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Focus
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Antiphospholipid syndrome

Definitions

Antiphospholipid antibodies (aPL) represent a heterogeneous group of antibodies against anionic phospholipids (cardiolipin, phosphatidylserine) or neutral phospholipids (phosphatidylethanolamine) and plasma proteins binding with phospholipids such as β2-glycoprotein I or prothrombin.

aPL can be detected by means of:

- Dependent PL coagulation tests: for lupus type anticoagulants or antiprothrombinases.
- ELISA tests for anticardiolipin antibodies or anti-β2-Glycoprotein I (β2GI) antibodies.

Antiphospholipid syndrome (APS) is defined by a number of **clinical and pathological criteria**.

Sapporo clinical criteria

A group of experts met in 1999 to define the clinical criteria of APS.

Vascular thrombosis: one or more episodes of arterial or venous thrombosis irrespective of the organ and tissue, confirmed by imaging, Doppler or histopathology (which should not detect vascularitis).

Obstetrical manifestations:

- One or more unexplained miscarriages (after 10th week of gestation) (normal morphology)
- One or more premature births (before 34th week of gestation), due to eclampsia or placental insufficiency.
- Three or more miscarriages (before 10th week of gestation) without any anatomical, hormonal or genetic cause.

Pathological criteria

Anticardiolipin antibody (aCL): moderate to high levels of IgG and/or IgM, observed on 2 occasions 6 weeks apart, measured by means of standardised ELISA methods detecting so-called dependent β2GI anticardiolipin antibodies.

and/or

Lupus anticoagulant (antiprothrombinase CAC): detected according to ISTH guidelines on 2 occasions 6 weeks apart.

APS diagnosis

at least 1 clinical criterion + one pathological criterion.

APS occurs in 2 forms: the primary syndrome and secondary syndrome.

The primary syndrome is characterised by the combination of the above criteria only: anti-PL + clinical.

The secondary syndrome combines the above criteria with an autoimmune disease. A number of criteria make it possible to exclude primary APS, such as malar eruption, discoid lupus, oral or pharyngeal ulceration, full-blown arthritis, pleurisy without pulmonary embolism or heart failure, pericarditis without myocardial infarction, proteinuria › 0.5g/day with IC glomerulonephritis, lymphocytopenia ‹ 1000/mm3, AAN › 1/320, positive anti-ds DNA and ECT antibodies, a treatment known to induce aPL.

APS is associated with a number of pathological anomalies: positive direct Coombs, thrombocytopenia and lowered C4 fraction.

New pathological criteria: Sydney amendments in 2005

- LA (lupus anticoagulant) as per ISTH guidelines persisting for more than 12 weeks.
- Moderate to high aCL titres using standardised ELISA methods: IgG and/or IgM › 40 GPL/MPL (or › 99th percentile) persisting for more than 12 weeks.
- Anti-β2-glycoprotein I (using standardised ELISA): IgG and/or IgG › 99th percentile, persisting for 12 weeks.
- Finally, the interval between aPL detection and the first thrombotic signs must not exceed 5 years.

According to the **new Sydney amendment criteria**, APS is divided into different subgroups:

According to type of aPL identified

- **Type I:** in case of aPL combination
- **Type IIa:** isolated LA
- **Type IIb:** isolated aCL
- **Type IIc:** isolated anti-β2GPI

According to association with autoimmune disease or not

- **primary:** without AID (PAPS)
- **secondary:** with AID (SAPS)

According to progressive form

- Catastrophic aPL syndrome (CAPS).

Pathological APS diagnosis:

- Lupus type circulating anticoagulant and/or
- Anticardiolipin antibody and/or
- Anti-β2GPI.

Lupus type circulating anticoagulant screening by means of coagulation tests:

ISTH guidelines include 4 stages:

- Screening with detection of a prolongation of coagulation tests involving phospholipids.
- Detection of inhibitory activity (M+T).

- Confirmation of phospholipid dependence of inhibitor.
- Exclusion of other coagulation anomaly.

Immunological tests:

Anti-phospholipid antibodies:

- **ELISA anti-cardiolipin antibody assay:**

Anti-cardiolipins target cardiolipin and anionic PL. A distinction is made between: cofactor-independent aCL detected in infections and neoplasia and cofactor-dependent aCL detected in some autoimmune diseases. The isotypes to be detected are IgG, which are the most closely associated with the condition, IgM are frequently transitory, following infections and are rarer in APS. IgA are relatively non-informative.
The complexity of the ELISA aCL assay is associated with the great difficulty in developing standardised techniques. The quantification and expression of the results in GPL/MPL are performed according to the "Harris" universal standard so as to harmonise results as much as possible. There is an established correlation between a high aCL level and the risk of APS. Moreover, some situations other than APS are associated with the presence of anti-phospholipids: autoimmune diseases, malignant diseases, infectious diseases, others, etc.

- **Other anti-phospholipid antibodies detected using ELISA methods:**

Anti-phosphatidylethanolamine antibodies (aPE): phosphatidylethanolamine is a neutral PL, the main constituent of the cell membrane with an important role in coagulation. Anti-PE are not as well documented: they would appear to be detected in cases of APS without aPL, dependent on plasma cofactors (kininogens, prekallicrein, factor IX, etc.). Their diagnostic significance has not been demonstrated by multicentre studies to date.

Anti-protein cofactor antibodies:

- **Anti-Beta2-GPI antibodies:** β2 GPI or apolipoprotein H is a 326 AA protein synthesised by the liver. Anti-β2-GPI are assayed on an irradiated microplate. The isotypes are type IgG and IgM; the antigen used is a purified human β2GPI (however, there is considerable variability depending on the preparation and the batch, explaining the technique standardisation problems).
- **Anti-prothrombin antibodies (aPT):** represent a considerable proportion of the LA in patients with APS but are non-specific (particularly observed in many varied clinical contexts ranging from lupus to infectious episodes). They are seldom used in routine practice.
- **Anti-annexin V antibodies:** not many studies have been conducted to demonstrate their significance and these studies are sometimes contradictory

Clinical manifestations of APS:

Thrombotic events:

potentially affecting the entire vascular tree (arterial, venous, micro-circulation). The clinical profile of APS depends on the location (single or multiple) of the thromboses, which explains the great polymorphism of the manifestations described in the literature.

Delayed obstetrical complications:

more specific for APS: pre-eclampsia, eclampsia, placental rupture, etc

Catastrophic aPL syndrome:

thrombotic microangiopathy affecting multiple organs (at least 3) in a very short interval with death in 50% of cases due to multivisceral failure. The organs concerned are: the kidneys (78%), lungs (66%), CNS (56%), heart and skin (50%). DIC is observed in 25% of cases.

It is possible to differentiate cases of PAPS (primary) and SAPS (secondary): their profiles are similar, but more episodes of arthritis, livedo reticularis, thrombocytopenia and leukocytopenia are reported for the PAPS group.

The differences in the clinical symptoms observed in APS are linked with gender, and also the age of onset of the disease.

Clinical manifestations of APS

Thrombotic manifestations		Cardiac manifestations	
Deep vein thrombosis	389	Valvular insufficiency	116
Superficial phlebitis of lower limbs	117	Myocardial infarction	55
Arterial thrombosis limbs of the lower	43	Angor	27
Venous thrombosis of arm	34	Cardiomyopathy	29
Arterial thrombosis of arm	27	Vegetations	27
Subclavian vein thrombosis	18	Thrombosis on ACB	4
Jugular vein thrombosis	9		

Cervera R Arthritis Rheum 2002;4:1019-1027

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APS treatment

Primary prevention in absence of clinical signs:

- Elimination of vascular risk factors (smoking, pill)
- Eviction of aPL-inducing medication
- In the case of situations with an increased risk of thrombosis: low-dose aspirin treatment, or low-molecular-weight heparin at an isocoagulant dose.

Eliminating pathogenic aPL:

- Corticosteroids
- Other immunosuppressants
- Plasma exchanges (in cases of catastrophic syndrome)
- IV immunoglobulins

Preventing their harmful effects:

- Aspirin
- Anticoagulants: Standard heparin or low-molecular-weight heparin at curative doses in acute phase of thrombosis; AVK (INR between 2 and 3 for venous thrombosis prevention); AVK (INR between 3 and 4 for arterial thrombosis prevention)

APS and obstetrics:

- Aspirin ± HBPM low-molecular-weight heparin depending on the cases.

New molecules are used in APS treatment:

- **Hydroxychloroquine (Plaquenil®):** reduces aPL thrombogenicity in animals and aPL titre in humans.
- **Rituximab (anti-CD20 monoclonal antibody):** reduces aPL titre in humans, currently used in the treatment of rheumatoid arthritis.

Dominique BRUNENGO, based on a paper by Laurence Guis, Laboratoire Biomnis, Paris, France.