

Antiphospholipid syndrome

Author : Doctor Maria Tektonidou¹

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¹Consultant Rheumatologist, Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias street, 11527 Athens, Greece. balts@otenet.gr

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Abstract

The antiphospholipid syndrome (APS) is characterized by venous and/or arterial thrombosis, recurrent pregnancy loss and the presence of antiphospholipid antibodies. The antiphospholipid antibodies (anticardiolipin, anti-β₂GPI antibodies, lupus anticoagulant) interacting with various coagulation proteins, platelets or endothelial cells may contribute to disease pathogenesis. Incidence remains unknown, however the reported prevalence of antiphospholipid antibodies in the general population is low (1-4.5%) and increases with age. The main clinical manifestations associated with APS are thromboses, pregnancy morbidity, thrombocytopenia, neurological symptoms, livedo reticularis, hemolytic anemia. The antiphospholipid antibodies have been detected in approximately 1/3 of the patients with systemic lupus erythematosus (SLE). High anticardiolipin antibodies titers, lupus anticoagulant and especially anti-β₂GPI antibodies are important predictors of APS clinical manifestations in SLE patients. The management of thrombosis includes long-term, high-intensity warfarin therapy [International Normalized Ratio (INR) superior or equal to 3]. For pregnancy morbidity the recommended therapy is low-dose aspirin (80 mg/day) plus subcutaneous unfractionated heparin or low-molecular-weight heparin.

Keywords

Antiphospholipid syndrome, anticardiolipin antibodies, anti-β₂GPI antibodies, lupus anticoagulant.

Disease name and synonyms

The antiphospholipid syndrome (APS) or Hughes syndrome is characterized by venous and/or arterial thrombosis, recurrent pregnancy loss and the presence of antiphospholipid antibodies.

The syndrome was first described in 1983 by Graham Hughes as anticardiolipin syndrome [1]. This term was then replaced by the term, antiphospholipid syndrome, when it became clear that antibodies against phospholipids other

than cardiolipin, were also associated with APS clinical manifestations.

The antiphospholipid antibodies mainly associated with APS are the following:

a) anticardiolipin antibodies (aCL) or antibodies against other negatively-charged phospholipids *i.e* phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol.

b) lupus anticoagulants (LAs) which are immunoglobulins directed against plasma proteins (prothrombin or annexin V) that are bound to phospholipids; LA blocks thrombin generation and therefore clot formation *in vitro*

c) anti-beta2 glycoprotein I (anti-beta-2GPI) antibodies which recognize a plasma protein known as apolipoprotein H or beta-2glycoprotein I and have higher specificity than aCL for thromboses [2].

When no other underlying disease is associated with APS, it is called "primary APS". It is called "secondary APS" when it is associated with other autoimmune diseases, especially systemic lupus erythematosus (SLE) [3]. The syndrome of acute vascular occlusion involving multiple organs occurs in a minority of patients with aCL and is defined as "catastrophic APS".

Excluded diseases/differential diagnosis

Since the main clinical manifestations of APS are thromboses (arterial and/or venous), other thrombophilic conditions should be ruled out.

The clinical conditions that have to be excluded for arterial thrombosis are cigarette smoking, hypertension, hyperlipidemia, diabetes mellitus, medications like oral contraceptives or estrogens, hyperhomocystinemia, polycythemia and hyperviscosity syndrome [4].

The acquired risk factors for venous thrombosis are immobilization, surgery, pregnancy, malignancies, oral contraceptives or estrogens, nephrotic syndrome, congestive heart failure or obesity.

Hereditary causes for thrombosis are rare. However, according to recent estimates, all the deficiencies of protein C, S antithrombin III, affecting less than 1% of the population, increase the risk of deep vein thrombosis approximately tenfold. Activated protein C resistance, caused by mutated factor V (Leiden), occurs in 20% of the patients with thrombosis increasing the risk about eightfold. A mutation in the 3-untranslated region of the prothrombin (factor II) *F2* gene (prothrombin 20210 A) increases the risk twofold to threefold. Hyperhomocystinemia and high concentrations of factor VIII are responsible for a significant proportion of thrombotic events (10% each). Other blood protein/platelet defects associated

with hypercoagulation are tissue plasminogen activator, plasminogen activator inhibitor and factor XII defects or dysfibrinogenemia [4] (table 1).

The above-mentioned congenital thrombophilic abnormalities have also been associated with increased risk of fetal loss, due to placental vascular disorders. Recurrent miscarriage has also to be differentiated from other anatomic, chromosomal or endocrine causes.

ACQUIRED RISK FACTORS		CONGENITAL RISK FACTORS
Arterial thrombosis	Venous thrombosis	
Smoking	immobilisation	deficiency of protein C
Hypertension	surgery	deficiency of protein S
Diabetes mellitus	malignancies	deficiency of antithrombin III
Hyperlipidemia	nephrotic syndrome	activated protein C resistance (factor V Leiden)
Oral contraceptives	oral contraceptives	prothrombin 20210 allele
Polycythemia	congestive heart failure	plasminogen activator inhibitor-1 polymorphisms
Hyperviscosity	syndrome obesity	increased factor VIII
		factor XII defects
		dysfibrinogenemia
		homocysteinemia

Table 1. Risk factors for thrombosis

Diagnosis criteria/definition

Diagnostic criteria for APS were first described by Asherson. They included thrombosis (arterial and/or venous), recurrent abortions (>2), thrombocytopenia and positive aCL or LA, occurring twice with an interval of at least 3 months. Alarcon-Segovia *et al.* suggested more detailed clinical criteria (arterial and/ or venous thrombosis, recurrent fetal loss, livedo reticularis, hemolytic anemia, leg ulcers) and introduced classification groups according to the number of clinical manifestations and the aCL titers (definite, probable and possible APS).

In 1998, during the 8th symposium on antiphospholipid antibodies, preliminary consensus classification criteria for APS were established [5]

Definite APS was considered to be present when at least one clinical criterion and one of the following laboratory criteria were met:

Clinical criteria: one or more episodes of venous, arterial or small vessel thrombosis and/or pregnancy morbidity.

Pregnancy morbidity was defined as follows:

a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or

- b) one or more premature deaths at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or
 c) three or more unexplained consecutive abortions before the 10th week of gestation (anatomic, hormonal or chromosomic causes are excluded).

Laboratory criteria: IgG and/or IgM aCL in medium or high titers measured by a standard enzyme-linked immunoassay and/or LA detected according to the guidelines of the International Society of Thrombosis and Hemostasis, twice or more, with an interval of at least 6 weeks between tests. Thus, in clinical practice a diagnostic workup for antiphospholipid antibodies should be considered in all patients with venous or arterial thrombosis and fetal loss for which there is no alternative explanation, particularly in the presence of recurrent manifestations.

Prevalence

Actual frequency of APS in the general population is unknown. No defined racial predominance exists for primary APS, although a higher prevalence of SLE occurs in black and Hispanic populations. A female predominance exists, particularly for secondary APS.

The reported prevalence of antiphospholipid antibodies in the general population is low (1-4,5%), and increases with age [6]. In patients with venous thrombosis the presence of antiphospholipid antibodies varied from 3% to 17% [7]. The frequency of aCL in patients with arterial thrombosis such as myocardial infarction and recurrent stroke ranged between 5-15% and 5-46% respectively in different studies. The strongest association has been found in patients with stroke under the age of 50 years.

Tests for aCL are positive in nearly 1/3 of patients with SLE. The occurrence rate of APS in patients with SLE is 34-42%. High anticardiolipin antibodies titers, lupus anticoagulant and especially anti- β 2GPI antibodies are important predictors of APS clinical manifestations in SLE patients [8].

In women with recurrent abortions the strongest association with aCL was found with the mid-trimester pregnancy losses.

Antiphospholipid antibodies have also been found in patients with infection (human immunodeficiency virus HIV, syphilis, leprosy, hepatitis C, cytomegalovirus CMV) and patients taking certain drugs. These antibodies do not show anti- β 2GPI activity and, in general, they are not associated with thrombotic events.

Clinical description

In APS, thrombosis may occur in any part of arterial and venous circulation. Thus, every organ system can be affected by a broad spectrum of clinical manifestations leading to chronic, slow but progressive organ dysfunction. These include:

Cerebrovascular manifestations: cerebral ischemia (arterial thrombosis involves the brain in up to 35% of cases, causing transient ischemic attacks or strokes [21]), venous sinus thrombosis, chorea, migraine, transverse myelopathy, seizures, Sneddon syndrome, multi-infarct dementia, retinal venous thrombosis, multiple-sclerosis-like symptoms, psychosis.

Cardiac manifestations: valvular disease (most commonly mitral regurgitation) affects 10-35% of the patients [21], Libman-Sachs endocarditis, coronary artery disease, cardiomyopathy, intracardiac thrombosis.

Vascular disease: peripheral deep vein or recurrent superficial thromboses. Venous thrombosis, particularly of the lower limb, occurs in up to 50% of patients with the syndrome.

Pulmonary manifestations: pulmonary embolism, pulmonary hypertension, intraalveolar pulmonary hemorrhage, adult respiratory distress syndrome (ARDS), fibrosing alveolitis.

Renal manifestations: renal vein and/or artery thrombosis (main branches), glomerular and small artery thrombosis, cortical atrophy.

Endocrine system disease: Addison's disease, hypopituitarism.

Hematological manifestations: thrombocytopenia, autoimmune hemolytic anemia, bleeding (extremely rare)

Gastrointestinal manifestations: Budd-Chiari syndrome, esophageal necrosis, intestinal ischemia, hepatic necrosis.

Skin manifestations: livedo reticularis, skin ulceration, cutaneous necrosis and infarction, gangrene of digits, splinter hemorrhage (table 2).

Obstetric manifestations: The risk of pregnancy loss in women with antiphospholipid antibodies is greatest from the 10th week of gestation onward (fetal period). This is in contrast to pregnancy loss in the general population, which is most frequent during the first 9 weeks of gestation. The complications in pregnancy can also include preterm labor, low birth weight, preeclampsia, and stillbirth.

A minority of patients with APL syndrome (0.8%) may present a multiorgan venous or arterial thrombosis with rapid onset and high mortality (50%). In recognition of the dramatic nature of the clinical presentation, this has been called "catastrophic" antiphospholipid syndrome [22]. Typically, there is an acute thrombotic

microangiopathy affecting small-calibre blood vessels in multiple organs: 50% of cases included the kidneys, lungs, central nervous system, heart and skin. In about 25% of the cases it may be complicated by disseminated intravascular coagulation.

Clinical manifestations	percentage (%)
Livedo reticularis	49
Thrombosis	
venous	43
arterial	5
CNS involvement	44
Thrombocytopenia	41
Recurrent abortions (>2)	26
Hemolytic anemia	23
Leg ulcers	8

Table 2. Prevalence of clinical manifestations in 82 APS patients (M.Tektonidou, *et al.* QJM 2000;9:523-30)

Management of thrombosis

Treatment with intravenous heparin or low-molecular-weight heparin (LMWH) is started, when a thrombotic event and the specific laboratory tests are documented and when other thrombophilic causes are excluded. The dose of warfarin is gradually increased until a therapeutic level is achieved (heparin is then discontinued). The risk of recurrent thrombotic events in patients with APS is high with a tendency arterial thrombosis to be followed by another venous thrombosis [9,10]. Low-dose aspirin alone or low-intensity warfarin does not prevent the recurrence. High-intensity-dose warfarin [International Normalized Ratio (INR)>3] and long-term therapy are indicated, especially in arterial thromboses [10]. In patients with recurrent thromboses despite warfarin treatment, increased warfarin dose to achieve higher INR and additional therapy with low-dose aspirin are recommended. The incidence of bleeding complications in these patients is much lower than the benefit of long-term anticoagulation. There is a general agreement that patients with recurrent thrombotic episodes (20% to 70% of the cases) require life-long anticoagulation therapy. Patients with catastrophic antiphospholipid syndrome are usually treated with full anticoagulation (though it may be refractory to anticoagulant therapy alone), and data from uncontrolled studies have suggested that plasmapheresis may improve survival [22].

Prophylaxis in asymptomatic patients with positive aCL or LA

Avoiding of risk factors for thrombosis such as smoking, oral contraceptives, hyperlipidemia,

hypertension or diabetes, is primarily recommended. In clinical practice, treatment with low-dose aspirin is empirically used although no prospective study has examined the role of prophylactic management. Hydroxychloroquine as an antiplatelet agent has been referred in SLE patients and animal models. Low-intensity INR has also been proposed as a prophylactic therapy by some authors. Full anticoagulation is not indicated in the absence of significant clinical manifestations of the syndrome, particularly thrombosis.

Management of pregnancy

In women with previous thrombosis or pregnancy morbidity as described before, the recommended therapy is low dose aspirin (80 mg) with subcutaneous unfractionated heparin (10.000 units every 12 hours) or LMWH [11]. Use of corticosteroids has been associated with various maternal and fetal complications and is generally avoided. LMWH is commonly used in APS because of single dosing per day and lower risks of hemorrhage, thrombocytopenia and osteoporosis than unfractionated heparin, although it is more expensive. Initial weight-adjusted dose for enoxaparine is 1 mg/kg and 50 U/kg for dalteparine. Treatment should begin as soon as a viable intrauterine pregnancy is documented. LMWH should be discontinued at the 36th week of gestation and replaced by unfractionated heparin. In women who present adverse pregnancy outcomes despite treatment, other less well-studied therapies (immune globulin, plasmapheresis or azathioprine) are introduced [12].

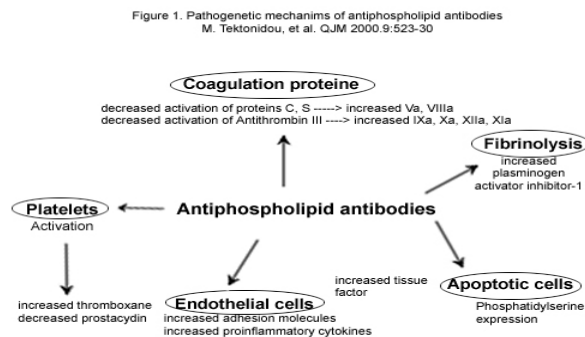
Prophylaxis in women with positive aCL without a history of pregnancy morbidity has not been clearly identified. In clinical practice, persistently positive aCL are usually treated with low-dose aspirin (80 mg daily).

Etiology

APS is an autoimmune disorder of unknown cause. Antibodies against negatively-charged or neutral phospholipids or phospholipid-binding proteins (β 2GPI, prothrombin, annexin V) interacting with different coagulation proteins (protein C, S, thrombomodulin), platelets and vascular endothelial cells, contribute to APS pathogenesis. The exact mechanism by which antiphospholipid antibodies induce a thrombophilic state is not known. A number of pathogenetic mechanisms have been proposed: inhibition of protein C, S and antithrombin III activity, increased platelet adhesion and aggregation, activation of vascular endothelium, impaired prostacyclin production and increased

thromboxane production, inhibition of fibrinolysis, increased monocyte expression of tissue factor, exposure of anionic phospholipids on the surface of apoptotic cells leading to specific interaction with circulating phospholipid-binding proteins [13,14] (figure 1).

Pregnancy morbidity in APS has been associated with decidual vasculopathy and placental infarction. Inhibition of trophoblast proliferation by anti-β2GPI antibodies, displacement of annexin V from trophoblast membranes by antiphospholipid antibodies and antibodies against trophoblasts, have also been implicated to the pathogenesis [15].



Genetic factors

Family studies have suggested that genetic factors may trigger APS. Approximately 1/3 of the close relatives of APS patients have aCL. 16 HLA specificity most often reported in aCL-positive patients are HLA-DR4, DR53, DQB1*0303 (DQ7), and DR5 in Mexicans. It was also shown that certain HLA class II alleles (HLA-DQB1*0302, DQA1*0301) and the HLA-DRB1*1302 - DQB1*0604 haplotype have been strongly associated with anti-β2GPI antibodies. 17 Other studies also provided evidence that antiphospholipid antibodies were associated with haplotypes containing deficiency alleles of the fourth complement component, C4.

Diagnostic methods

Laboratory examinations include solid-phase assays for antiphospholipid antibodies and coagulation-based tests for LA. The first aCL test by an enzyme-linked immunoassay was established in 1983. Commercial reagents and kits can be found easily now. National and

international workshops have contributed to the standardization of the method. Despite these efforts, a considerable degree of variations between laboratories still exists. The aCL test has > 98% sensitivity and 60% specificity [18].

Guidelines on LA performance have been published [19]. The basic criteria for the presence of LA are the following:

- prolongation of a phospholipid-dependent test,
- correction of the prolonged coagulation studies by mixing with normal platelet-poor plasma,
- confirmation of the phospholipid-dependent nature of the inhibitors,
- exclusion of other coagulopathies.

There is no standardized assay for LA activity. The characteristics of the reagents, the concentration of clotting factors and the presence of other inhibitors influence LA sensitivity. Therefore at least two tests should be performed when the clinical index of suspicion is high. The tests most widely used are the activated partial thromboplastin time (aPTT), dilute Russell's viper venom time (dRVVT) and kaolin clotting time (KCT). The dRVVT is more specific than KCT, since fewer coagulation reactions are involved. Other less used LA screening tests are the dilute thromboplastin time, the textarin and Taipan time.

If any of these tests is negative, then a more specific test should be performed such as anti-β2GPI or AphL ELISA Kit. The anti-β2GPI ELISA, performed in a phospholipid free fashion, has 74% sensitivity and 82% specificity. The AphL ELISA Kit, utilizing a mixture of negatively charged phospholipids as antigen, was shown to be 98% sensitive and 99% specific [18]. A broader range of antibodies (VDRL, aCL, other antiphospholipid antibodies, anti-β2GPI, anti-prothrombin) in patients with thrombotic events may better delineate the syndrome.

Genetic counseling

Genetic counseling in APS cannot be given.

Unresolved questions

After the first description of APS, important information has been accumulated about this heterogeneous syndrome. However, different questions remain unanswered concerning pathogenesis, diagnosis or treatment. Mechanisms induced thrombosis, the site of antibody attack, relation with other coagulopathies, other APS-related clinical manifestations (migraine, cognitive dysfunction, pulmonary hypertension, livedo reticularis, seizures) and their pathogenesis,

antiphospholipid antibodies as a risk factor for atherosclerosis, specificity of laboratory tests, treatment decisions and long-term prognosis, are some of the various questions and proposals for investigation [20].

References

1. Hughes GR. Thrombosis, abortion, cerebral disease and the lupus anticoagulant. *Br Med J* 1983;287:1088-9.
2. Mc Neil HP, Simpson RJ, Chesterman CN, Krillis SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta2-glycoprotein I (apolipoprotein H). *Proc Natl Acad USA* 1990;87:4120-4.
3. Vianna JL, Khamashta MA, Ordi-Ros J, *et al.* Comparison of the primary and secondary antiphospholipid syndrome: an European multicenter study of 114 patients. *Am J Med* 1994;96:3-9.
4. Fessler BJ. Thrombotic syndromes and autoimmune diseases. *Rheum Dis Clin North Am* 1997;23:461-79.
5. Wilson WA, Gharavi AE, Koike T, *et al.* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;42:1309-11.
6. Manoussakis MN, Tzioufas AG, Silis MP, *et al.* High prevalence of anticardiolipin and other autoantibodies in healthy elderly population. *Clin Exp Immunol* 1987;68:557-65.
7. Manoussakis MN, Gharavi AE, Drosos AA, Moutsopoulos HM. Anticardiolipin antibodies in unselected autoimmune rheumatic disease patients. *Clin Immunol Immunopathol* 1987;44:297-307.
8. Tektonidou MG, Ioannidis JPA, Boki KA, Vlachoyiannopoulos PG, Moutsopoulos HM. Prognostic factors and clustering of serious clinical outcomes in antiphospholipid syndrome. *QJM* 2000;93:523-30.
9. Vlachoyiannopoulos PG, Tsiakou E, Chalevelakis G, Raptis SA, Moutsopoulos HM. Antiphospholipid syndrome: clinical and therapeutic aspects. *Lupus* 1994;3:91-6.
10. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid antibody syndrome. *N Engl J Med* 1995;332:993-7.
11. Rai R, Cohen H, Dave M, Regan L. Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;314:253-7.
12. Branch DW, Peaceman AM, Druzin M, *et al.* A multicenter placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. *Am J Obstet Gynecol* 2000;182:122-7.
13. Gharavi AE, Pierangeli SS, Colden-Stanfield M, Liu XW, Espinola RG, Harris EN. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in vivo and in vitro. *J Immunol* 1999;163:2922-7.
14. Amengual O, Atsumi T, Khamashta MA, Hughes GR. The role of the tissue factor pathway in the hypercoagulable state in patients with the antiphospholipid syndrome. *Thromb Haemost* 1998;72:276-81.
15. Rand JH, Wu XX, Andree HA, *et al.* Pregnancy loss in the antiphospholipid antibody syndrome. A possible thrombogenic mechanism. *N Engl J Med* 1997;337:154-60.
16. Goel N, Ortel TL, Bali D, *et al.* Familial antiphospholipid syndrome: criteria for disease and evidence for autosomal dominant inheritance. *Arthritis Rheum* 1999;42:318-27.
17. Ioannidis PA, Tektonidou MG, Vlachoyiannopoulos PG, *et al.* HLA associations of anti-beta2glycoprotein I response in a Greek cohort with antiphospholipid syndrome and meta-analysis of four ethnic groups. *Hum Immunol* 1999;60:1274-80.
18. Harris EN, Pierangeli SS. 'Equivocal' antiphospholipid syndrome. *J Autoimmunity* 2000;15:81-5.
19. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Haemost* 1995;74:1185-90.
20. Lockshin MD. Prognosis and future directions. In: Hughes's syndrome, antiphospholipid syndrome. Khamashta MA, ed. Springer, London, pp.459-62, 2000.
21. Cervera R, Piette JC, Font J, *et al.* Antiphospholipid syndrome: Clinical and immunological manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002;46:1019-27.
22. Hanly JG. Antiphospholipid syndrome: an overview. *CMAJ*. 2003;168:1675-82. Asherson RA, Cervera R, Piette JC, *et al.* Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;77:195-207.