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Diagnosis and classification of 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 recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons. The aPL are positive in approximately 13% of patients with stroke, 11% with myocardial infarction, 9.5% of patients with deep vein thrombosis and 6% of patients with pregnancy morbidity. The original classification criteria for the APS were formulated at a workshop in Sapporo, Japan, in 1998, during the 8th International Congress on aPL. The Sapporo criteria, as they are often called, were revised at another workshop in Sydney, Australia, in 2004, during the 11th International Congress on aPL. At least one clinical (vascular thrombosis or pregnancy morbidity) and one laboratory (anticardiolipin antibodies, lupus anticoagulant or anti-β_2-glycoprotein I antibodies) criterion had to be met for the classification of APS.

1. Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β_2 glycoprotein-I (β_2GPI) antibodies [1]. 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, mainly systemic lupus erythematosus (SLE), but occasionally with other autoimmune conditions [1], infections [2], drugs [1], and malignancies [3] (Table 1).

Primary APS patients rarely progresses to SLE. Only 8% of 128 patients, who were followed up for about 9 years, developed lupus, and a positive Coombs' test was a clinically significant predictor of progression [4].

The aPL can appear in different scenarios, such as asymptomatic "carrier" patients for aPL, "classical" APS with recurrent venous and/or arterial thrombosis, APS affecting otherwise healthy women with recurrent pregnancy loss, patients with aPL positivity with non-thrombotic aPL manifestations (i.e. thrombocytopenia, hemolytic anemia or *livedo reticularis*) [5] or, in a small subset of patients, as a life-threatening form characterized by a rapid development of microthrombosis that led to rapid multiorgan failure, which is termed catastrophic APS [6].

2. Epidemiology

Prevalence of the aPL in the general population ranges between 1 and 5%. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons [7].

Recently, the APS ACTION group (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking) published a literature review focused in the prevalence of aPL in the general population with pregnancy morbidity, stroke, myocardial infarction (MI) and deep vein thrombosis (DVT). The authors estimated that aPL are positive in approximately 13% of patients with stoke, 11% with MI, 9.5% of patients with DVT and 6% of patients with pregnancy morbidity [8].

The prevalence of the catastrophic APS is scarce (less than 1% of all cases of APS) [6] but its potentially lethal outcome emphasizes its importance in clinical medicine today [9,10]. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the

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European Forum on Antiphospholipid Antibodies. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 400 patients whose data has been fully registered. This registry can be freely consulted at the Internet (http://infmed.fcrb.es/es/web/caps).

3. History

The association of thrombosis, recurrent fetal losses and thrombocytopenia with the LA phenomenon was observed in early publications in the 60's, but it was not until 30 years ago that Graham R.V. Hughes linked major cerebral disease (e.g. recurrent strokes) with abortions and the LA in an editorial published in the British Medical Journal [11]. The original concept of the APS, however, has been expanded over the years and now includes diverse complications as heart valve lesions, adrenal insufficiency and even avascular necrosis of bone, among many others [5,12].

A major advance came in the early 1990s with the simultaneous recognition by different groups that aPL required a plasma protein "cofactor" to bind cardiolipin on ELISA plates [13,14]. β2GP1 was identified as this cofactor. Since then, a number of "cofactors" including prothrombin, have been described.

4. Pathogenesis

Despite the strong association between aPL and thrombosis, the pathogenic role of aPL in the development of thrombosis has not been fully elucidated. Available data indicate that many of the autoantibodies associated with APS are directed against a number of plasma proteins and proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. The involvement of aPL in clinically important normal procoagulant and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules may offer a basis for definitive investigations of possible mechanisms by which aPL may develop thrombotic events in patients with APS (Table 2) [15,16].

5. Clinical manifestations

The clinical picture of the APS is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. The baseline characteristics of a cohort of 1000 patients with APS ("Euro-Phospholipid Project") are collected in Table 3 [17]. 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. After a 5-year follow-up of the 1000 patients with APS from the "Euro-Phospholipid Project", a bunch of new APS features appeared over time [18]. Those manifestations included thrombocytopenia (3.7%), *livedo reticularis* (2.6%), stroke (2.4%), transient ischemic attacks (2.3%), DVT (2.1%), pulmonary embolism (2.1%), epilepsy (1.7%), valve vegetations (1.4%) and MI (1%), among others.

Table 1
Diseases where aPL have been described.

Systemic autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary Sjogren's syndrome, dermato- and polymyositis, vasculitis (polyarteritis nodosa, microscopic polyarteritis, giant cell arteritis, Behçet's disease, relapsing polychondritis, leucocytoclastic vasculitis).
Infections: Viral (HIV infection, mononucleosis, rubella, parvovirus, hepatitis A, B, C, mumps), bacterial (syphilis, Lyme disease, tuberculosis, leprosy, infective endocarditis, rheumatic fever, *Klebsiella*), protozoal (malaria, toxoplasmosis).
Malignancies: Solid tumors (lung, colon, cervix, prostate, liver, kidney, thymus, esophagus, maxilla, ovary, breast), hematologic (myeloid and lymphatic leukemias, polycythemia vera, myelofibrosis), lymphoproliferative diseases (Hodgkin's disease, non-Hodgkin's lymphoma, lymphosarcoma, cutaneous T-cell lymphoma/Sezary syndrome), paraproteinemias (monoclonal gammapathies, Waldenström macroglobulinemia, myeloma).
Non-malignant hematologic conditions: Idiopathic thrombocytopenic purpura, sickle cell disease, pernicious anemia.
Drugs: Procainamide, phenothiazines, ethosuximide, chlorothiazide, quinine, oral contraceptives, anti-TNFα therapies.
Other conditions: Diabetes mellitus, autoimmune thyroid disease, inflammatory bowel diseases, dialysis, Klinefelter's syndrome, Ehlers–Danlos syndrome.

6. Laboratory abnormalities

A wide variety of laboratory abnormalities can be found in patients with APS, depending on the organ involvement. The most common immunological features are depicted in Table 4. Detection of the LA must be performed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies) [19].

7. Classification criteria

In 1999, a preliminary classification criterion was established after an expert workshop held in Sapporo, Japan [20]. More recently, another workshop was held in Sydney, Australia, in which the experts proposed some modifications to the previous criteria, such as the inclusion of anti-β2GPI antibodies. Although no new clinical criteria were added, some particular features were remarked on, such as associated APS features, including cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy, and non-thrombotic central nervous system manifestations (i.e. cognitive dysfunction) [21] (Table 5).

The preliminary classification criteria for catastrophic APS were formulated at a workshop in Taormina, Italy, in 2002, during the 10th International Congress on aPL, and published as a consensus statement in 2003 (Table 6) [22].

8. Assessment of the classification criteria

The revised APS classification criteria [21] provide a more uniform basis for selecting patients for APS research by emphasizing

Table 2
Possible pathogenic mechanisms of the aPL [15,16].

Inhibition of anticoagulant reactions
Inhibition of β_2GPI anticoagulant activity
Inhibition of the protein C pathway
Inhibition of protein C activation
Inhibition of activated protein C
Inhibition of antithrombin activity
Displacement of annexin A5
Cell-mediated events
On endothelial cells
Enhanced endothelial cell procoagulant activity
Increased expression and activation of tissue factor
Expression of adhesion molecules
Impaired fibrinolysis
Dysregulation of eicosanoids
Decreased endothelial cell prostacyclin production
Increased platelet thromboxane A_2 production
Impaired function of endothelial nitric oxide synthase
On monocytes
Expression of tissue factor
Increase oxidative stress
On platelets
Enhanced platelet activation/aggregation
On plasmacytoid dendritic cells
Increased expression of toll-like receptor 7 and toll-like receptor 8

Table 3
Most common manifestations in the APS, according to the "Euro-Phospholipid Project".

Manifestations	%
Peripheral thrombosis	
Deep vein thrombosis	38.9
Superficial thrombophlebitis in legs	11.7
Arterial thrombosis in legs	4.3
Venous thrombosis in arms	3.4
Arterial thrombosis in arms	2.7
Subclavian vein thrombosis	1.8
Jugular vein thrombosis	0.9
Neurologic manifestations	
Migraine	20.2
Stroke	19.8
Transient ischemic attack	11.1
Epilepsy	7.0
Multiinfarct dementia	2.5
Chorea	1.3
Acute encephalopathy	1.1
Pulmonary manifestations	
Pulmonary embolism	14.1
Pulmonary hypertension	2.2
Pulmonary microthrombosis	1.5
Cardiac manifestations	
Valve thickening/dysfunction	11.6
Myocardial infarction	5.5
Angina	2.7
Myocardiopathy	2.9
Vegetations	2.7
Coronary by-pass rethrombosis	1.1
Intraabdominal manifestations	
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	2.7
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	1.5
Splenic infarction	1.1
Cutaneous manifestations	
Livedo reticularis	24.1
Ulcers	5.5
Pseudovasculitic lesions	3.9
Digital gangrene	3.3
Cutaneous necrosis	2.1
Osteo-articular manifestations	
Arthralgia	38.7
Arthritis	27.1
Avascular necrosis of bone	2.4
Ophthalmologic manifestations	
Amaurosis fugax	5.4
Retinal artery thrombosis	1.5
E.N.T. manifestations	
Nasal septum perforation	0.8
Hematological manifestations	
Thrombocytopenia (<100,000/μl)	29.6
Hemolytic anemia	9.7
Obstetric manifestations (pregnant female = 590)	
Pre-eclampsia	9.5
Eclampsia	4.4
Abruptio placentae	2.0
Fetal manifestations (pregnancies = 1580)	
Early fetal losses (<10 weeks)	35.4
Late fetal losses (≥10 weeks)	16.9
Live births	47.7
Prematures	10.6

risk stratification. They strongly recommend investigating coexisting inherited and acquired thrombosis risk factors in patients with APS, especially in those who are included in clinical trials. A recent assessment of the 2006 revised APS classification criteria has shown that only 59% of the patients meeting the 1999 APS Sapporo classification criteria met the revised criteria [23]. Therefore, it is expected that these revised criteria will have positive implications in APS research by way of limiting the inclusion of a heterogeneous group of patients and also by providing a risk-stratified approach. Furthermore, although the APS classification criteria are not meant for clinical purposes, they are the best available tool to avoid overdiagnosis of APS in clinical practice.

Regarding the classification criteria for the catastrophic APS, a validation study showed that they have a sensitivity of 90.3%, a specificity of 99.4%, a positive predictive value of 99.4% and a negative predictive value of 91.1% [24].

9. Assessment of thrombosis risk in APS patients

Several attempts have been made in order to identify the individual risk of thrombosis in patients positive for aPL [25–27]. A study of pregnant women with APS reported that patients with triple aPL positivity (i.e. positivity for LA, aCL, and anti-β_2GPI) and/or previous thromboembolism had an increased likelihood of poor neonatal outcomes than patients with double or single aPL positivity and no thrombosis history. More recently, a global APS score (GAPSS) was developed in a cohort of 211 SLE from a single center [27]. GAPSS is derived from the combination of independent risk for both thrombosis and loss of pregnancy, taking into account a panel of seven different aPLs conventional cardiovascular risk factors, the autoimmune antibody profile (i.e. antinuclear, anti-dsDNA or anti-ENA antibodies) and the use of thromboprophylactic drugs. The authors assigned the risk factors identified by multivariate analysis weighted points proportional to the β-regression coefficient values. Finally, 6 factors were included in the model and include IgG/IgM aCL (5 points), IgG/IgM anti-β_2GPI antibodies (4 points), LA (4 points), IgG/IgM anti-phosphatidylserine–prothrombin complex antibodies (3 points), hyperlipidemia (3 points) and arterial hypertension (1 point). A GAPSS cut-off value of ≥10 points appears to have the best diagnostic yield. Until date, GAPSS score has not been validated by other groups, but it is a promising tool for thrombosis risk assessment in APS patients.

10. Therapy

Elimination of aPL 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 immunotherapy is generally not indicated, unless required for the treatment of the underlying condition, e.g. SLE, or in acute life-threatening situations, such as the catastrophic APS. The risk of recurrence of thrombosis is 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 [28].

In cases of first venous event, low-risk aPL profile or a known transient precipitating factor (e.g. oral contraceptives), anticoagulation could be limited to 3–6 months and antiaggregants, as well as avoidance of the triggering factors, may indeed be sufficiently effective for future thromboprophylaxis [29].

Patients with definite APS with a first venous thrombosis event should receive oral anticoagulant therapy to a target INR 2.0-3.0. Patients with definite APS and arterial thrombosis should receive oral anticoagulant therapy to a target around 3.0 or receive a combined therapy with antiaggregant plus anticoagulation with an INR target between 2.0 and 3.0 [30].

Long-term anticoagulation with oral vitamin K antagonists such as warfarin is the cornerstone treatment in APS. However, novel oral anticoagulation therapies have been developed during the last years; these therapies are direct anti-Xa inhibitors and included rivaroxaban, apixaban and edoxaban as well as a direct thrombin

Table 4
Most common immunological findings in the APS, according to the "Euro-Phospholipid Project".

Parameter	%
aCL	87.9
IgG and IgM aCL	32.1
IgG aCL alone	43.6
IgM aCL alone	12.2
LA	53.6
LA alone	12.1
LA and aCL	41.5
ANA	59.7
Anti-dsDNA	29.2
Anti-Ro/SS-A	14
Anti-La/SS-B	5.7
Anti-RNP	5.9
Anti-Sm	5.5
Rheumatoid factor	7.8
Cryoglobulins	3.6

inhibitor named dabigatran etexilate. Although these are promising therapies for patients with arterial or venous thrombosis, data in APS is scare and prospective clinical trials usually do not include patients with APS.

The thrombocytopenia occurring 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. In these cases, immunosuppressive therapy (e.g. azathioprine), intravenous immunoglobulins or rituximab may be effective.

A recently published non-randomized prospective pilot study has shown the efficacy and safety of rituximab for the treatment of non-criteria aPL manifestations in patients with classic APS [31]. According to the results, rituximab may be effective in controlling some non-criteria aPL manifestations, such as thrombocytopenia and skin ulcers.

It is important to consider that the presence of moderate to severe thrombocytopenia in patients with on-going thromboses is not a contraindication for anticoagulation.

Management of the catastrophic APS includes an aggressive approach with a combine treatment that includes anticoagulation with heparin, high dose steroids, plasma exchange and/or intravenous immunoglobulins [22]. For patients with refractory catastrophic APS, rituximab and eculizumab are good alternatives. A recent publication [32] demonstrated that 75% of patients with refractory catastrophic APS recovered from the acute catastrophic APS episode; however, 20% of them died at the time of the event. Eculizumab, a humanized monoclonal antibody against complement protein C5, is currently approved for the treatment of paroxysmal nocturnal hemoglobinuria and is a promising therapy in catastrophic APS [33]. Eculizumab treatment benefits patients with microangiopathies, reducing intravascular hemolysis and blocking complement-mediated pathogenic effects. Eculizumab is also a promising therapy for patients with APS with renal post-transplant thrombotic microangiopathy [34].

11. Prevention

In patients with aPL who have never suffered from a thrombotic event (primary thromboprophylaxis), 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.

Individual decisions should be made based on several aspects, including the aPL profile (type of antibodies, level and persistence), the coexistence of other pro-thrombotic factors, the presence of an underlying autoimmune disease (specially SLE) [30] and, potentially, the GAPSS score.

Care should be also taken with the administration of oral contraceptives. 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 mg daily), specially in those with added risk factors [35]. However, a recently published trial has not

Table 5
Revised classification criteria for the APS [21].

Clinical criteria

1. Vascular thrombosis[a]

One or more clinical 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.

2. 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 direct examination of the fetus, *or*
   (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (a) eclampsia or severe preeclampsia defined according to standard definitions, or (b) recognized features of placental insufficiency,[b] *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 one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria[c]

1. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile, or >mean + 3SD of 40 healthy controls), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay.
2. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies).
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma, present on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay, according to recommended procedures.

- Definite APS is present if at least one of the clinical criteria and one[c] of the laboratory criteria are met, with the first measurement of the laboratory test performed at least 12 weeks from the clinical manifestation.[d]

[a] Coexisting inherited or acquired factors for thrombosis are not reason for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the *presence*, and (b) the *absence* of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index $\geq$ 30 kg/m^2, microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

[b] Generally accepted features of placental insufficiency include: (1) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (2) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (3) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (4) a post natal birth weight less than the 10th percentile for the gestational age.

[c] Investigators are strongly advised to classify APS patients in studies into one of the following categories: I: More than one laboratory criteria present (any combination). IIa: Anti-cardiolipin antibody present alone. IIb: Lupus Anticoagulant present alone. IIc: Anti-β_2 glycoprotein-I antibody present alone.

[d] Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

Table 6
Preliminary criteria for the classification of catastrophic APS [22].

1. Evidence of involvement of three or more organs, systems and/or tissues.[a]
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.[b]
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies).[c]

Definite catastrophic APS: All 4 criteria.
Probable catastrophic APS:
- All 4 criteria, except for only two organs, systems and/or tissues involvement.
- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS.
- 1, 2 and 4.
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

[a] Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or proteinuria (>500 mg/24 h).

[b] For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

[c] If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS (9).

confirmed the benefits of aspirin in the APS primary thromboprophylaxis [36]. For higher risk patients (patients with SLE and persistently positive LA), primary thromboprophylaxis with hydroxychloroquine and low-dose aspirin is recommended [30].

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.

Low-dose aspirin (50–100 mg daily) administered from the beginning of pregnancy until just prior to delivery is the accepted standard for the prevention of fetal loss today. This may be combined with daily subcutaneous heparin in the face of previous fetal losses using aspirin [37,38]. In cases of ongoing anticoagulation, warfarin administration should be discontinued as soon as pregnancy is diagnosed, since it is teratogenic, and switched to heparin. 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 [39].

Some potential alternatives for the treatment of refractory obstetric APS include double anti-aggregant therapy, intravenous immunoglobulins, and biologic therapies, especially anti-tumor necrosis factor alpha agents and plasma exchange sessions [40].

12. Outcome and organ damage

Given that APS affect predominantly young patients, assessment of organ damage is crucial but publications in that field are limited. A retrospective analysis was recently published that focused in morbidity, mortality, and organ damage in 135 APS patients (89 primary APS and 46 with secondary APS) [41]. Patients were clustered according to the initial event: arterial thrombosis, DVT or pregnancy morbidity. One-fourth of the patients progressed to organ damage in a mean time of 10 years from disease onset. The highest morbidity was attributed to neurologic damage, which was more common among patients with arterial thrombosis as an initial manifestation.

During the follow-up study period of the “Euro-Phospholipid Project”, 5-year survival rate of 94% was reported [18]. During this follow-up period, 53 (5.3%) patients died. The main causes of death included bacterial infection (21%), MI (19%), stroke (13%), hemorrhage (11%), malignancy (11%), catastrophic APS (9%) and pulmonary embolism (9%), among others. Finally, we have not attempted to cover all aspects of the anti-phospholipid antibody syndrome. For additional reading and including the immunological basis, there are several recent reviews [42–45].

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References

[1] Cervera R, Reverter JC, Khamashta MA. Antiphospholipid syndrome in systemic autoimmune diseases. Amsterdam: Elsevier; 2009.
[2] Cervera R, Asherson RA, Acevedo ML, Gomez-Puerta JA, Espinosa G, De La Red G, et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004;63:1312–7.
[3] Gomez-Puerta JA, Cervera R, Espinosa G, Aguilo S, Bucciarelli S, Ramos-Casals M, et al. Antiphospholipid antibodies associated with malignancies: clinical and pathological characteristics of 120 patients. Semin Arthritis Rheum 2006;35:322–32.
[4] Gomez-Puerta JA, Martin H, Amigo MC, Aguirre MA, Camps MT, Cuadrado MJ, et al. Long-term follow-up in 128 patients with primary antiphospholipid syndrome: do they develop lupus? Medicine (Baltimore) 2005;84:225–30.
[5] Asherson RBS, Gomez-Puerta JA, Cervera R. History, classification, and subsets of the antiphospholipid syndrome. Amsterdam: Elsevier; 2009.
[6] Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.
[7] Mehrania T, Petri M. Epidemiology of the antiphospholipid syndrome. Amsterdam: Elsevier; 2009.
[8] Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, de Jesus GR, Erkan D. The estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis. Arthritis Care Res (Hoboken) 2013.
[9] Cervera R, Espinosa G, Bucciarelli S, Gomez-Puerta JA, Font J. Lessons from the catastrophic antiphospholipid syndrome (CAPS) registry. Autoimmun Rev 2006;6:81–4.
[10] Cervera R, Bucciarelli S, Plasin MA, Gomez-Puerta JA, Plaza J, Pons-Estel G, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the “CAPS Registry”. J Autoimmun 2009;32:240–5.
[11] Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J 1983;287:1088–9.
[12] Petri M. Epidemiology of the antiphospholipid antibody syndrome. J Autoimmun 2000;15:145–51.
[13] McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci U S A 1990;87:4120–4.
[14] Galli M, Comfurius P, Maassen C, Hemker HC, de Baets MH, van Breda-Vriesman PJ, et al. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990;335:1544–7.
[15] Espinosa G, Cervera R, Font J, Shoenfeld Y. Antiphospholipid syndrome: pathogenic mechanisms. Autoimmun Rev 2003;2:86–93.
[16] Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med 2013;368:1033–44.
[17] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.
[18] Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Kiss E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009;68:1428–32.
[19] Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995;74:1185–90.
[20] Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.
[21] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

[22] Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530–4.
[23] Kaul M, Erkan D, Sammaritano L, Lockshin MD. Assessment of the 2006 revised antiphospholipid syndrome classification criteria. Ann Rheum Dis 2007;66:927–30.
[24] Cervera R, Font J, Gomez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, et al. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005;64:1205–9.
[25] Ruffatti A, Calligaro A, Hoxha A, Trevisanuto D, Ruffatti AT, Gervasi MT, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis Care Res (Hoboken) 2010;62:302–7.
[26] Otomo K, Atsumi T, Amengual O, Fujieda Y, Kato M, Oku K, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. Arthritis Rheum 2012;64:504–12.
[27] Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the global anti-phospholipid syndrome score. Rheumatology (Oxford) 2013;52:1397–403.
[28] Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. J Am Med Assoc 2006;295:1050–7.
[29] Coloma Bazan E, Donate Lopez C, Moreno Lozano P, Cervera R, Espinosa G. Discontinuation of anticoagulation or antiaggregation treatment may be safe in patients with primary antiphospholipid syndrome when antiphospholipid antibodies became persistently negative. Immunol Res 2013;56:358–61.
[30] Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on Antiphospholipid Antibodies. Lupus 2011;20:206–18.
[31] Erkan D, Vega J, Ramon G, Kozora E, Lockshin MD. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis Rheum 2013;65:464–71.
[32] Berman H, Rodriguez-Pinto I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev 2013;12:1085–90.
[33] Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Arthritis Rheum 2012;64:2719–23.
[34] Canaud G, Kamar N, Anglicheau D, Esposito L, Rabant M, Noel LH, et al. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes. Am J Transplant 2013;13:2179–85.
[35] Alarcon-Segovia D, Boffa MC, Branch W, Cervera R, Gharavi A, Khamashta M, et al. Prophylaxis of the antiphospholipid syndrome: a consensus report. Lupus 2003;12:499–503.
[36] Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007;56:2382–91.
[37] Tincani A, Branch W, Levy RA, Piette JC, Carp H, Rai RS, et al. Treatment of pregnant patients with antiphospholipid syndrome. Lupus 2003;12:524–9.
[38] Carmona F, Font J, Azulay M, Creus M, Fabregues F, Cervera R, et al. Risk factors associated with fetal losses in treated antiphospholipid syndrome pregnancies: a multivariate analysis. Am J Reprod Immunol 2001;46:274–9.
[39] Cervera R, Balasch J. The management of pregnant patients with antiphospholipid syndrome. Lupus 2004;13:683–7.
[40] Gomez-Puerta JA, Cervera R. Are there additional options for the treatment of refractory obstetric antiphospholipid syndrome? Lupus 2013;22:754–5.
[41] Grika EP, Ziakas PD, Zintzaras E, Moutsopoulos HM, Vlachoyiannopoulos PG. Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome. J Rheumatol 2012;39:516–23.
[42] Arachchillage DJ, Cohen H. Use of new oral anticoagulants in antiphospholipid syndrome. Curr Rheumatol Rep 2013;15:331.
[43] Gris JC, Bouvier S. Antiphospholipid syndrome: looking for a refocusing. Thromb Res 2013;131(Suppl. 1):S28–31.
[44] Comarmond C, Cacoub P. Antiphospholipid syndrome: from pathogenesis to novel immunomodulatory therapies. Autoimmun Rev 2013;12:752–7.
[45] Andreoli L, Fredi M, Nalli C, Reggia R, Lojacono A, Motta M, et al. Pregnancy implications for systemic lupus erythematosus and the antiphospholipid syndrome. J Autoimmun 2012;38:J197–208.