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The Antiphospholipid Syndrome

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Abstract

The antiphospholipid syndrome (APS) defines the clinical association between antiphospholipid antibodies and a syndrome of hypercoagulability or thrombophilia (the term of "sticky blood" is sometimes used in APS).

Antiphospholipid antibodies comprise a broad family of antibodies including both lupus anticoagulants and anticardiolipin antibodies. The pathogenesis of APS remains unclear.

Nevertheless, an understanding of the biology, clinical and laboratory diagnosis, and clinical manifestations of APS are important to the neurologist because the brain is commonly affected by the disease. These points are addressed herein focusing on neurological manifestations of APS. Treatment of APS of which anticoagulation is the cornerstone is also discussed.

Definitions

The antiphospholipid syndrome (APS) was first described by Hughes in 1983 (1) : that is a thrombophilic disorder in which venous or arterial thrombosis, or both, may occur.

The term APS denotes the clinical association between antiphospholipid antibodies and thrombophilia (this being defined as a syndrome of hypercoagulability).

Antiphospholipid antibodies are serologic markers of the syndrome ; they are represented by anticardiolipin antibodies (ACA) and lupus anticoagulant (LA) or both.

APS often occurs in systemic lupus erythematosus (SLE) or other diseases : it is called "secondary" antiphospholipid syndrome.

Most patients, however, do not meet the criteria for SLE or other diseases : this condition wherein there is a combination of recurrent thrombosis and antiphospholipid antibodies is called the "primary" antiphospholipid syndrome.

Other features of APS are thrombocytopenia and recurrent spontaneous abortion.

Antiphospholipid antibodies

There are different subgroups of antiphospholipid antibodies (2), this classification being based on the method of detection.

1. LA antibodies

Lupus anticoagulant antibodies are identified by different coagulation assays, in which they prolong clotting times and were first described in patients with SLE hence their name.

They are associated with thromboembolic events rather than clinical bleeding what can sometimes give rise to confusion.

Ruling out the presence of LA antibodies needs that 2 or more assays sensitive to these antibodies evaluating distinct portions of the coagulation cascade are negative (2, 3).

LA antibodies cannot usually be detected in case of anticoagulant therapy.

2. Anticardiolipin antibodies

ACA are detected by immunoassays (usually enzyme-linked immunosorbent assays) that measure immunologic reactivity to a phospholipid (cardiolipin) or a phospholipid-binding protein (β_2-glycoprotein I) (2, 4).

The specificity of ACA for APS increases with titer and is higher for the IgG than for the IgM epitope (2).

3. Other antiphospholipid antibodies

There are antiphospholipid antibodies directed against phospholipids other than cardiolipin (e.g. phosphatidyl serine and phosphatidylethanolamine) and against phospholipid-binding proteins other than cardiolipin-bound β_2-glycoprotein I (e.g. annexin).

However, the clinical utility of these antibodies remains unclear and must not be at present considered to assess the diagnosis of APS.

Pathogenesis

The pathogenesis of APS remains unclear. Several hypotheses have been proposed to explain the thrombogenic mechanism of antiphospholipid antibodies (2). Briefly, four theories are suggested. The first one implicates activation of endothelial

Table 1

International consensus statement on preliminary classification criteria for APS

Clinical criteria

– Vascular thrombosis ;
  at least one clinical episode of arterial, venous, or small-vessel thrombosis, occuring within any tissue or organ.
– Complications of pregnancy :
  at least one unexplained dead of morphologically normal fetus ≥ 10 weeks of gestation OR
  at least one premature birth of morphologically normal neonate ≤ 34 weeks of gestation OR
  at least three unexplained consecutive spontaneous abortions < 10 weeks of gestation.

Laboratory criteria

– Anticardiolipin antibodies :
  IgG or IgM antibodies present at moderate or high level levels on two or more occasions at least six weeks apart, as measured by a standardized ELISA for β2-glycoprotein I-dependent ACA.
  Distinction between moderate or high levels of ACA and low levels has not been standardized. The used treshold separating low from moderate levels of ACA is 15-20 International "phospholipid" Units in many laboratories but other definitions exist.
– Lupus anticoagulant antibodies :
  LA antibodies on 2 or more occasions at least 6 weeks apart according to the guidelines of the International Society on Thrombosis and Haemostasis (3).

cells. The second theory focuses on oxidant-mediated injury of vascular endothelium : autoantibodies to oxidized LDL can occur in association with ACA and there may be a crossreaction (5). A third theory suggests that antiphospholipid antibodies could interfere with or modulate the function of phospholipid-binding proteins involved in the regulation of coagulation by antiphospholipid antibodies. The fourth theory proposes that APS could have similarities with thrombosis linked to heparin-induced thrombocytopenia (6, 7).

Epidemiology

The prevalence of antiphospholipid antibodies, both LA antibodies and ACA, is 1 to 5 percent among young, apparently healthy subjects (8). Prevalence as with other antibodies increases with age and various coexistent chronic diseases. The prevalence is higher among patients with SLE, ranging from 12 to 30 percent for ACA and 15 to 34 percent for LA antibodies (2).

It is to be noted that many patients have laboratory evidence of antiphospholipid antibodies without clinical consequences and therefore, a critical issue is to identify the patients with antiphospholipid antibodies who are at increased risk for developing a thrombotic event. Some risk factors have been found out : history of thrombosis, presence of LA antibodies, elevated level of IgG ACA, each of which could increase the risk of thrombosis up to five times.

Persistence of antiphospholipd also increases the risk. However, except for a previous thrombotic event, no any individual risk factor is sufficiently predictive to warrant treatment.

Diagnosis

An international consensus statement on preliminary criteria for the classification of the antiphospholipid syndrome was published in 1999 (9).

The revision of these criteria is an ongoing process but the consensus provides a rational tool for approaching the diagnosis of APS. In this statement (Table 1), a diagnosis of definitive APS requires the presence of at least one of the clinical criteria and at least one of the laboratory criteria ; no limits are placed on the interval between the clinical event and the positive laboratory findings.

Clinical manifestations

In APS, virtually any organ can be involved (2, 10) (Table 2) , and the range of disorders spans a diverse spectrum. Most manifestations can occur as a result of thromboembolism of large vessels, thrombotic microangiopathy, or both but other ones are of uncertain pathogenic origin (such as thrombocytopenia which is a frequent finding but not included in the clinical diagnostic criteria). Specifically neurological and some cardiac manifestations are discussed herein, to give a broad spectrum of the possible causes of neurological disorders.

There are many potential cardiac manifestations of APS (Table 3).

Emboli arising from mitral or aortic valves or cardiac cavities may contribute to the development of multifocal cerebral ischemia. Cardiac valvular abnormalities are present in up to 63 percent of patients with APS (11). Many of these abnormalities are of little importance but valvular thickening may be accompanied by vegetations (nonbacterial

Table 2

Possibly affected organ systems in APS

Arterial
Cardiac
Cutaneous
Endocrine or reproductive
Gastrointestinal
Hematologic
Neurologic
Obstetrical
Ophtalmologic
Pulmonary
Renal
Venous
Miscellaneous (bone, nose...)

Table 3

Cardiac manifestations of APS

Angina
Myocardial infarction
Valvular vegetations
Valvular abnormalities
Intracardiac thrombi
Nonbacterial thrombotic endocarditis (Libman-Sacks)
Peripheral embolization
Atherosclerosis
Myocarditis

Table 4

Neurological manifestations of APS

Transient ischemic attack
Thrombotic or embolic cerebrovascular accident
Chorea
Seizures
Multi-infarct dementia
Transverse myelitis
Encephalopathy
Pseudotumor cerebri
Mononeuritis multiplex
Cerebral venous thrombosis
Amaurosis fugax
Microthrombi or microinfarctions
Migraines

thrombotic or Libman-Sacks endocarditis) in about 4 percent of patients and occasionally overt thrombi (11) ; the mitral and less frequently aortic valves are most commonly involved. Diagnosis of Libman-Sacks endocarditis is difficult and is usually made by means of transoesophageal echocardiography. Antiphospholipid antibodies have been associated with a variety of neurological disorders, mostly linked to focal neuroparenchymal ischemia or infarction. (Table 4). In APS, venous thrombosis is the most common manifestation and usually involves the deep venous system of the legs ; cerebral venous sinuses are rarely affected. The brain is the most common site of arterial occlusions : strokes and transient ischemic attacks account for almost 50 percent of them (12). The antiphospholipid antibody-associated brain ischemic event is stronger in adults younger than 50 years and the risk of stroke is greatest in individuals with high levels of IgG ACA. Other related antiphospholipid antibodies neurologic symptoms include chorea, seizures, transverse myelopathy and migraines. Recurrent cerebrovascular events may lead to multi-infarct dementia.

Catastrophic antiphospholipid syndrome

A minority of patients with the APS develop an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body. It is a real thrombotic storm (13) often resulting in death and was first described by Asherson. The catastrophic APS is defined by the clinical involvement of at last three different organ systems over a period of days or weeks with histopathological evidence of multiple occlusions of large or small vessels (14).

Treatment

Management of APS addresses four main areas : prevention of APS, treatment and prevention of further thrombotic events, treatment of catastrophic APS, and management of pregnancy associated with antiphospholipid antibodies. Only therapeutic modalities non related with pregnancy are addressed herein.

1. Prevention of APS

Avoiding thrombosis in patients with antiphospholipid antibodies is the desired goal. The first way is certainly to eliminate any factors predisposing to thrombosis (e.g. immobilization, estrogen therapy) and probably to modify secondary risk factors for atherosclerosis (refer to the possible oxidant-mediated vascular injury theory). Aspirin 325 mg/day did not protect male physicians with ACA against deep vein thrombosis and pulmonary embolism (15).

Hydroxychloroquine may be protective against thrombosis in SLE patients with secondary APS (16).

2. Treatment of thrombosis in APS

Three retrospective studies have shown a beneficial role of anticoagulation (17, 18, 19). In a series of 147 patients with the APS (19), antithrombotic treatments were subdivided in different categories : neither aspirin nor warfarin ; low-dose aspirin (75 mg/d) ; warfarin either low intensity (INR < 3)

or high intensity (INR ≥ 3). The warfarin groups were further subdivided according to whether there was concomitant use of aspirin. The first thrombotic event was venous in 80 patients (54%) and arterial in 67 patients (47%). The study demonstrated that patients with thromboses both arterial and venous, and antiphospholipid antibodies should receive long-term anticoagulation therapy, with or without low-dose aspirin, in which an INR of 3 or above is maintained ; aspirin alone was ineffective in reducing the rate of recurrent thrombosis. It was also shown (17, 18, 19, 20) that discontinuation of anticoagulants seems to be associated with an increased risk of thrombosis (up to 70 %), and even death, especially in the first six months : anticoagulation should therefore be long term, if not lifelong. However, there is still debate about the optimum intensity of anticoagulation. In a series of 66 patients with APS and previous thrombosis, oral anticoagulants were given to a target INR of 3.5 (21) ; the risk of intracranial and fatal bleeding was similar than in groups of patients treated to low target ratios. That reinforces the idea that a moderate-to-high intensity of anticoagulation (target INR of 3.5) is probably desirable in most patients. A direct comparison of the efficacy of standard and high-intensity warfarin is in progress in the WAPS trial (Warfarin for the Prevention of Recurrent Thrombosis in the Anti-Phospholipid Syndrome).

A last point warrants mention : there is a possible interference of antiphospholipid antibodies in the INR measurement complicating the monitoring of the level of anticoagulation.

3. Treatment of catastrophic APS

In patients with the catastrophic APS, or in those developing life-threatening complications at an INR greater than 3.5, therapeutic recommendations are based on case reports : heparin, steroids, plasmapheresis, intravenous immune globuline, fibrinolytic agents, or cyclophosphamide should be considered (13, 14).

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