ANTIPHOSPHOLIPID SYNDROME

1. Global learning outcome

This module will enable the participant to recognise, diagnose and treat patients with antiphospholipid syndrome.

2. Specific learning outcomes

1. Recognise that the antiphospholipid syndrome is not a rare disease and that patients with symptoms suggestive of antiphospholipid syndrome are frequently seen in daily clinical practice.
2. Recognise that the antiphospholipid syndrome involves a wide spectrum of clinical manifestations.
3. Although major thrombotic events are the hallmark of the disease other subtle manifestations such as cognitive impairment or mood disorders are also frequent.
4. Design a diagnostic screening algorithm for the individual patient
5. Develop treatment strategies for patients with antiphospholipid syndrome, tailored to the clinical picture.
6. Critically evaluate the limited scientific evidence for the diagnosis and treatment of patients with antiphospholipid antibodies with and without the antiphospholipid syndrome.

3. Background

The first description of antiphospholipid antibodies (aPL), a complement-fixing antibody that reacted with extracts from bovine hearts, was by Wasserman in 1906 whilst he was carrying out his research into the development of the serological test for syphilis (1). In 1941, the relevant antigen was identified as cardiolipin, a mitochondrial phospholipid (2) and basis for the Venereal Disease Research Laboratory (VDRL) test for syphilis. Blood screening for this disease led to the observation that many patients with SLE had a positive VDRL test, without any other clinical or serological evidence of syphilis (3).
The knowledge of the “lupus anticoagulant phenomenon” goes back to 1950’s when Conley and Hartmann reported prolongation of the coagulation times, occasionally the prothrombin time, in patients with SLE (4). This was followed by the first report of “circulating anticoagulant” and recurrent abortions (5), the association of the “circulating anticoagulant” and the biological false positive serological test for syphilis (BFP-STS) (6) and its association with thrombotic manifestations in SLE patients (7). Only in 1972 Feinstein and Rapaport introduced the term “lupus anticoagulant” to describe it as an inhibitor directed against coagulation cascade phospholipids, particularly at the prothrombin conversion to thrombin step (8).

In 1983, a solid phase immunoassay for anticardiolipin antibodies (aCL) was developed (9). This assay was much more sensitive than the VDRL test for detecting aCL in patients with SLE and early observations of the association of aPL with thrombotic events were confirmed (9). At the time this complex clinical syndrome was named ‘anticardiolipin syndrome’ (10-12). This was most certainly a distinct syndrome, occurring in ANA-negative lupus patients, atypical lupus patients and even in individuals with no lupus at all (13). In 1987 the name “anticardiolipin syndrome” was changed to “antiphospholipid syndrome” (APS) from the observation that patient's sera were also cross-reactive with other phospholipids apart from cardiolipin (14). The term “primary antiphospholipid syndrome” was also introduced (15) and soon after, two large series of patients were published (16, 17).

In 1992, Asherson et al (18) reported a series of patients with APS who developed acute multiorgan failure, defining this clinical situation as “catastrophic APS”.

The APS is now defined more precisely as a disorder in which the presence of aPL is associated with the clinical features of arterial and/or venous thrombosis, and pregnancy morbidity (11, 19).

4. Definition and epidemiology

The APS is a thrombophilic disorder characterised by arterial and/or venous thrombosis and/or pregnancy morbidity, always associated with the presence of a specific group of autoantibodies called aPL. When APS is present by itself, it is referred to as primary APS; and when it is part of a systemic disorder/autoimmune disease, classically SLE, it is known as secondary APS. A number of conditions have been reported in association with aPL as listed in table 1.

There appear to be very few, if any differences between the clinical complications associated with the primary and the secondary form of the syndrome (20) and the rates of arterial or venous thrombosis or fetal loss do not appear to be different (20-22).
Table 1: Conditions reported in association with aPL

<table>
<thead>
<tr>
<th>Connective tissue disorders</th>
<th>Infection</th>
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<tbody>
<tr>
<td>SLE</td>
<td>Leprosy</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Scleroderma</td>
<td>Hepatitis C</td>
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<tr>
<td>Myositis</td>
<td>Cytomegalovirus</td>
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<tr>
<td>Drugs</td>
<td>Parvovirus</td>
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<tr>
<td>Hydralazine</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Other</td>
</tr>
<tr>
<td>Quinine/quinidine</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Interferon $\alpha$</td>
<td>Accelerated atheroma</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Diabetes</td>
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<tr>
<td>Systemic vasculitis</td>
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However, the distinction between the primary APS and APS due to SLE can sometimes be difficult since some features such as thrombocytopenia, anemia, renal and central nervous system involvement may be seen in both conditions (23).

Due to the association with SLE and pregnancy loss, the APS is largely recognised as a disease of young women. This reflects a reporting bias since young patients with thrombosis and pregnancy loss are more likely to be investigated albeit the syndrome has also been reported in children, elderly and in male subjects (23).

Using standardised techniques, aPL are detected in less than 1% of apparently normal individuals and in up to 3% of the elderly population without clinical manifestations of the APS. The estimated prevalence of aPL in patients with SLE varies ranging from around 20% (24, 25) to 60% (26-28). A European study of 1000 patients revealed that APS was associated with SLE in 36% of the cases (29). Prevalence of aPL in other connective tissue diseases or infections varies; the predominant isotype is of IgM class in low titres and usually is not associated with aPL-related clinical features.

APS has a significant impact in survival and increasing evidence shows that thrombosis contributes to the damage accrued in patients with SLE. A retrospective study shows that 50% of the SLE patients with aCL developed APS in a 10-year follow-up (30). APS independently contributes to irreversible organ damage as well as mortality in these patients (31, 32). The risk of recurrent thrombotic events is substantially increased in patients with established APS with thrombosis, especially if tight anticoagulation is not maintained (33).
5. Antiphospholipid antibodies

aPL are a family of immunoglobulins of IgG, IgM, IgA or a combination of these isotypes, which were initially thought to recognise anionic phospholipids. Over the years, this concept has changed and different specificities have been described for aPL (Table 2) (34).

Table 2: Different specificities of antiphospholipid antibodies

- **Antibodies to phospholipids**

  | Cardiolipin |
  | Phosphatidylserine |
  | Phosphatidic acid |
  | Phosphatidylinositol |
  | Phosphatidylcholine |
  | Phosphatidylethanolamine |

- **Antibodies to phospholipid binding proteins**

  | β2GPI | Factor XII |
  | Prothrombin | C4b binding protein |
  | Annexin V | Complement C4 and C5 |
  | Protein C | Heparan sulphate |
  | Protein S | Thrombin |
  | Low and High molecular weight kininogens | Other |

aPL are not uncommon since they have been found in about 25% of patients with unexplained venous thrombosis, 20% of young patients with stroke (35), around 18% of patients with premature coronary artery thrombosis (36, 37) and in about 30% of patients with recurrent pregnancy loss (38).

The risk of thrombosis (39), recurrent pregnancy loss (39-41) and thrombocytopenia (39) has been associated with high levels of antibodies to cardiolipin (aCL). IgG isotypes are more related with clinical complications when compared with IgM (42). The role of IgA aCL is still controversial (43-46).

Autoantibodies to phospholipids other than cardiolipin have been less well studied and characterised. An explanation for this is that reactivity to other phospholipids has often been found to correlate with aCL reactivity and cardiolipin was the anionic phospholipid most focused upon (47).
Lupus anticoagulant (LA) is a functional measurement of the capacity of heterogeneous aPL that interfere with phospholipid-dependent stages of blood coagulation in vitro and inhibit both the intrinsic and common pathways of coagulation (48). Paradoxically, LA are associated with a thrombotic tendency rather than bleeding, generally associated with coagulation inhibitors. LA has been reported in a wide variety of patient populations, ranging from autoimmune diseases (e.g. SLE, rheumatoid arthritis), drug exposure (e.g. chlorpromazine, procainamide, hydralazine), infections and lymphoproliferative disorders to individuals with no apparent underlying disease (48). The estimated prevalence in patients with SLE varies ranging from 6-65% (28, 42, 49). Not all patients with LA have aCL and vice versa. The proportion of SLE patients with both LA and aCL varies from 61 to 91% (49-51). This wide variation in prevalence reflects differences in assay methods and case-mix of patients.

The LA assays have been thought to detect antibodies against anionic phospholipids. However, recent data indicates that certain LA are specific for either phospholipid-bound β2-Glycoprotein I (β2GPI) (52) or prothrombin (53, 54).

5.1. Antibodies to phospholipid binding proteins

5.1.1. β2-Glycoprotein

In 1990, two independent groups (55, 56) identified β2GPI as the plasma cofactor required for aCL binding to cardiolipin. β2GPI is a normal plasma glycoprotein, a single chain 50 kD polypeptide. Its function is unclear, although it may function as a natural anticoagulant (57, 58). β2GPI antibodies are more specific than aCL in predicting thrombosis, differentiating pathogenic (autoimmune) from non-pathogenic (infection or drug induced) antibodies, since β2GPI is an absolute requirement for binding of autoimmune aCL to cardiolipin in ELISA (56, 59).

Most antibodies associated with APS and detected in standard aCL and/or LA assays are directed against β2GPI or prothrombin. aPL can also be detected in immunoassays utilising purified protein antigens in the absence of phospholipids (60, 61). Initial clinical studies of anti-β2GPI ELISAs suggest that positivity in these assays is more closely associated with clinical manifestations of the APS than positivity in conventional aCL ELISAs (59).

This is predominantly due to enhanced diagnostic specificity; although anti-β2GPI assays have also identified a small number of patients who have clinical manifestations of the APS but are negative in conventional aPL assays (62).
5.1.2. Prothrombin

Prothrombin appears to be a common antigenic target of aPL (63). However, its clinical significance is far from clear. Most of the studies available in the literature investigated the clinical significance of antiprothrombin antibodies detected by ELISA using prothrombin coated on irradiated plates and positive correlations with the clinical manifestations of the APS have been reported (64-66).

Petri et al (64) were the first to show antiprothrombin antibodies positive predictive value for thrombosis in patients with SLE. However, Pengo et al (67) could not confirm these data when studying patients with thrombosis, undoubtedly reflecting the heterogeneity and lack of appropriate standardisation for the detection of these antibodies. Galli et al (68) found antiprothrombin antibodies in 58% of their APS patients but failed to demonstrate any association with thrombotic events in this group. On the other hand, Puurunen et al (65), Horbach et al (69) and Muñoz-Rodriguez et al (70) reported a positive correlation between antiprothrombin antibodies and thrombosis in SLE. We also found a correlation between the presence of antiprothrombin antibodies and the occurrence of vascular events when we studied 207 patients with SLE (66).

In 1997, Galli et al (68) suggested that the prevalence of antiprothrombin antibodies increased up from 58% when using prothrombin coated on irradiated plates (aPT) to 90% when prothrombin was presented complexed to phosphatidylycerine (aPS-PT). Our group reported that aPS-PT conferred an odds ratio of 2.8 for venous thrombosis and of 4.1 for arterial thrombosis in patients with SLE (71). Atsumi et al (72) supported these data by showing that the presence of aPS-PT conferred an odds ratio of 3.6 for APS in 265 Japanese patients with systemic autoimmune diseases.

Antibodies directed to prothrombin have also been shown to be responsible for the LA activity (53). This was later confirmed by Horbach et al (73) and Atsumi et al (72). In all cases, the authors suggested that the LA activity might not be caused by antiprothrombin antibodies alone but by a combination of different types of antibodies (e.g. anti-β2GPI). Moreover, multivariate logistic regression analysis showed that the coexistence of IgG antiprothrombin and LA activity was a significant risk factor for venous thromboembolism (74).

5.1.3. Annexin V

Annexin V, one member of the annexin family, has high affinity for anionic phospholipids enabling it to displace coagulation factors from phospholipid surfaces (75). This protein is present in placenta and vascular endothelium and behaves as a potent natural anticoagulant. Antibodies against this protein have been investigated as a possible explanation of recurrent abortions or fetal death in APS (76, 77).
Rand et al (77) suggested that aPL can displace annexin V from cellular surfaces, resulting in prothrombotic surfaces exposure which may then initiate the thrombotic complications seen in these patients. Based on this hypothesis, van Heerde et al (78) studied plasma levels of annexin V in an attempt to confirm that the levels of this protein were increased in patients with aPL. The authors showed that levels of annexin V were increased in SLE patients, independently of the presence of aPL. Moreover, no correlation with thromboembolic history was found. Based on these observations, the authors refuted Rand’s hypothesis, suggesting that displacement of annexin V is not a common mechanism for thrombosis in patients with aPL. Recently, Rand et al (79), using atomic force microscopy, showed that a monoclonal aPL disrupted the annexin V crystallisation pattern over the phospholipid bilayer, reducing the anticoagulant effect of the protein and promoting thrombin generation. This is the first morphological evidence that aPL disrupt the formation of the annexin V anticoagulant shield although confirmation of these data is essential.

5.1.4. Components of the protein C pathway

Protein C and protein S are natural inhibitors of coagulation. Congenital deficiency of these proteins is associated with an increased risk of venous thrombosis (80). Once activated, protein C inactivates, together with protein S, factors Va and VIIIa (81).

Some data suggest that autoantibodies could be directed against components of protein C pathway (82), which includes protein C (83), protein S (84, 85) and thrombomodulin (86).

Protein C and protein S are vitamin K-dependent plasma proteins, activated by the thrombin-thrombomodulin complex. They also bear Gla-domain as a phospholipid-binding site. Oosting et al (82) reported that IgG fractions from some patients with aPL and/or a history of thrombosis interfere with the anticoagulant activity of protein C and protein S. Interestingly, some patients have antibodies to β2GPI, prothrombin, protein C and protein S and all combinations of them. Data from our unit showed that monoclonal aCL bound to protein C in the presence of both cardiolipin and β2GPI. These data suggest that protein C could be a target of aCL by forming a complex with cardiolipin and β2GPI, leading to protein C dysfunction (83).

Early reports described transient and reversible deficiency in protein S function at the time of thromboembolism in patients with APS (87, 88). Some studies have suggested that aPL may cause a functional deficiency by binding to the free form of protein S (89, 90), exerting neutralising properties. Parke et al (91) reported that patients with aPL had low levels of free protein S.
These findings were reinforced by Song et al (92) when they reported that 44% of the SLE patients in their study had free protein S antigen levels below the lower limit established for the normal population. They also found anti-protein S in 26% of their SLE patients. Data from our unit showed that anti-protein S are frequent in SLE patients with thrombosis and pregnancy morbidity and that these antibodies do not interfere with free protein S in plasma since its level and/or functional activity is not impaired (85).

Merrill et al (84) investigated the clinical significance of anti-protein S antibodies in 139 patients with SLE and/or aPL. They found a prevalence of 53%. Notably, the combination of β2GPI and protein S reactivity was associated with an increased historical incidence of thrombosis when compared to the risk of either anti-β2GPI or anti-protein S alone, suggesting that these antibodies may be predictive of thrombosis. Preliminary data from our unit (93) showed that the presence of anti-protein S antibodies might increase the risk of having such an event since 35% of patients with anti-protein S had a history of a thrombotic event, giving a new insight in the possible involvement of antibodies directed to protein S in the APS.

5.1.5. Other phospholipid binding proteins

A number of other autoantibodies have been detected in patients with APS, including antibodies to vascular heparan sulfate proteoglycan (94) heparin (95), phosphatidylethanolamine (96), high and low molecular weight kininogen, prekallikrein and Factor XI (97) and thrombin (98).

Antibodies to factor XII have also been described (99-101). In our experience, their presence is associated with thrombosis and adverse obstetric history making these antibodies a novel marker for the APS (102).

Arvieux et al (103) suggested that some aCL might recognise not only β2GPI but also thrombin-modified antithrombin, C4b binding protein and lipopolysaccharide binding protein. Recently, Rampazzo et al (104) isolated and identified 3 other cardiolipin-binding proteins, complement component C4, complement factor H and a kallikrein-sensitive glycoprotein in patients with APS. Munakata et al (105) described complement-fixing aCL suggesting that these antibodies are more specific than the standard aCL assay in relation to thrombotic episodes. For the time being, the association of such antibodies with APS and their clinical significance is not yet known.
6. Origin and pathogenic mechanisms of antiphospholipid antibodies

The origin of aPL and mechanisms involved in their production are not understood. The origin of aPL was extensively investigated and several research groups have induced high levels of aPL in experimental animals by immunisation with β2GPI (106-108). However, although immunisation with foreign β2GPI can induce pathogenic aPL, it is unlikely that aPL production is induced with foreign β2GPI in APS patients. The observation that aPL of the autoimmune type may be associated with thrombosis in patients with Epstein-Barr virus, cytomegalovirus (109, 110), hepatitis C (111-113), adenovirus (114) or parvovirus (115) suggests that certain infections may induce autoimmune aPL that are not transient.

Recent data shows that aPL may be induced in experimental animals by immunisation with products from bacteria or viruses, supporting the hypothesis that these antibodies may be generated after incidental exposure or infection, a mechanism involving “molecular mimicry” (116). Immunisation of mice with viral and bacterial peptides with function and sequence similarity to the phospholipid-binding site of β2GPI (Table 3) induced high levels of aPL and aβ2GPI (116). These peptide-induced aPL are also able to enhance thrombosis and activate endothelial cells in vivo and in vitro (117).

Table 3: Viral and bacterial peptides with function and sequence similar to the phospholipid binding site of β2-glycoprotein I

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Sequence</th>
<th>Origin</th>
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<tbody>
<tr>
<td>GDKV</td>
<td>GDKVSFFCKNKEKKC</td>
<td>β2-Glycoprotein I</td>
</tr>
<tr>
<td>TADL</td>
<td>TADLAIASKKKKRPSPKPE</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>TIFI</td>
<td>TIFIIFCSEKRRKKQAAT</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>VITT</td>
<td>VITTLYYRRKKKPSDT</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>SGDF</td>
<td>SGDFETYNGGKMKMAFATS</td>
<td>Bacillus subtilis</td>
</tr>
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</table>

A number of studies have also discussed the mechanisms involved in aPL-mediated thrombosis and pregnancy loss. Nevertheless, the link between aPL, APS and thrombosis has not been elucidated.

Several hypotheses have been proposed to explain the pathogenic effects of these autoantibodies. As a consequence of initial damage, anionic phospholipids are exposed on the cell surface (e.g. endothelium, trophoblasts, platelets), the surfaces of which become reactive, inducing the production of procoagulant substances. The phospholipids are covered by phospholipid binding proteins, such as β2GPI or prothrombin.
If aPLs are present against such surface-bound proteins, aPLs may bind them and subsequently induce the production of procoagulant substances such as tissue factor, plasminogen activator inhibitor (PAI-1), or adhesion molecules (118) (Figure 1). This activation might explain clotting events in APS patients.

**Figure 1 - Hypothetical mechanism at the endothelial cell level**

 Activation signal (1) → anionic phospholipids (2) → Endothelial cell → TF, Adhesion molecules (5) → PBP (3) → aPL (4) → THROMBOSIS

PBP: phospholipid binding proteins; aPL: antiphospholipid antibodies; TF: tissue factor; PAI-1: plasminogen activator inhibitor 1. After an activation signal or damage (1), anionic phospholipids are exposed on the cell membrane (2). The PBP binds to them on the surface (3). Circulating aPL recognise these complexes, binding to them (4). The endothelial cell is thus activated, via specific pathways or via Fcγ receptors, inducing release of procoagulant substances (5), with the consequent activation of the coagulation pathway, platelet aggregation and thrombosis.

Some of the evidence for a cause-and-effect role for aCL comes from animal models of APS induced by immunisation of mice. Pregnant mice passively and actively immunised with human or mouse aCL develop fetal loss and thrombocytopenia (119). Interestingly, injection of the aCL cofactor (β2GPI) into animals results in the development of circulating aPL, while cardiolipin injected alone is relatively non-immunogenic (106).
Furthermore, an *in vivo* experiment demonstrated that human aCL from thrombotic patients infused into mice induced larger and more persistent thrombi than normal immunoglobulins (120). This data supports a direct role for the antibodies in the pathogenesis of thrombosis.

Several additional abnormalities have been reported to be related with aPL such as acquired deficiencies of protein S (91), abnormalities in prostacyclin production (121), autoantibodies against endothelial cell proteins including thrombomodulin (122) and heparin sulfate (95), and antibodies against platelet-activating factors (123). Recent studies from our unit have shown that increased tissue factor expression (124-126) and induction of endothelin I (127), the most potent endothelium-derived contracting factor, may be involved in the pathogenesis of thrombosis in the APS.

*In vitro* studies have also shown that aPL recognition of both anionic phospholipids and adhered β2GPI on trophoblast cell structures might represent a potential pathogenetic mechanism for defective placentation in women with the APS (128).

Recent data also suggests that *in vivo* complement activation is also required for aPL-mediated tissue injury. Holers et al (129) reported that complement blockade at the point of C3 activation prevented fetal loss and growth restriction in a murine model of APS induced by passive transfer of human aPL-IgG antibodies. Furthermore, Girardi et al (130) shows that C5-deficient mice are protected from aPL-induced pregnancy complications since the fetal resorption rate was lower and the embryo weight higher than the control mice, respectively. Recently, it has been shown that neutrophils, in response to aPL antibody-generated C5a, are able to express tissue factor potentiating inflammation in the deciduas and leading to miscarriages (131).

### 7. Genetics of the antiphospholipid syndrome

A number of studies have examined HLA antigens in patients with the primary and secondary APS. Most studies have involved small number of patients. In primary APS, an association has been noted with DR53, DR4, DQ7 and DR5 (132-135). In APS associated with SLE, an increased frequency of DR7 has been reported (134, 136, 137).

HLA DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302 and DQB1*0303-DQA1*0201-DRB1*0701 haplotypes have been suggested as responsible for anti-β2GPI antibody production(138, 139), giving a new insight into the molecular epitope(s) that might induce or react with autoimmune aPL. HLA DQB1*0301, DQB1*0302, DQB1*0303 and DQB1*06 alleles may be genetic determinants of LA (140).
Some reports have addressed the issue of a familial predisposition to the development of APS. Several reports have shown a higher incidence of aCL in first-degree relatives of patients with SLE or primary APS (141-148). Recently, Goel et al (149) in their family studies on APS have performed aPL and pedigree analysis suggesting a Mendelian autosomal dominant mode of inheritance for this disorder. Modelling studies strongly rejected environmental and autosomal recessive inheritance for the disease.

A number of other genetic variants have been investigated as risk factors for the development of APS. In particular, polymorphisms in genes involved in thrombus formation have been explored. Factor V Leiden is the most common thrombophilia in Caucasoid populations. However, the presence of Factor V Leiden did not alter the clinical features of APS (150-153). Prothrombin promotor G20210A, another common genetic risk for venous thrombosis, was found to be rare in patients with APS, which means that this genetic variant did not affect venous thrombosis in patients with aPL (154-156). Other genetic polymorphisms noted in patients with APS are methylenetetrahydrofolate reductase C677-->T (MTHFR), an enzyme involved in the re-methylation of homocysteine to produce methionine (150), angiotensin-converting enzyme (157) and plasminogen activator and plasminogen activator inhibitor-1 (158).

8. Clinical manifestations

8.1. Thrombosis

The APS is a noninflammatory autoimmune disease where the most critical pathological process is thrombosis, which results in most of the clinical features suffered by these patients.

Arterial or venous thrombosis together with or without an adverse pregnancy history can be present. Deep vein thrombosis has been the most commonly reported venous manifestation, often recurrent and accompanied by pulmonary embolism. Occlusion of the intracranial arteries are the most common arterial manifestation, with the majority of patients presenting with stroke.

As any organ and any size of vessel can be affected; thus, the range of clinical features is extremely wide.
8.1.1. Central nervous system

There is a very broad spectrum of CNS involvement in APS. Cerebral ischemia associated with aPL is the most common arterial thrombotic manifestation (22, 30). Many studies have found that aPL are associated with an increased risk for cerebral ischemia (35, 159-163) but some have not (164-166). The age of onset in APS is several decades earlier that in the typical stroke population and the ischemic events may occur in any territory.

A less common form of cerebral thrombotic disease associated with aPL is sagittal venous sinus thrombosis (167, 168). As with stroke, this manifestation in patients with aPL occurs at a younger age than in individuals without aPL.

Migraine is one of the most prominent complains in patients with APS (169) but its association with aPL is still controversial. Several studies failed to demonstrate an association between the presence of aPL and migraine (170, 171). A recent study has shown that although the prevalence of headache in SLE is similar to that reported for the general population, aPL are more significantly prevalent in the group of patients with headache compared to those without (172).

Cognitive deficits associated with APS may vary from mild neurocognitive disorders to severe vascular dementia. Patients affected by mild cognitive dysfunction often complain of poor concentration or forgetfulness. Verbal memory deficits, decreased psychomotor speed and decreased overall productivity have been correlated with aPL (173-175). Whether these cognitive deficits result from recurrent cerebral ischemia or whether there is other underlying mechanisms remains unknown. Psychiatric problems, such as mood disorders and psychosis, have also been associated with aPL (176).

Some patients with APS may exhibit features often seen in multiple sclerosis (177). Myelitis, balance and sensory problems not surprisingly often lead to an erroneous diagnosis of multiple sclerosis. Differential diagnosis is difficult, and compounded by a number of features, notably: single-point-in-time MRIs may fail to differentiate and borderline positive aPL levels may be dismissed as being of no significance. Serial MRIs may help to distinguish (the picture in multiple sclerosis is changing), as may an EEG (178). The clinical findings of livedo and a dry Schirmer’s test point towards APS. So also may be a previous history of thrombosis or pregnancy loss, an abnormal localisation of the lesions on MRI, and the response to anticoagulant therapy might be helpful in the differential diagnosis (179). Anecdotally, some patients who apparently have multiple sclerosis but who are positive for aPL have benefited from anticoagulation though this is often a difficult clinical decision (180).
Seizures have been consistently associated with the presence of aPL (181-183). APS patients with epilepsy seem to have a higher prevalence of focal ischemic events and amaurosis fugax and a higher frequency of valvular pathology (184). The etiology is still unknown but some authors have suggested direct interaction between aPL and neuronal tissue (185-187).

Less frequently described manifestations of APS include chorea (13, 188, 189), transverse myelopathy (190-193), Guillain-Barre syndrome (172, 194), sensorineural hearing loss (195, 196) and ocular syndromes with retinal and choroidal ischemia (16, 197-199). Although the pathological lesion is likely to be thrombotic (small vessel ischemia), there is some evidence for direct neurotoxicity (200).

8.1.2. Heart

Several cardiac lesions apart from coronary artery disease have been reported in association with aPL (201). Heart valve lesions are the most common cardiac manifestations described in patients with aPL. The prevalence of valvulopathy has been reported in 35% to 75% of patients with APS, according to different series (202, 203). Most of the cases are asymptomatic with around 5% of the cases progressing to cardiac failure requiring valve replacement. Valve masses (vegetations) and diffuse valvular thickening are the two morphologic ecocardiographic patterns most frequently see in APS. The predominant functional abnormality is regurgitation, whereas stenosis is rarely seen. Although mitral valve is the most commonly affected site, followed by the aortic valve (204), isolated tricuspid valve involvement has also been described (205). It is likely that thrombosis on a damaged valve and healing with fibrosis are key players in the valve deformity. Whether aPL are instrumental in the initial damage of the valves remains to be elucidated, but deposits of immunoglobulins (including aCL) and complement in diseased valves have been documented, suggesting a role in the development of valvular pathology (206).

Infective endocarditis is uncommon, but a condition of pseudoendocarditis has been described in both SLE and primary APS and is characterised by fever, murmurs, valve vegetations, splinter hemorrhages, increased aPL and negative blood cultures (207).

Coronary artery disease is also well documented in patients with APS and the association between aPL and myocardial infarction or cardiac death has been confirmed by prospective studies (208, 209). Isolated unstable angina has also been reported occasionally in patients with the APS (16). It is our recommendation that all patients developing myocardial infarction under the age of 40 should be tested for aPL.
Uncommon cardiac manifestations of APS include intracardiac thrombus, which can be misdiagnosed as a cardiac tumour (210, 211), myocardial dysfunction (212) and syndrome X, characterised by angina-like chest pain, a positive exercise test and angiographically normal coronary arteries (213).

The increased prevalence of an abnormal ankle-brachial index (a bedside test which reliably identifies lower extremity peripheral artery disease) suggests that patients with APS are at increased risk of atherosclerosis (214-216).

**8.1.3. Lungs**

Patients with APS may develop a broad spectrum of pulmonary involvement. The most common pulmonary manifestation of the APS is pulmonary embolism and infarction, usually seen as the first manifestation of the disease (217, 218). Recurrent pulmonary embolism may lead to thromboembolic pulmonary hypertension (219).

Pulmonary hypertension is found in around 1.8% to 3.5% of the patients with APS (20). Several cases of pulmonary hypertension complicating primary APS have been described (16, 220).

Adult respiratory distress syndrome is a very rare but devastating clinical syndrome with a mortality of 52%, usually seen in patients with catastrophic APS (218, 221).

Although quite uncommon, some patients may present with diffuse alveolar hemorrhage as the first manifestation of APS. This potentially life-threatening condition is usually diagnosed by open lung biopsy which shows microvascular thrombosis and secondary alveolar hemorrhage with or without pulmonary capillaritis (222).

**8.1.4. Kidney**

The description of the APS has brought about a radical review of the pathophysiology of renal lupus. A significant contribution to pathology as well as to treatment and prognosis has been made by the re-assessment of the degree of microvascular thrombosis in lupus kidney biopsies, especially in aPL-positive individuals.
The kidney is a major target organ in the APS where both arterial and venous vessels, as well as the intraparenchymatous arteries and microvasculature may all be affected (223). As renal damage in SLE is primarily due to immune complex-mediated glomerulonephritis, patients with SLE and secondary APS can develop kidney involvement due to a combination of both processes (224). Moreover, the impairment of renal function in SLE patients with aPL can also occur in the absence of APS-related manifestations. In this case, distinguishing between SLE-nephritis (immune complex disease) from APS-nephritis (thrombotic disease) can only be accomplished by kidney biopsy (225).

Renal artery occlusion and renal artery stenosis have been described in APS patients with hypertension (226-229). The localised and stenotic (thrombotic) arterial lesions are totally different in appearance from the picture of renal artery disease seen in atheroma in older patients. The hypertension in APS patients treated with careful anticoagulation is, significantly, much better controlled (230). Renal infarction may result from partial or total, transient or permanent occlusion of the renal arteries. Thrombosis of the renal veins (231, 232) and thrombotic microangiopathy (223) has also been described in APS. Tektonidou et al found a strong association between APS nephropathy, arterial thrombosis and livedo reticularis (233).

8.1.5. Skin

The most frequent skin manifestations are livedo reticularis and skin ulcers (234-237).

Livedo reticularis is characterised by a mottled purple reticular pattern with different localisation, extension, infiltration, and regularity of the fishnet pattern. In APS it is usually disseminated and have an irregular branching or broken pattern (219). Its association with aPL has been described in several studies (13, 234, 235, 238). In APS, livedo reticularis is usually persistent and anticoagulation has no effect on its extent or severity. It is clear that livedo reticularis is a marker of poor prognosis and more severe disease in APS and as such is a powerful physical sign when suspecting this disorder (237, 239).

Skin ulcers are frequently present in the extremities. However, extensive cutaneous necrosis associated with aPL has been reported in the literature (240).

Subungual splinter hemorrhages appear as tiny linear longitudinally oriented, reddish-brown to black, distal subungual lesions that fail to blanch under pressure. Subungual splinter hemorrhages are seen in around 5% of the patients with APS and their presence in a patient with aPL may alert the physician to the occurrence of other thrombotic events (241, 242).
Digital gangrene has been described in patients with aPL (235, 243). A variety of other cutaneous lesions, including purpura, tender nodules, papules and palmar-plantar erythema, anetoderma have been described in APS (235, 244, 245).

8.1.6. Liver and gastrointestinal tract

Intestinal ischemia and perforation due to thrombosis are rare but well described, especially in the context of the catastrophic APS. We have recently reported a sizeable series of patients with APS and celiac artery stenosis. Many of the patients had “classical” features of mesenteric ischemia with abnormal pain after large meals, upper abdominal bruits and so on. Others were relatively asymptomatic, presumably because of good collateral circulation (246).

Liver thrombosis, including Budd-Chiari syndrome, was a feature of the original clinical description of the syndrome (10). Liver function abnormalities are, in fact, common in APS patients, possibly as a result of either vascular “sludging” or small vessel thrombosis (247).

8.1.7. Hemocytopenias

Thrombocytopenia is a frequent haematological manifestation of APS, seen in around 25% of the patients (248, 249). Thrombocytopenia is rarely severe; platelet counts are usually between 50-100x10^9, and bleeding is not a common problem (250). The exact role of aPL in the development of thrombocytopenia is still not known. Some data showed that specific anti-platelet glycoprotein antibodies found in patients with aPL may also be involved. Galli et al (251) found antibodies to the platelet membrane glycoproteins IIb/IIIa and Ib/IX in 40% of aPL positive patients and a positive correlation between these antibodies and thrombocytopenia. Godeau et al (252) also showed antibodies to a panel of platelet membrane glycoproteins in the sera of patients with thrombocytopenia and APS. Although why aPL are so frequently associated with anti-platelet glycoprotein antibodies still remains to be elucidated, these data suggest that antibodies to the platelet membrane glycoproteins may act along with aPL in the development of thrombocytopenia.

Hemolytic anemia may be present in patients with APS and sometimes associated with thrombocytopenia, the so-called Evans syndrome. Although a positive Coombs test is not rare in APS, hemolytic anemia is uncommon (250, 253, 254). A significant correlation between aPL and hemolytic anemia has been found by different groups (234, 255-257).

A small number of cases of marrow infarction have been described (258).
8.1.8. Musculoskeletal

Avascular necrosis of bone is most commonly of the femoral head, but also of other bones such as the navicular is a complication of APS, presumably as a result of ischemia in vulnerable sites (259-261). Tektonidou et al (259) found MRI scanning to be a sensitive test with 20% of primary APS patients showing evidence of avascular necrosis. Metatarsal fracture and other spontaneous fractures have been reported in the spine, ribs and elsewhere (261, 262). The patients presented with fractures that occurred spontaneously or after trivial trauma and many had normal bone mineral density and were not taking corticosteroids.

More recently, reflex sympathetic dystrophy was reported in a patient with APS (263).

8.1.9. Endocrine system

The spectrum of clinical manifestations in APS is constantly growing to involve almost every organ system in the body. Although unusual, endocrinologic complications of APS have also been reported (264). Adrenal insufficiency is the most common endocrinologic manifestation and can be the presenting symptom of APS. A few cases of hypopituitarism and ovarian and testicular involvement have been reported. aPL has been detected in the sera of diabetic patients, probably associated with some macroangiopathic complications and in patients with autoimmune thyroid disease.

8.2. Pregnancy

APS is frequently diagnosed following investigation for recurrent miscarriage, pregnancy morbidity being one of the major manifestations of the syndrome. In pregnancies that do not end in miscarriage or fetal loss, there is high incidence of early onset pre-eclampsia, intrauterine growth restriction, placental abruption and premature delivery (265).
8.2.1. Pregnancy morbidity

Pre-eclampsia has been reported to be highly prevalent in patients with APS (265-269), being the major contributor to preterm delivery in these patients. The association between aPL and pre-eclampsia has been confirmed in 2 prospective studies of unselected patients (270, 271) but not by others (272, 273).

The risk of HELLP, a syndrome characterised by haemolysis, elevated liver enzymes and low platelets, is increased in APS with a wide reported rate observed (0.66 to 10.6%) (274-276). Around two third of the cases have been reported to be associated with preeclampsia/eclampsia (276).p

Placental insufficiency may also be manifested by fetal growth restriction, found in approximately 30% of the patients with APS (265, 266, 268, 269). Two early prospective studies failed to demonstrate a relationship between aPL and fetal growth impairment (270, 272). However, a more recent study (271) showed that 12% of aPL positive women had small-for-gestational age babies compared to 2% of the aPL negative women.

Fetal distress has been reported in up to a 50% of the offspring (265), although its association with aPL has not been confirmed.

Pre-eclampsia and fetal growth restriction are responsible of preterm delivery occurring in around 30% of pregnant women with APS (265, 268).

Placental pathology may show extensive infarction, necrosis, and thrombosis (266, 277-280). However, these histological abnormalities are non-specific and are not always present in the placenta of women with APS (281).

Many investigators have found a statistically higher rate of aPL in women with infertility, though not all agree (282). Proof that aPL are associated with a specific type of infertility or influence pregnancy outcome with assisted reproductive technology is lacking.

8.2.2. Pregnancy loss

Women with aPL have an unusually high proportion of pregnancy losses within the fetal period (≥10 weeks of gestation) (267, 283), in contrast with unselected women with sporadic or recurrent miscarriage where the pregnancy losses occur more commonly in the pre-embryonic period (less than 6 weeks of gestation) or the embryonic period (6-9 weeks of gestation). The prevalence of aPL in the general obstetric population is low (<2%), so universal screening is not warranted (284).
However, any woman with a history of three or more first trimester miscarriages should be tested for these antibodies. Rai et al (285) have reported that 15% of women with a history of three or more consecutive miscarriages have persistently positive aPL results.

The prospective fetal loss rate in primary APS is reported to be 50% to 70% (286, 287), with some studies suggesting a rate as high as 90% in patients with SLE/APS (266, 288). Previous poor obstetric history (270, 289, 290) along with antibody level (291), particularly of the IgG isotype (292) remain the most important predictors of future risk.

9. Catastrophic antiphospholipid syndrome

The term catastrophic APS (CAPS) is used to define an accelerated form of APS resulting in multiorgan failure concurrently over a short period of time, typically days to weeks. Catastrophic APS is an infrequent but life threatening situation, seen in approximately 1% of the patients with APS (29). It still remains a serious complication with a poor prognosis. Preliminary classification criteria for CAPS have been elaborated (293) and recently validated after analysing data from an International Registry of patients with this condition (CAPS registry) (294).

It is recognised that precipitating factors, such as infections, postpartum and surgery may contribute to the development of catastrophic APS (294). Additional precipitating clinical features include malignancy, medication, anticoagulation withdrawal, and SLE exacerbation (295). Cerebral involvement (mainly consisting of stroke), cardiac involvement, and infections are the main causes of death in patients with CAPS. The presence of SLE was related to a higher mortality rate (296), leading to death in around 47% of the cases (294). Surviving an episode of CAPS is typically associated with a good prognosis as only 26% develop further APS-related episodes (297). Recurrence of CAPS in the same patient is unusual.

10. Diagnosis of the antiphospholipid syndrome

The diagnosis of the APS depends greatly upon laboratory diagnostics. In clinical practice, laboratory diagnosis of APS relies on the demonstration of a positive aCL antibody test by an in-house or commercially available enzyme-linked immunosorbent assay (ELISA) or on the presence of LA by a coagulation-based test (298, 299). The aCL test is positive in about 80% of patients with APS, the LA test is positive in about 20%, and both are positive in about 60% of cases (29). Persistence of the positive tests must be demonstrated and other causes and underlying factors considered. It is important that both tests be performed in patients suspected of having APS.
These assays not only detect aCL and/or LA but also a heterogeneous group of antibodies that bind serum proteins (the so called phospholipid binding proteins), such as β2 glycoprotein I (β2GPI) and/or prothrombin.

The diagnostic value of all available assays to detect aPL is a matter of ongoing debate. Although the presence of LA correlates best with thrombosis (300), accurate determination is not always possible due to anticoagulant treatment. Data on the predictive value of alternatives such as the anti-β2GPI assay are insufficient and prospective cohort studies are needed (301). However, some laboratories include testing for these antibodies as part of their routine screening for APS.

11. Classification criteria for APS

An international consensus statement on classification criteria for definite APS was published in 1999 (302). A patient with APS must meet at least one of two clinical criteria (vascular thrombosis or pregnancy complications) and at least one of two laboratory criteria (aCL and/or LA). Other features such as thrombocytopenia, hemolytic anemia, transient ischemic attacks, livedo reticularis, chorea, migraine, cardiac valve disease and transverse myelopathy or myelitis that have been reported to be associated with aPL were not included as essential features due to the lack of strong clinical and experimental evidence (23, 302).

These criteria were designed to provide uniform groups for clinical studies, rather than diagnostic aids. Although they have been shown to be specific and sensitive for the classification of the primary and secondary APS (303) the absence of “major” or “essential” features in the presence of “minor” features should not discourage the clinician from making the diagnosis if other causes of such features have been ruled out (23).

A recent consensus update has included anti-β2GPI as a laboratory criterion for APS (304) and laboratories around the world are being encouraged to standardize their methodology for the detection of these antibodies (table 4).
Table 4: Simplified 2006 updated criteria for the classification of definite APS

<table>
<thead>
<tr>
<th>Clinical criteria</th>
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<tbody>
<tr>
<td>1) Vascular thrombosis: ≥1 arterial, venous or small vessel thrombosis in any tissue or organ, confirmed by imaging or histopathology in the absence of significant evidence of inflammation in the vessel wall</td>
</tr>
<tr>
<td>2) Pregnancy morbidity:</td>
</tr>
<tr>
<td>a) ≥1 unexplained death of a morphologically normal foetus at or beyond the 10th week of gestation, or</td>
</tr>
<tr>
<td>b) ≥1 premature births of a morphologically normal neonate at or beyond the 34th week of gestation, due to severe pre-eclampsia, eclampsia or placental insufficiency, or</td>
</tr>
<tr>
<td>c) ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation (maternal anatomic or hormonal abnormalities and chromosomal causes excluded)</td>
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<table>
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<tr>
<th>Laboratory criteria</th>
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<tbody>
<tr>
<td>1) IgG and/or IgM aCL, in medium or high titre, on 2 or more occasions, at least 12 weeks apart, measured by a standardised ELISA for β2-glycoprotein I-dependent aCL</td>
</tr>
<tr>
<td>2) IgG and/or IgM anti-β2GPI in titer &gt;99th percentile, on 2 or more occasions, at least 12 weeks apart, measured by a standardised ELISA</td>
</tr>
<tr>
<td>3) LA on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis</td>
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</table>

12. Seronegative APS

Current criteria for the classification of APS recommend the use of standardised enzyme-linked immunoassay that measure β2GPI-dependent IgG and IgM aCL and/or the LA according to the recommended criteria from the International Society on Thrombosis and Hemostasis Subcommittee on Lupus Anticoagulant-Phospholipid-dependent antibodies (305).

There are, however, a small number of patients with the classical features of APS, including pregnancy losses, thrombotic events and livedo reticularis, where the aPL testing is persistently negative, leading to the concept of ‘seronegative APS’. Although it is universally recognised that the routine screening tests (aCL and/or LA) might miss some cases, careful differential diagnosis and repeat testing are mandatory before the diagnosis of ‘seronegative APS’ can be made (306). A very tiny minority of these patients may have anti-β2GPI and/or antiprothrombin antibodies, but it may be that these patients have other explanation for their clinical features (307, 308).
13. Management of the antiphospholipid syndrome

Data regarding management and prognosis is limited and current therapeutic approaches are based mainly on the clinician’s best judgement. The thrombotic complications are unpredictable and the mechanisms triggering these events in individual patients are ill defined. Despite advances in studies of mechanisms of thrombosis in APS, and the development of newer tests for the diagnosis, the serological “fingerprint” of the patient most at risk for arterial or venous thrombosis, remains elusive.

13.1. Management of thrombosis-free aPL-positive subjects

The controversy concerning whether or not prophylactic treatment is indicated for patients with aPL who have no history of thrombosis remains unresolved as there are no available data to identify which patients with aPL will thrombose. To date, it is recommended that individuals with a persistently positive aCL (moderate/high titres) and/or unequivocally positive LA tests take low-dose aspirin (75-100mg daily) along with the removal or reduction of other risk factors for thrombosis (i.e. smoking, obesity, high blood pressure, hypercholesterolemia and estrogen-containing oral contraceptive pills) (309). Hydroxychloroquine could be safely prescribed as it has been shown to be protective against the development of thrombosis in aPL-positive patients with SLE (310).

13.2. Management after the first thrombotic episode

Patients with APS should be treated with long-term anticoagulation, although the optimal intensity of anticoagulation therapy is uncertain (311). Retrospective studies in the 1990s suggested that thrombosis in APS patients should be managed with high-intensity (target INR 3.0-4.0) oral anticoagulation (33, 312).

However, the more recent prospective studies suggest only an INR of 2.0-3.0 is required (313-315). As most of these studies were done in patients with venous thrombosis, some prefer to advocate an INR of 2.0-3.0 for those with venous thrombosis reserving intensive anticoagulation (INR 3.0-4.0) for those with recurrent venous thrombosis or arterial thrombosis.

Around 30% to 60% of APS patients with thrombosis will be subjected to recurrences (22, 30, 33, 312, 316, 317). Although there is wide recognition that patients with arterial events should have long-term anticoagulation, the length of anticoagulation in those with APS and venous thromboembolism has been hotly debated (318).
Data emerging suggests that following a documented aPL-associated thrombotic episode warfarin therapy should be continued for longer periods in these patients (possibly for life) than otherwise healthy individuals without aPL (319). It is not clear, however whether prolonged anticoagulation is necessary in APS patients whose first thrombotic episode developed in association with surgery, oral contraceptive pill, pregnancy or other circumstantial thrombotic risk factors.

Additional therapy with aspirin may be used in cases of recurrent venous thrombosis or arterial thrombosis, however, the effectiveness in this situation is not known. What is well known is that the risk of hemorrhage is increased when aspirin is used alongside oral anticoagulant therapy (320) and the physician must be aware of this.

Treatment of children with APS or aPL-related events has been similar to adults with this condition. Up to date there are no standard recommendations for therapy based on long-term observation of the outcome of APS in children. Antithrombotic therapy is recommended for children who present with thrombosis and have aPL but the duration and intensity of this therapy remains unclear. Intermediate intensity anticoagulation therapy have been suggested (321), however, the effectiveness of such therapy and the length of treatment required are unknown (322).

The role of steroids and immunosuppressive drugs in the treatment of patients with aPL and thrombosis is uncertain. Such drugs have severe side effects when given for prolonged periods and aPL are not always suppressed by these agents. Furthermore, some series of patients with APS have shown that corticosteroids and immunosuppressive therapy, prescribed to control lupus activity, did not prevent further thrombotic events (221). The use of these drugs is probably justified only in patients with life-threatening conditions with repeated episodes of thrombosis despite adequate anticoagulation therapy, namely catastrophic APS. In this rare but life-threatening condition, the combination of anticoagulation, steroids, and plasmapheresis or intravenous gammaglobulins (IVIG) has also been used with successful recovery in 58% of the patients (323).

13.3. Management in adverse pregnancy history

Pregnancy complicated by APS requires expert care and a team approach by obstetricians, physicians, and hematologists. Patients with APS should undergo preconceptional assessment and counselling. A detailed medical and obstetric history should be obtained, and the presence of significant levels of aPL should be confirmed. The patient should be informed of the potential maternal and obstetric problems, including fetal loss, thrombosis or stroke, pre-eclampsia, fetal growth impairment, and preterm delivery.
The pharmacological management of pregnancy in women with APS is the subject of much debate. It has included prednisone and aspirin, aspirin alone, low-dose aspirin and heparin, IVIg and even supportive care alone. There are several non-randomised studies in women with fetal loss suggesting that low-dose aspirin is effective (324). Randomised controlled trials are few, small and contradictory in their results (325). While aspirin alone may have a role in women with early pregnancy losses, most experts support the use of heparin therapy in addition to low-dose aspirin. A systematic review of randomised controlled therapeutic trials published recently showed that combination therapy with aspirin and heparin might reduce pregnancy loss in women with aPL by 54% (326).

Women with APS and previous thromboembolism are at extremely high risk in pregnancy and the puerperium and should be given antenatal thromboprophylaxis with subcutaneous heparin. Our recent experience demonstrated that a 90% live birth rate can be achieved in women with APS with significant past pregnancy morbidity and/or thrombosis (327).
SUMMARY

- APS is the most common acquired thrombophilia
- Venous and arterial thrombosis in young individuals and pregnancy morbidity are the hallmark of the disease
- Deep vein thrombosis has been the most commonly reported venous manifestation, often recurrent and accompanied by pulmonary embolism.
- Occlusion of the intracranial arteries is the most common arterial manifestation, with the majority of patients presenting with stroke.
- Given the clinical setting, testing for both aCL and LA is essential for the diagnosis of APS
- There appear to be very few, if any differences between the clinical complications associated with the primary and the secondary form of the syndrome and the rates of arterial or venous thrombosis or fetal loss do not appear to be different
- Differential diagnosis must be considered before labelling a patient as having "seronegative APS"
- Catastrophic APS is an infrequent but life threatening situation, resulting in multiorgan failure concurrently over a short period of time, typically days to weeks.
- Correct identification of patients with APS is important, because prophylactic anticoagulant therapy can prevent thrombosis from recurring
KEY REFERENCES

32, 33, 34, 120, 172, 250, 299, 302, 311, 325

Complete References


50. DA Triplett, JT Brandt, KA Musgrave and CA Orr. 1988. The relationship between lupus anticoagulants and antibodies to phospholipid. *JAMA;* **259:** 550-554


53. EM Bevers, M Galli, T Barbui, P Comfurius and RF Zwaal. 1991. Lupus anticoagulant IgG's (LA) are not directed to phospholipids only, but to a complex of lipid-bound human prothrombin. *Thromb Haemost;* **66:** 629-632


55. M Galli, P Comfurius, C Maasen, HC Hemker, MH de Baets, PJC van Breda-Vriesman, T Barbui, RFA Zwaal and EM Bevers. 1990. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet;* **336:** 1544-1547

56. HP McNeil, RJ Simpson, CN Chesterman and SA Krilis. 1990. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-bound inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci USA;* **87:** 4120-4124


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81. JE Gardiner, MA McGann, CW Berridge, CA Fulcher, TS Zimerman and JH Griffin. 1984. Protein S as a cofactor for activated protein C in plasma and in inactivation of purified factor VIII. Circulation; 70: 205


91. AL Parke, RE Weinstein, RD Bona, DB Maier and FJ Walker. 1992. The thrombotic diathesis associated with the presence of phospholipid antibodies may be due to low levels of free protein S. Am J Med; 93: 49-66


97. T Sugi and JA McIntyre. 2001. Certain autoantibodies to phosphatidylethanolamine (aPE) recognize Factor XI and Prekallikrein independently or in addition to the kininogens. *J Autoimmun*; **17**: 207-214

98. KK Hwang, J Grossman, S Visvanathan, RU Chukwuccham, VLJ Woodsm, DT Le, BH Hahn and PP Chen. 2001. Identification of anti-thrombin antibodies in the antiphospholipid syndrome that interfere with the inactivation of thrombin by antithrombin. *J Immunol*; **167**: 7192-7198


100. DW Jones, MJ Gallimore, IJ MacKie, SL Harris and M Winter. 2000. Reduced factor XII levels in patients with the antiphospholipid syndrome are associated with antibodies to factor XII. *Br J Haematol*; **110**: 721-726


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244. RA Asherson, S Jacobelli, H Rosenberg, P Mckee and GR Hughes. 1992. Skin nodules and macules resembling vasculitis in the antiphospholipid syndrome--a report of two cases. *Clin Exp Dermatol;* **17:** 266-269


246. SR Sangle, W Jan, IS Lau, AN Bennett, GR Hughes and DP D'Cruz. 2006. Coeliac artery stenosis and antiphospholipid (Hughes) syndrome/antiphospholipid anti-bodies. *Clin Exp Rheumatol;* **24:** 349


252. B Godeau, JC Piette, P Fromont, L Intrator, A Schaeffer and P Bierling. 1997. Specific antiplatelet glycoprotein autoantibodies are associated with the thrombocytopenia of primary antiphospholipid syndrome. *Br J Haematol;* **98:** 873-879


278. R Nayar and JM Lage. 1996. Placental changes in a first trimester missed abortion in maternal systemic lupus erythematosus with antiphospholipid syndrome; a case report and review of the literature. *Hum Pathol; 27*: 201-6


299. ML Bertolaccini and MA Khamashta. 2006. Laboratory diagnosis and management challenges in the antiphospholipid syndrome. Lupus; 15: 172-8


International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost;* **4:** 295-306


307. ML Bertolaccini, B Roch, O Amengual, T Atsumi, MA Khamashta and GRV Hughes. 1998. Multiple antiphospholipid tests do not increase the diagnostic yield in antiphospholipid syndrome. *Br J Rheumatol;* **37:** 1229-1232


315. W Lim, MA Crowther and JW Eikelboom. 2006. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA;* **295:** 1050-7


319. HI Brunner, WS Chan, JS Ginsberg and BM Feldman. 2002. Longterm anticoagulation is preferable for patients with antiphospholipid antibody syndrome. result of a decision analysis. *J Rheumatol;* **29:** 490-501


322. T Avcin, R Cimaz and PL Meroni. 2002. Recent advances in antiphospholipid antibodies and antiphospholipid syndromes in pediatric populations. *Lupus; 11*: 4-10


