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Clinical and epidemiological aspects in the antiphospholipid syndrome

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Abstract

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and pregnancy morbidity (mainly, recurrent fetal losses and premature births), frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or both. Other autoantibodies have also been detected in many patients with an APS, such as anti-β2 glycoprotein I (GPI), antimitochondrial (M5 type), antiendothelial cell, antiplatelet, antierythrocyte, and antinuclear antibodies.
The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases. Systemic lupus erythematosus (SLE) is the disorder in which an APS is most commonly associated. Less frequently, aPL and, rarely, an APS may also be encountered in other groups of patients (Table 1) (1).

Clinical presentation

"Simple" or "classic" syndrome

The clinical picture of the "simple" or "classic" APS is characterized by venous and arterial thromboses, pregnancy morbidity and thrombocytopenia.

Deep vein thrombosis (occasionally superficial thrombophlebitis) particularly affecting the veins of the lower limbs are the commonest venous occlusions seen. Strokes, often preceded by transient ischemic attacks, are the most frequent arterial events encountered in these patients. However, not only may a large variety of both veins and arteries be affected but small vessels might also be involved. Therefore, many diverse clinical manifestations due to vascular occlusions in the central nervous system, heart, lungs, liver, adrenal glands, kidneys, skin, eyes, etc, may now be associated with the presence of aPL. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations (Table 2). Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years (2–25).

Pregnancy morbidity in the APS includes recurrent fetal losses and premature births. Fetal losses can occur in any trimester of pregnancy, although they are commoner in the second and third trimester. There are a number of mechanisms that have been proposed in order to explain how these pregnancy complications occur. The most accepted implies that they are associated with thrombosis of the placental

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Table 1. Diseases with aPL

SYSTEMIC ATUTOIMMUNE DISEASES	INFECTIONS	MALIGNANCIES	NON-MALIGNANT HEMATOLOGIC CONDITIONS
Systemic lupus erythematosus	Viral	**Solid tumors**	Idiopathic thrombocytopenic purpura
Rheumatoid arthritis	HIV infection	Lung	Sickle cell disease
Systemic sclerosis	Mononucleosis	Colon/Caecum	Pernicious anemia
Primary Sjögren's syndrome	Rubella	Cervix	
Dermato- and polymyositis	Parvovirus	Prostate	DRUGS
Psoriatic arthropathy	Hepatitis A, B, C	Liver	Procainamide
Vasculitis	Mumps	Kidney (hypernephroma)	Phenothiazines
Polyarteritis nodosa/microscopic polyarteritis	Bacterial	Thymus (thymoma)	Ethosuximide
Giant cell arteritis	Syphilis	Maxilla	Chlorothiazide
Behçet's disease	Lyme disease	Ovary	Quinine
Relapsing polychondritis	Tuberculosis	Breast	Oral contraceptives
Leucocytoclastic vasculitis	Leprosy	**Hematologic**	OTHER CONDITIONS
Mesenteric inflammatory veno-occlusive disease	Infective endocarditis	Myeloid and lymphatic leukemias	Diabetes mellitus
Capillaritis	Rheumatic fever	Polycythemia vera	Autoimmune thyroid disease
Other vasculitis	*Klebsiella*	Myelofibrosis	Inflammatory bowel diseases
	Protozoal	**Lymphoproliferative diseases**	Dialysis
	Malaria	Hodgkin's disease	Klinefelter's syndrome
	Toxoplasmosis	Non-Hodgkin's lymphoma	
		Lymphosarcoma	
		Cutaneous T-cell lymphoma/Sézary syndrome	
		Paraproteinemias	
		Monoclonal gammapathies	
		Waldenström macroglobulinemia	
		Myeloma	

vessels and subsequent infarction resulting in placental insufficiency, fetal growth retardation, and ultimately fetal loss. Not all placentas examined, however, have shown areas of thrombosis or infarction and other mechanisms may be operative in these patients.

"Catastrophic" syndrome

This term was first used in 1992 (26) to define an accelerated form of the APS with consequent multiorgan failure. Here the predominant disturbance is on small vessels as opposed to large veins and arteries, which are predominantly involved in patients with "simple" APS.

Currently, more than 150 patients have been described suffering from this initially seemingly rare manifestation of the APS (27–31). From an analysis of these patients, all of whom demonstrated multiple occlusive events over a short period of time (days to weeks), it is clear that the vast majority in fact did not suffer from SLE or "lupus-like" disease, but from primary APS. A smaller number have had either rheumatoid arthritis, primary Sjögren's syndrome or systemic sclerosis. Precipitating factors, as in patients with the "simple" APS, included surgical procedures (both major and minor), infections, oral contraceptive therapy and anticoagulation withdrawal. "Catastrophic" APS occurred in the postpartum period in several patients. Multi-organ presentation and failure was the rule and most patients with catastrophic APS end up in intensive care units with physicians belonging to a wide variety of specialities in attendance. Renal and pulmonary involvement predominate, the majority of patients showing severe renal impairment. Approximately one third developed adult respiratory distress syndrome (ARDS). 50% demonstrate cerebral symptomatology – drowsiness and confusion may end in coma. Gastrointestinal, cardiac, hepatic, adrenal and pancreatic disturbances might occur. There is an abnormally high frequency of hypoadrenalism, often seen together with ARDS. Unusual organ involvement, such as testes and prostate, has been documented. Skin manifestations are also frequent. High levels of IgG aCL are found in more than 50% and thrombocytopenia may be severe. Hemolytic anemia and evidence of disseminated intravascular coagulation (DIC) may be evident. Death occurred in 50%. At *post-mortem*, overwhelming evidence of microthrombotic occlusive disease of small vessels was evident ("thrombotic microangiopathy"). Many organs, including particularly the kidneys, brain and heart, were affected by this process. A minority only of patients demonstrated large vessel occlusions (veins and arteries) in

Table 2. Clinical manifestations of the APS

LARGE VESSEL
Deep vein thrombosis
Large peripheral arterial occlusions
Aortic occlusions

CARDIAC
Myocardial infarction
Unstable angina
Coronary by-pass graft and angioplasty occlusions
Cardiomyopathy
  Acute
  Chronic
Valvular disease
  Valve thickening and deformity
  Vegetations
  Pseudo-infective endocarditis
Intracardiac thrombus
Cyanotic congenital heart disease
Complications of cardiovascular surgery

OBSTETRIC
Maternal complications
  Toxemia
  Pre-eclampsia
  HELLP syndrome
  Cardio-pulmonary post-partum syndrome
  Chorea gravidarum
  Post-partum cerebral infarct
  Maternal death
Fetal complications
  Abortion
  Fetal death
  Intrauterin growth retardation

HEMATOLOGIC
Thrombocytopenia
Coombs' positivity and hemolytic anemia
Neutropenia

NEUROLOGIC
Trombotic infarctions
Sneddon's syndrome
Transient ischemic attacks
Multiinfarct dementia
Acute ischemic encephalopathy
Embolic stroke
Cerebral venous and dural sinus thrombosis
Psychosis
Cognitive defects
Transient global amnesia
Pseudomultiple sclerosis
Migraine and migranous stroke
Epilepsy
Movement disorders
  Chorea
  Hemiballismus
  Cerebellar ataxia
Spinal syndromes
  Transverse myelopathy
  Guillain-Barré syndrome
  Anterior spinal artery syndrome
  Lupoid sclerosis
Ophthalmic complications
  Retinal vascular occlusions
  Acute retrobulbar optic neuritis
  Ischemic optic atrophy

DERMATOLOGIC
Livedo reticularis
Skin ulcerations
Small painful leg ulcers of livedoid vasculitis
Cutaneous necrosis
Macules and nodules
Multiple subungual splinter hemorrhages
Gangrene and digital necrosis
Anetoderma
Discoid lupus
Intravascular coagulation necrosis of the skin
Pyoderma gangrenosum

PULMONARY
Pulmonary embolism and infarction
Pulmonary hypertension
Pulmonary arterial occlusions
  Major pulmonary arterial thrombosis
  Pulmonary microthrombosis
Adult respiratory distress syndrome
Intraalveolar pulmonary hemorrhage
Fibrosing alveolitis
Post-partum syndrome

RENAL
Glomerular capillary thrombosis in lupus nephritis
Intra-renal vascular lesions ("thrombotic microangiopathy")
Renal artery occlusions
Renal vein thrombosis

HEPATIC
Budd-Chiari syndrome
Portal hypertension
Hepatic veno-occlusive disease
Nodular regenerative hyperplasia
Hepatic infarction

DIGESTIVE
Esophageal necrosis
Gastric ulceration
Small and large bowel vascular occlusions
Mesenteric inflammatory vaso-occlusive disease
Inflammatory bowel disease
  Ulcerative colitis
  Crohn's disease
Pancreatitis
Cholecystitis
Occlusion of splenic vessels

contrast to patients with a "simple" APS and one can speculate as to whether the same etiopathogenic process is operating in this group of patients and whether the patients with catastrophic APS represent a rather different "subset" of patients with the APS in whom the accent of the disease is on the microvasculature particularly.

Preliminary criteria for classification

Preliminary classification criteria for the APS were formulated during a workshop in 1998 (32) in order to facilitate studies of treatment and causation (Table 3). It is hoped that they will be tested in prospective studies. However, it should be emphasized that these classification criteria are not intended to be used outside of the context of clinical and scientific investigations of APS.

Treatment

Elimination of aPL, particularly the LA, may be accomplished by several therapeutic regimens, including high dose steroid administration, immunosuppression (e.g. cyclophosphamide) or plasma exchange. The decrease or elimination is, however, temporary and antibodies rapidly return (within 1–3 weeks) on cessation of therapy. Therefore, therapy should not primarily be directed at effectively reducing the aPL levels and the use of immunother-

Table 3. Preliminary classification criteria for the antiphospholipid syndrome

Clinical criteria

Vascular thrombosis: One or more episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

Pregnancy morbidity:

a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by diret examination of the fetus, or

b. One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency, or

c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria

Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titer, on 2 or more occasions, at least 6 weeks apart, measured by a standardised enzyme-linked immunosorbent assay for β2-glycoprotein I-dependent anti-cardiolipin antibodies.

Lupus anticoagulant present in plasma, on 2 or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies) in the following steps:

a. Prolonged phospholipid-dependent coagulation demonstrated on a screening test, e.g. activated partial thromboplastin time, kaolin clotting time, dilute Russell's viper venom time, dilute prothrombin time, Textarin time

b. Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma. Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid. Exclusion of other coagulopathies, e.g. factor VIII inhibitor or heparin, as appropriate.

Definite APS is considered to be present if at least 1 of the clinical criteria and 1 of the laboratory criteria are met.

apy is generally not indicated, unless required for the treatment of the underlying condition, eg. SLE, or in acute life-threatening situations, such as the catastrophic APS.

Energetic attempts must be made to avoid or to treat any associated risk factors – e.g. antihypertensives, cholesterol-lowering agents, treatment of active nephritis, avoidance of smoking or sedentarism, etc. Care should be also taken with the administration of oral contraceptives.

Asymptomatic patient

Prophylaxis of arterial thrombosis in the general population is controversial, as it is in patients with aPL. However, there may be a case for the prophylactic treatment of individuals with high levels of IgG aCL or persistent LA activity with antiaggregants (aspirin, 75 – 150 mgr daily), specially in those with added risk factors.

On the other hand, prophylaxis of venous thrombosis is required for patients undergoing surgical procedures (particularly hip surgery), those requiring long stays in bed, or during the puerperium. The use of low-molecular weight subcutaneous heparin is recommended in those circumstances.

Treatment of thrombosis

A recent prospective study has found that in patients with a first event of venous thromboembolism treated for 6 months with oral anticoagulants, the risk of recurrence during the following 42 months is higher in those with elevated titres of aCL (33) and this agrees with previous retrospective studies in patients with primary APS or SLE (34 – 36). The predictive value of the aCL increases with the antibody levels (33, 37) but it has also been found an increased risk of recurrence at low titres. The risk of recurrence was markedly increased in the first 6 months after discontinuation therapy, suggesting a "rebound" phenomenon. Therefore, for patients who have already experienced thrombotic events, life-long treatment with anticoagulants is essential. Several important considerations need to be emphasized:

1. Anticoagulant resistance has been encountered in several of these patients, who may require up to 20 mg/day of warfarin in order to achieve an international normalized ratio (INR) within the therapeutic range (between 2 – 3). Although it has been proposed that the INR in patients with aPL should be kept at higher levels (between 3 – 4) (34), this recommendation awaits further prospective

randomized clinical trials – such as the WASP (Warfarin in the Antiphospholipid Syndrome Project)- in order to assess the risk/benefit ratio of high INR

2. Because of the common finding of fluctuating levels of the INR, frequent and regular visits to anticoagulation clinics are recommended, as well as education of patients and medical personnel as to the dangers of noncompliance as well as the taking of drugs which might interfere with the actions of warfarin and its absorption.

3. In the specific case of thrombotic stroke, in addition to the control of other risk factors, the use of newer antiplatelet agents and the role of aspirin/warfarin therapy await the results of the WARSS (Warfarin Aspirin Recurrent Stroke Study) and the AWAPLS (Aspirin and Warfarin in Antiphospholipid Syndrome) studies (36).

Prophylaxis of fetal losses

Low-dose aspirin (50 – 100 mg daily), administered from the begining of pregnancy until just prior to delivery, sometimes combined with daily subcutaneous heparin, especially in the face of previous fetal losses using aspirin, is the accepted standard for the prevention of fetal loss today. The risk of maternal osteoporosis may be minimized by the administration of low-molecular weight heparin, although this complication has also been occassionally encountered with this new heparin (38, 39). Warfarin administration should be discontinued as soon as pregnancy is diagnosed, since it is teratogenic.

In addition, close monitoring of pregnancy with doppler techniques, in order to detect early placental vascular insufficiency, and delivery with the first signs of fetal distress are mandatory. Other forms of therapy, such as intravenous gammaglobulin or plasmapheresis, have been attempted with some success in patients with particularly poor obstetric history.

Thrombocytopenia

The thrombocytopenia occuring during the course of the APS is usually mild and does not require any active intervention. However, in a minority of cases it can be severe and refractory to prednisone therapy. Low-dose aspirin and even warfarin has proved useful in some cases (40, 41), but its administration may not be without risk, especially in patients with less than 20 000 platelets/mm^3. In these cases, immunosuppressive therapy (eg. azathioprine), danazol (42), intravenous immunoglobulins, and even splenectomy, may be effective (43).

Catastrophic antiphospholipid syndrome

Despite the use of adequate anticoagulation with heparin, pulse steroids and cyclophosphamide, many of these patients still suffer from repeated thrombotic events. Plasma exchange or intravenous immunoglobulins are advised and most patients receiving any of these additional therapies have survived (28, 29).

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