# 2 Antiphospholipid (Hughes) Syndrome: An Overview

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## Introduction

The cardinal features of the antiphospholipid syndrome (APS), first described in1983 by Dr Graham Hughes and his team at the Hammersmith Hospital, included recurrent arterial and venous thromboses, fetal losses, and thrombocytopenia. Although a wide variety of clinical features have been added over the last 22 years, these major features have stood the test of time. The aim of this chapter is to give a clinical overview of the spectrum of these clinical features, the assessment of aPL, and their impact on morbidity and mortality.

## Demographics

APS is now recognized as a common disorder and is certainly not a "small print" disease. Its importance lies in the fact that once diagnosed, this a treatable condition. The difficulty is that for many patients diagnosis is often delayed, sometimes for years, with consequent disability, loss of livelihood, inability to start a family, or even death.

The prevalence of antiphospholipid antibodies (aPL) in otherwise healthy populations is less than 1% and up to 5% in older healthy populations. In autoimmune diseases, especially systemic lupus erythematosus (SLE), however, the prevalence is much higher. There have been several large studies of the prevalence of aPL in SLE patients. Perhaps the largest is the Euro-Lupus study that found a prevalence of 24% IgG anticardiolipin antibodies (aCL), 13% IgM aCL, and 15% lupus anticoagulant (LA) in a cohort of 1000 patients with SLE [1]. The prevalence of aPL and definite APS may increase with longer follow up, further pregnancies, and repeat testing for aPL. Thus, Perez-Vazquez et al showed that the prevalence of APS increased from 10% to 23% after 15–18 years in a large cohort of SLE patients [2]. A further study of 1000 APS patients has detailed the clinical features of the disorder [3].

## Definition and Classification of APS

An international consensus statement on classification criteria for definite APS was published after a workshop in 1998 (Table 2.1) and validated [4, 5]. These

**Table 2.1.** Classification criteria for the antiphospholipid syndrome.

**Clinical criteria**

1. Vascular thrombosis:
   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 weeks 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 at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency or
   (c) Three more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic, or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

**Laboratory criteria**

1. Anticardiolipin antibody of IgG and/ or IgM isotype in blood, present in medium or high titre, on two or more occasions, at least 6 weeks apart, measured by a standard enzyme linked immunosorbent assay for $\beta_2$-glycoprotein 1-dependent anticardiolipin antibodies.
2. Lupus anticoagulant present in plasma on two or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

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

classification criteria were developed for use in research studies rather than as diagnostic criteria which have to date not been developed. Other well-recognized features of APS, such as thrombocytopenia, hemolytic anemia, transient ischaemic attacks, transverse myelitis, livedo reticularis, valvular heart disease, demyelinating syndromes, chorea, and migraine, were not thought to have as strong an association as the final criteria and were excluded as classification criteria, possibly resulting in lower sensitivity but higher specificity [5]. In clinical practice, however, the physician should still consider the diagnosis and commence treatment according to clinical judgment after exclusion of other causes of these clinical features.

There are numerous traps for the unwary and many other conditions can be associated with aPL but are not necessarily associated with thrombosis. Thus, aPL may occur in infections such as human immunodeficiency virus (HIV) and malignancy and may also follow exposure to certain drugs. aPL in these circumstances are not necessarily pathogenic and these conditions should therefore be considered in any differential diagnosis of APS.

## Indications for aPL Testing

There is a compelling case for aPL to be tested routinely in all patients who are newly diagnosed with an autoimmune connective tissue disease, especially SLE or Sjögren's syndrome, because the prevalence of aPL in these disorders ranges between 30% and 50% [6]. The finding of aPL at disease onset may have significant consequences later in the disease course in terms of predicting morbidity and mortality [7]. In other clinical contexts, patients who suffer thrombotic events at relatively young ages should also be considered for testing. Thus, patients with strokes,

**Table 2.2.** Indications for the measurement of antiphospholipid antibodies.

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| Connective tissue disease especially SLE |
| Venous/arterial thrombosis before the age of 45 years |
| Thrombosis after trivial provocation |
| Association of arterial and venous thrombosis |
| Association of thrombosis and fetal loss |
| Recurrent events |
| Family history |
| Thrombosis in an unusual site: retinal vein, portal, cerebral venous sinus, renal vein |
| Recurrent superficial thromophlebitis |
| Recurrent miscarriage |
| Coumarin-induced skin necrosis |

myocardial infarctions, and venous thromboses under the age of 50 may be at risk of further thrombotic events if they are aPL positive. Similarly, women with pregnancy morbidity should also have aPL measured. There is a wide spectrum of aPL-related pregnancy morbidity, including miscarriage, fetal death, intra-uterine growth restriction, intra-uterine death/still birth, pregnancy-induced hypertension, pre-eclampsia, and eclampsia. There is increasing evidence though that other thrombophilic disorders may also be associated with obstetric problems [8].

The timing of measurement may be important. Some authors have suggested that aPL may be consumed during a thrombotic episode, though this remains controversial. Alternatively, due to endothelial activation and exposure of cryptic antigens, aPL may appear after the thrombotic event as an "epiphenomenon" [9]. For these reasons aPL should be measured between 6 weeks and 3 months post-thrombosis to confirm results. Steroid therapy and the development of the nephrotic syndrome may also be associated with a falsely negative result [10, 11].

A recent intriguing paper has suggested that aPL may appear many years prior to the diagnosis of an autoimmune connective tissue disease such as lupus. Moreover, aPL-positive patients appeared to be at risk of more severe lupus later in the disease course [12]. This data is in keeping with their previous findings for anti-nuclear antibodies appearing long before the onset of clinical features of SLE. These studies suggest that immune dysregulation leading to autoantibody production may precede the appearance of symptoms by many years.

## What Should Be Measured?

The recommendation is that both IgG and IgM aCL isotypes should be tested as well as LA. The significance of IgA aCL antibodies remains controversial but may be more relevant in SLE populations with African ancestry in contrast to Caucasians [13, 14]. The relevance of IgA aCL is discussed in detail elsewhere in this book. Although aPL testing has been standardized, there remain major inconsistencies when standard sera are sent to various laboratories. Testing for LA is also inconsistent but there seems to be a consensus that aCL are sensitive and LA testing is more specific in the diagnosis of APS. Anti–$\beta_2$-glycoprotein I antibodies correlate well with clinical features of APS as well as with other aPL and will be discussed in detail in this book. However, most routine laboratories do not offer anti–$\beta_2$-glycoprotein I

antibodies because in general there is no added value above conventional aPL testing and the assay lacks standardization.

# Prevalence of aPL

## General Population

The prevalence of aPL in the general population is low. Large studies have shown prevalences of between 2% and 7%. For example, in 543 blood donors under 65 years of age, Fields et al found an aCL prevalence of 2% [15]. The Antiphospholipid Antibodies in Stroke Study (APASS) Group also found a prevalence of aCL in 4.3% of 257 hospitalized non-stroke patients with a mean age 66 [16]. This was similar to the prevalence of 7.1% for at least one positive aCL in 1014 in-patients studied by Schved et al with a mean age of 66.7 years: the most frequent associations were with carcinoma or alcohol abuse [17 ].

## Elderly

Many autoantibodies become more prevalent with increasing age and aPL is no exception. Fields found that 12% of 300 healthy individuals older than 65 years had IgG or IgM aCL antibodies and that there was an association with positive antinuclear antibodies (ANA) but not rheumatoid factor [15]. The significance of these autoantibodies remains unclear and could be related to the increasing prevalence of associated conditions in the elderly, such as malignancy and drug treatment.

## Venous Thromboembolism

In patients with unselected venous thromboembolism, the prevalence of aCL varies from 3% to 17% and LA from 3% to 14%. The highest prevalence of 17% was found by Schulman et al, who tested 897 patients with venous thromboembolism as part of a treatment trial with a follow up of 4 years, in whom aCL were tested 6 months post–deep vein thrombosis (DVT). Interestingly, of 20 recurrent episodes, aCL was negative in 14 at the time of the recurrent episode [18].

## Arterial Thrombosis

In the situation of stroke, Nencini et al found 18% of young patients, mean age 38 years, were positive for aPL (LA and aCL), whereas the APASS study found 9.7% of first stroke patients had a positive aCL. In myocardial infarction the prevalence of aCL is between 5% and 15% [19, 20].

## Fetal Loss

There is a wide range of prevalences of aPL in otherwise healthy women who have had pregnancy morbidity, ranging from 7% to as high as 42%. The reasons for this are discussed in more detail elsewhere in this book.

## Risk of Positive aPL Tests for Thrombosis and Recurrent Events

There is now abundant evidence in the literature that aPL are particularly associated with a risk of thrombosis, especially recurrent events and pregnancy morbidity. The risk appears to be higher for LA than aCL but when high titer aCL are considered, the risks are also high. For example, Kearon assessed recurrence rates in 162 patients with "idiopathic" DVT participating in a treatment trial where the hazard ratio for recurrence was 2.3 for aCL and 6.8 for LA, although only the hazard ratio for LA was significant in terms of the risk of recurrent thrombosis [21]. In a meta-analysis, Wahl examined the risk of venous thromboembolism in aPL-positive patients without autoimmune disease or previous thrombosis. The odds ratio was 11.1 for LA and 1.6 for aCL. However, that risk rose to 3.2 if higher titers of aCL were examined [22]. There were 90 DVTs in the American Physicians Health Study and aCL levels greater than the 95th percentile [greater than 33 glycophospholipid (GPL) units] had a relative risk of venous thromboembolism of 5.3 [23].

In terms of arterial disease, the American Physicians Study did not find a significant association of aCL with first stroke [23]. In a seminal paper, Nencini et al found 18% of young strokes were positive for aPL tested after a first stroke compared to 2% of controls. They also found that the recurrence rate for stroke was higher in the aPL group compared to a group of stroke patients that were negative [19].

The APASS group compared first stroke to a control population of non-stroke hospitalized patients. aCL were positive in 24 of 248 of the stroke patients compared to 11 of 257 control patients. The odds ratio for stroke in patients who were aCL positive was calculated at 2.33 [16]. The APASS group concluded that aCL were a risk factor for first ischemic stroke and the extent of association was comparable to that between stroke and hypertension [16]. Recent large studies have supported this. A Framingham cohort and offspring study of 2712 women and 2262 men found that positive aCL at baseline were an independent risk factor for future ischaemic stroke and transient ischaemic attack in women but not men [24]. However, in a surprising paper extending the APASS study, Levine et al appear to come to diametrically opposite conclusions to their earlier findings and now conclude that aPL neither predict recurrent cerebral events nor a differential response to aspirin or warfarin and say that routine testing for aPL in ischemic stroke patients is not warranted [25]. This study has, however, been heavily criticized on methodological grounds and is discussed further in the chapter on neurological complications.

Kittner reviewed a number of studies and concluded that the strength of association between aCL and stroke in patients over 50 years was comparable to hypertension with an odds ratio of 2.2. In a young population less than 50 years the odds ratio may rise to 8.3 [26]. Further information on arterial disease derives from the Helsinki heart study. In this study healthy men with a low-density lipoprotein (LDL) cholesterol greater than 5.2 mmol/L, with a mean age of 49 years, were studied for cardiac end points. In the highest quartile of aCL patients, the odds ratio for myocardial infarct was significant at 2.0. In multivariate analyses the risk was independent of other risk factors and, interestingly, aCL levels were higher in smokers [20].

In SLE, the evidence for an association between aPL and arterial and venous events as well as pregnancy morbidity is strong. The largest study to date, the Euro-

Lupus study of 1000 patients, showed a correlation between the presence of IgG aCL and thrombosis as well as fetal loss and LA correlated with thrombosis [27]. Wahl performed a meta-analysis of the risk of venous thromboembolism and examined 26 studies comprising 2249 patients. The odds ratio for LA and venous events was 6.32 and 2.17 for aCL. When recurrent venous events were examined these ratios increased to 11.6 and 3.91, respectively [28].

## Mortality, Morbidity, and Damage Associated with aPL

APS has a significant impact on survival. For example, in a retrospective study of 52 patients with aCL followed over 10 years, 29% of APS patients (31 patients) had recurrent events and in the asymptomatic group (21 patients) half developed APS: mortality was 10% [29]. In another study, Jouhikainen et al compared 37 LA–positive SLE patients with 37 age- and sex-matched SLE patients without LA. During a median follow up of 22 years, 30% in the LA group died in contrast to 14% in the control group [30]. Among patients with venous thromboembolism, the mortality in Swedish patients was 15% at 4 years in those with aCL and 6% in those without antibodies ($P = 0.01$)[18]. The largest prospective study of 1000 SLE patients showed that after 10 years of follow up there were 68 deaths of whom 18 (26.5%) died from thrombosis associated with aPL [7]. The most common thrombotic events were cerebrovascular accidents (11.8%), coronary occlusions (7.4%), and pulmonary emboli (5.9%).

There is increasing evidence that thrombosis contributes to the damage accrued in patients with SLE, which in turn may contribute to morbidity as well as mortality. Two recent studies have clearly demonstrated that APS with thrombotic manifestations independently contributes to irreversible organ damage as well as mortality in lupus patients [31, 32]. Thus, Ruiz-Irastorza's study of over 200 SLE patients extending over 25 years demonstrated both higher damage scores and increased mortality in APS patients, most of whom had suffered arterial thromboses [32].

## Risk Factors for Thrombosis in APS: Two Hit Hypothesis

It is clear that not all aPL-positive patients will inevitably develop clinical features of Hughes syndrome. The precise reasons for this remain unclear and suggest that additional factors are required for a first thrombotic event or pregnancy-related feature. However, previous events in the context of persistent moderate-to-high aCL levels and/or LA are the most powerful predictors of future events. Thus, in a cohort of 360 patients in the Italian aPL Registry followed prospectively for 3.9 years, with either a positive LA or aCL, 34 patients developed a thrombotic event: an incidence of 2.5%/patient-year, with a rate of 5.4%/patient-year in those with a previous thrombosis and 0.95%/patient-year in asymptomatic subjects [33]. Clearly the mere presence of aPL is not sufficient for an event. Patients with aCL greater than 40 units and previous thrombosis were important risk factors for future events. Similarly, the greater the different numbers of aPL detected in a given patient the greater the risk of thrombosis [34]. The importance of previous thrombosis as a risk factor was highlighted by the recurrence rate in our patients at St Thomas' Hospital, where

those with APS and previous thrombosis had a recurrence rate of 20%/patient-year of follow-up [35]. In pregnancy, patients with a prior history of miscarriages or vascular occlusions have a significantly higher rate of adverse pregnancy outcome [33].

There are numerous other risk factors that may contribute to the development of a first thrombotic event in the presence of aPL. A recent study of 404 patients with aPL showed that at the time of the initial thrombosis, 50% of patients had had coincident risk factors for thrombosis: previous surgery and prolonged immobilization were significantly associated with venous thrombosis, and hypercholesterolemia and arterial hypertension with arterial thrombosis [36].

Virchow's observations on the three factors relevant to clot formation still hold good today: factors related to the blood (hypercoagulability), factors related to the speed of flow, and factors related to the vessel wall itself. The complex mechanisms by which aPL may affect platelets and endothelial cells to produce a procoagulant state will be discussed in detail in other chapters. However, evidence is emerging of abnormalities of the vessel wall that may be relevant to APS. Accelerated atherosclerosis is undoubtedly a feature of SLE that contributes to mortality [37]. However, studies in patients without lupus who are aPL positive have shown increased carotid intima-media thickness associated with an increased risk of arterial thrombosis [38]. Another study found a higher prevalence of an abnormal ankle–brachial index in patients with primary APS compared to healthy controls, suggesting widespread vascular abnormalities [39]. Further evidence of vessel wall abnormalities comes from data showing a higher prevalence of renal artery stenosis in association with aPL in patients with SLE. This suggests that vessels that have high velocity turbulent flow may be at increased risk of vascular abnormality in the presence of aPL [40]. Our recent unpublished data suggests a similar phenomenon with coeliac artery stenosis in aPL-positive patients. Even at the capillary level there may be abnormalities. Nailfold videocapillaroscopy in patients with primary APS showed abnormal morphology with smaller capillary diameters than controls, although these changes could not be correlated to impairment of functional parameters [41]. The authors suggested that the smaller capillary diameters resulted in lower local tissue perfusion and hypoxia, although these parameters were not directly measured. If correct though, these conditions would clearly favor a procoagulant state.

Several studies have shown that risk factors can be additive. In venous thrombosis in the young, Rosendaal found that the risk of thrombosis rose sharply with the number of risk factors and that fewer factors were required for thrombosis in older subjects [42]. Several groups have reported the additional presence of coagulation abnormalities, such as factor V Leiden, in patients with APS. Factor V Leiden and aCL can both cause the activated protein C resistance phenotype and, not surprisingly, the combination has been associated with severe thrombosis [43, 44]. Methylenetetrahydrofolate reductase $\therefore$C 677 $\rightarrow$ T substitution (increased homocysteine) may also have an effect on age at first occlusive event [44]. Furthermore, Peddi reported the development of catastrophic APS in a patient with SLE, aCL, and antithrombin III deficiency [45].

## Conditions Associated with Secondary APS

A wide spectrum of disorders has been associated with APS although primary APS, where there is no underlying disease, is common and may even exceed the

**Table 2.3.** Antiphospholipid antibodies in other conditions.

| Autoimmune connective tissue disorders | Drugs |
|---|---|
| Systemic vasculitis | Chlorpromazine |
| Malignancy | Quinine/quinidine |
| Crohn's disease | Hydralazine |
| Infection | Procainamide |
| Syphilis/lyme | Phenytoin |
| Human immunodeficiency virus | Interferon-$\alpha$ |
| Hepatitis C | |
| Cytomegalovirus | |
| Mycoplasma | |

prevalence of secondary APS, especially if women who only have aPL-related pregnancy morbidity are included. It has been estimated that up to half of patients with APS do not have an associated systemic disease [46]. Some conditions reported in association with aPL are listed in Table 2.3.

Thrombotic manifestations of APS are not usually seen in infection- or drug-associated aCL, although occasional reports of thrombosis in infections such as acquired immune deficiency syndrome (HIV/AIDS) and cytomegalovirus (CMV) suggests that in patients with APS, especially where there may be atypical features, an underlying infection should be considered [47, 48]. Procainamide has been shown to produce $\beta_2$-glycoprotein I–dependent antibodies that are potentially pathogenic [49].

## Differences Between Primary and Secondary APS

In general, there are no significant differences in the cardinal clinical features of APS, such as arterial or venous thrombosis or pregnancy morbidity, whether the syndrome is primary or secondary to an underlying connective tissue disorder [33, 50]. Shah et al found IgM aCL more commonly in SLE than primary antiphospholipid syndrome (PAPS) but no difference in thrombotic rates [29]. Although Vianna et al found that PAPS and APS secondary to SLE had similar clinical features, heart valve disease, autoimmune hemolytic anemia, lymphopenia, neutropenia, and low C4 levels were more common in patients with SLE [50].

The distinction between PAPS and APS due to SLE can sometimes be difficult. Thrombocytopenia, anemia, renal, and central nervous system (CNS) disease may be seen in both conditions. Anti-dsDNA or antibodies to extractable nuclear antigens are not found in PAPS and their presence usually suggests SLE as a secondary cause. Piette has been a strong advocate of exclusion criteria for PAPS and these are listed in Table 2.4 [51]. In terms of genetic differences between primary and secondary APS, a recent study has suggested that there are differences in FcgammaRIIA-R/H131 polymorphisms in patients with APS secondary to SLE [52].

The number of cases reported in the literature of patients with PAPS evolving into SLE is small [53,54]. Silver et al and Mujic et al have reported the evolution in small numbers (7/71 and 3/80, respectively) but Asherson et al and Vianna et al did not find any [55,56]. The short period of follow up may have been responsible for

**Table 2.4.** Exclusion criteria to distinguish SLE–associated antiphospholipid syndrome from PAPS.

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|---|
| Malar or discoid rash |
| Oral, pharyngeal, or nasal ulceration |
| Frank arthritis |
| Pleurisy/pericarditis |
| Persistent proteinuria > 0.5 g/day, due to biopsy-proven immune-complex–related glomerulonephritis |
| Lymphopenia < 1000 cells/L |
| Antibodies to dsDNA (crithidia or radioimmunoassay), or ENA |
| ANA >1:320 |
| Treatment with drugs known to produce aPL |
| Follow up < 5 years from the initial clinical manifestation. |

the latter result (5 and 2 years, respectively) as several patients have developed the syndrome after 10 years. The presence of high titer ANA (>1:320), low complement levels, and lymphopenia may be predictive [53–56].

## Seronegative APS

It is well recognized that seronegative forms of other autoimmune disorders such as rheumatoid arthritis and lupus exist and there is increasing recognition that patients with classical features of Hughes syndrome may be persistently aPL negative [57]. Clearly these patients can be difficult to diagnose though there may be several clinical clues. For example, APS is probably the only procoagulant state that can give rise to both arterial and venous thromboses as well as pregnancy morbidty, and in our experience the presence of livedo reticularis is a good marker for APS. Sometimes, aPL may appear only after prolonged follow up but in the majority of these patients there may be serological markers that are yet to be described.

## Catastrophic APS

The catastrophic APS has emerged as a dramatic if rare presentation of APS with a high mortality despite expert management. The etiology of this variant of APS remains obscure although there are often factors such as recent surgery or sepsis that herald its onset. The syndrome will be described in detail in Chapter 16, although it is worth noting that immunosuppression, especially with cyclophosphamide, is relatively contraindicated and plasma exchange may be beneficial [58].

## Clinical Features

Hughes syndrome, like SLE, is truly multisystem in nature and any organ or system in the body may be affected. The spectrum of clinical features associated with aPL continues to expand and will be covered extensively in the following chapters (Table 2.5). The cardinal features remain arterial and venous thrombosis, pregnancy morbidity, and thrombocytopenia. Since the last edition of this book, a number of

**Table 2.5.** Clinical associations.

| | |
|---|---|
| **Central Nervous System** | **Bone** |
| Chorea | Avascular necrosis |
| Migraine | Bone marrow necrosis |
| Psychosis | Fractures |
| Epilepsy | |
| CVA/TIA | **Obstetric** |
| Hypoperfusion on SPECT scanning | Recurrent miscarriage |
| Sensorineural hearing loss | Pre-eclampsia |
| Transverse myelopathy | Growth retardation |
| Cognitive impairment | HELLP syndrome |
| Pseudotumor cerebri | |
| Cerebral vein/artery thrombosis | **Renal** |
| Retinal venous thrombosis | Glomerular thrombosis |
| Multiple sclerosis like syndrome | Renal artery stenosis |
| Renal artery thrombosis | Renal insufficiency |
| | Renal vein thrombosis |
| **Gastrointestinal** | |
| Hepatic necrosis | **Pulmonary** |
| Acalculous cholecystitis | Pulmonary embolism |
| Budd–Chiari | Pulmonary hypertension |
| Intestinal ischemia | ARDS |
| Coeliac artery stenosis | |
| | **Endocrine** |
| **Vascular disease** | Adrenal failure |
| Atherosclerosis | Hypopituitarism |
| Cardiac valvular disease | |
| Acute myocardial infarction | **Hematological** |
| Failed angioplasty | Thrombocytopenia |
| Diastolic dysfunction | Autoimmune hemolytic anemia |
| Intracardiac thrombosis | Thrombotic microangiopathy |
| Cardiomyopathy | |
| Buerger 's disease | |
| | |
| **Skin** | |
| Livedo reticularis | |
| Cutaneous ulcers | |
| Dego's Disease | |
| Splinter hemorrhages | |
| Superficial thrombophlebitis | |
| Distal cutaneous ischemia | |

CVA, cerebrovascular accident; TIA, transient ischemic attack; SPECT, single positron emission computerized tomography; HELLP, hemolytic anaemia, elevated liver function tests and low platelets; ARDS, adult respiratory distress syndrome.

associations have been described, including renal artery stenosis and other renal complications. An interesting development has been the emergence of orthopedic manifestations such as rib and metatarsal fractures that follow previous descriptions of avascular necrosis. A separate chapter has been devoted to this.

## Conclusion

In conclusion, the following observations can be made. aPL are present in approximately 2% to 4% of the normal population and the prevalence increases with age.

There is a high prevalence among patients with autoimmune connective tissue disorders, especially SLE. There is an association with both venous and arterial thrombosis as well as with pregnancy morbidity, but the strength of association varies amongst studies. This probably reflects different populations, study designs, and different assays and definitions used. In several studies the risk of thrombosis appears to be higher with LA and the data suggests a true association rather than epiphenomenon. In a given patient, both aCL and LA should be measured. A significant impact on long-term survival has been noted and aPL also contribute significantly to accumulated damage in diseases such as SLE. The clinical spectrum of APS features is enormous and continues to expand. It behoves us all as clinicians and health care professionals to consider an early diagnosis of Hughes syndrome, with its distinct clinical and serological features, to reduce the risk of morbidity and mortality in our patients.

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