex of phospholipid and β_2 -GPI. This explains why the assay was more sensitive with 10% FCS or bovine serum. The amount of β_2 -GPI used as the blocking medium and in the dilution buffer has a decisive effect on the sensitivity and specificity of ELISA aPL determinations. The concentration of β_2 -GPI in FCS is approximately 600 $\mu\text{g/ml}$. Hence, the concentration of β_2 -GPI is approximately 60 $\mu\text{g/ml}$ in dilution buffers containing 10% FCS. The β_2 -GPI concentration is only 2 $\mu\text{g/ml}$ at the 1:100 dilution generally used in ELISA systems. Therefore, the serum concentration of β_2 -GPI is not high enough to achieve sufficient sensitivity or, especially, specificity. For reasons of standardization, defined amounts of human β_2 -GPI should be added to the dilution buffer. The use of Tween 20 in the sample dilution buffer is a controversial issue in the literature. Last but not least, the ion strength of the dilution buffer has a great effect on the signal-to-noise ratio [34].

Incubation Time. The incubation time must be long enough (approximately 1 h) to ensure solid-phase saturation and, hence, the binding of even low-avidity antibodies [37]. Incubation of the plates at 37°C seems to yield nonvalid results.

Isotypes. Determination of the IgG, IgM, and IgA isotypes is of great clinical importance (see above) and is

dependent on the specificity of the conjugates used for determination.

Quantitative Analysis. A quantitative analysis of aPL using standards should be performed, first, because the curve is sigmoidal and nonlinear and, second, because the aPL titer is important for establishing the diagnosis as well as for assessing the course of the disease (see above). A minimum of five standard points should be used. Despite numerous efforts, the standardization of the available ELISA still leaves a lot to be desired. Lyophilized standards, first for IgG and IgM antibodies and later for IgA antibodies, have been introduced as a result of international workshops [38, 39]. One GPL unit was thereby defined as 1 $\mu\text{g/ml}$ of IgG antibody and MPL and APL units were similarly defined as 1 $\mu\text{g/ml}$ IgM and IgA antibodies, respectively. Hence, these antibodies obtained by affinity chromatography were standardized according to mass units, not immunological activity. Because of non-uniform cut-off computations among other things, the aPL prevalences given in the literature tend to vary. According to accepted criteria of the signal-to-noise theory, the cut-off value should be calculated as ' $x + 3s$ ', where ' x ' is the mean of a sufficiently large group of healthy controls and ' s ' represents the standard deviation [40].

β_2 -Glycoprotein I Antibodies. In addition to the role of β_2 -GPI as a cofactor for aPL binding, several independent research groups [11–13] have shown that (at least a portion of) 'aPL' are directed against β_2 -GPI and that they can be detected in vitro if the antigen is coated on negatively charged surfaces. Matsuura et al. [41] showed that strong aPL binding occurs when β_2 -GPI is coated on electron or gamma-irradiated plates in the absence of anionic phospholipids. It is assumed that the β_2 -GPI undergo a conformational change that exposes the cryptic epitope that is the target for aPL.

β_2 -GPI antibodies are detected using only human β_2 -GPI isolated from human plasma by precipitating it with perchloric acid followed by heparin affinity chromatography and other chromatographic techniques if necessary. The initial perchloric acid precipitation step seems to be of importance for preventing proteolytic cleavage of β_2 -GPI, which is functionally inactive. The coating concentration of β_2 -GPI should range between 3 and 10 $\mu\text{g/ml}$. Absolutely lipid-free inert proteins such as bovine serum albumin should be used as the blocking medium. FCS is therefore not recommended as a blocking medium. Isotype determination is performed using monospecific conjugates purified by affinity chromatography. In addition to the IgG and IgM antibodies, determination of IgA antibodies also appears to play an important role [42].

Table 7. Exclusion criteria for primary APS [43]

Malar rash
Discoid rash
Oral or pharyngeal ulceration, excluding nasal septum ulceration or perforation
Frank arthritis
Pleuritis, in the absence of pulmonary embolism or left-sided heart failure
Pericarditis, in the absence of myocardial infarction or uremia
Persistent proteinuria >0.5 g/day, due to biopsy-proven immune-complex-related glomerulonephritis
Lymphopenia <1,000/ μ l
Antibodies to native DNA, by radioimmunoassay or Crithidia fluorescence
Anti-extractable nuclear antigen antibodies
Antinuclear antibodies of > 1:320
Treatment with drugs known to induce aPL

In summary, it can be concluded that, according to the classification criteria for APS at least one laboratory parameter must be positive on two occasions at least 8 weeks apart in addition to the clinical criteria.

Diagnosis and Differential Diagnosis

The overlap of APS symptoms with those of other autoimmune diseases, especially systemic lupus erythematosus, is of particular importance. The criteria in table 7 were therefore developed for exclusion of SLE and PAPS.

Therapy

The optimal therapy for APS is still being debated because of the lack of large-scale treatment studies. Patients with acute vessel occlusion may receive fibrinolytics if there are no contraindications. After the first incidence of phlebothrombosis, the patient must receive sufficient continuous anticoagulation with coumarin derivatives. Retrombosis often occurs within 1 year after discontinuation of anticoagulants.

Recurrent thrombotic complications are also to be expected in arterial thrombosis (particularly stroke) associated with high titers of aCL-IgG or LA. Anticoagulation therapy with platelet aggregation inhibitors should also be considered in this case.

The concomitant occurrence of thrombocytopenia and thrombosis is of major importance. These patients re-

quire especially careful monitoring. Khamashta [44] recommended the following procedure: anticoagulation with an international normalized ratio of 2.0–3.0 in platelet counts of 50–100 GPT/l, and additional corticosteroid administration in platelet counts of less than 50 GPT/l. Dapsone, danazol and chloroquine were reported to have positive effects, even in corticosteroid-resistant thrombocytopenia. Potential interactions with azathioprine and warfarin must be taken into account if administered simultaneously. When azathioprine is discontinued, the anticoagulant effect of warfarin is increased, and bleeding may occur. Fibrinolysis and plasmapheresis have been tried in 'catastrophic' antiphospholipid syndrome.

Various therapies have been used for treatment of recurrent abortion: low-dose aspirin, prednisone, low-dose heparin, intravenous high-dose immunoglobulin, and various combinations.

Based on the data of the available studies [45], the following recommendations can currently be made regarding prophylaxis in women with a history of abortions and positive aPL tests:

- 75 mg of aspirin per day after diagnosis of pregnancy;
- After detection of fetal heart sounds, additional dosage of unfractionated heparin (e.g., 5,000 units every 12 h) or
- low-molecular heparin (5,000–10,000 units per day);
- therapy can be discontinued in the 34th gestational week; if there is a history of thrombosis, anticoagulation can be continued for 6 weeks or, better yet, 2 months postpartum;
- due to the risk of heparin-induced osteoporosis, calcium supplements, vitamin D₃, and 1 h of fast walking or other physical activity are also recommended.

If the recommended therapy fails to achieve satisfactory results or if thrombocytopenia is corticosteroid-resistant, intravenous high-dose immunoglobulin administration (very expensive) in conjunction with low-dose aspirin can also be considered in isolated cases [review in ref. 46]. Women with aPL should not take estrogen-containing contraceptives, because they significantly increase the risk of thrombosis in these patients.

In patients with underlying SLE, treatment of the underlying disease depending on its activity level and organ manifestations is also recommended in addition to all measures against hemostasis (the prophylactic effects of chloroquine and hydroxychloroquine have also been discussed in recent years). Immunosuppressive therapy alone is not sufficient in patients with thrombotic complications.

Prophylactic treatment of patients with persistent aPL or LA but no clinical symptoms of APS remains questionable. We still do not understand why some of these patients develop thrombosis and others do not. It is absolutely essential to eliminate all additional risk factors for the development of thrombosis (e.g., hypertension, hypercholesterolemia, smoking, or estrogen-containing contra-

ceptives) in patients with LA and/or aPL. Khamashta and Hughes [47] recommend a dose 75 mg of aspirin per day in patients with persistent LA and/or moderate or high IgG-aCL titers, even in those without a history of thrombosis. Careful clinical monitoring of this patient population is also necessary in light of their very high risk of thrombosis.

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