Chapter 2

Epidemiology of the Antiphospholipid Syndrome

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2.1 INTRODUCTION

The term antiphospholipid syndrome (APS) is used to describe an autoimmune disorder, characterized by thrombosis, either arterial or venous, and pregnancy morbidity in the setting of persistently positive antiphospholipid antibodies (aPL). These antibodies include the lupus anticoagulant (LA), anticardiolipin (aCL) and anti-\(\beta\)2-glycoprotein I antibodies. APS was first described in the early 1980s in association with systemic lupus erythematosus (SLE) \cite{1}, although abnormal clotting time in this population had been recognized decades earlier \cite{2}. Since then, it has been recognized that this syndrome can occur both with (secondary APS) and without (primary APS) an underlying systemic autoimmune disorder. Catastrophic APS (CAPS) is the term used to describe the rare phenomenon of life-threatening, multiple-organ thrombosis associated with aPL.

APS is classified according to the 2006 update of the Sapporo criteria \cite{3}, which are outlined in Box 2.1. The Sydney consensus conference also recommended that for the purposes of research, patients should be stratified according to their laboratory criteria (ie, more than one laboratory criterion, LA alone, anticardiolipin alone or anti-\(\beta\)2 glycoprotein I positivity in isolation). There are also a number of other possible, noncriteria manifestations associated with APS. These include, among others, thrombocytopenia, livedo reticularis, renal involvement, and valvular heart disease \cite{4}.

The classification criteria for CAPS have been outlined by Asherson et al. \cite{5}. ‘Definite’ CAPS is defined as thromboses in three or more organs developing in less than a week, microthrombosis in at least one organ and persistent aPL positivity. If a patient has three out of these four criteria, then the patient is classified as having ‘probable’ CAPS.
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This chapter provides a summary of the available literature on the prevalence of APS and of aPL in the general population, in thrombotic diseases and in SLE.

2.2 APS IN THE GENERAL POPULATION

The actual incidence of APS is unknown. Estimates have indicated an incidence of around 5 new cases per 100,000 persons per year, with a prevalence of around 40–50 cases per 100,000 persons [4]. A review by Andreoli et al. [6] examined the prevalence of aPL in different thrombotic conditions and used this estimate to calculate a crude estimation of incidence. They calculated that 6% of women with pregnancy morbidity have positive aPL, 13.5% with stroke, 11% with myocardial infarction, and 9.5% with deep venous thrombosis (DVT). Based on census data for the United States, they estimated 280,000 antiphospholipid-related events annually. CAPS is rare, accounting for only 1% of all APS, but the associated high mortality makes it an important entity and research agenda [7,8].

**BOX 2.1 Classification Criteria for APS**

**Classification criteria**

**Clinical criteria**

1. Vascular thrombosis:
   - a. ≥1 clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ.

2. Pregnancy morbidity:
   - a. ≥1 unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation,
   - b. ≥1 premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia or recognized placental insufficiency, or
   - c. ≥3 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. Lupus anticoagulant present in plasma, on ≥2 occasions at least 12 weeks apart.

2. Anticardiolipin antibody of IgG and/or IgM isotype, in medium of high titre (>40GPL or MPL, or > the 99th percentile), on ≥2 occasions at least 12 weeks apart.

3. Anti-β2 glycoprotein 1 antibody of IgG and/or IgM isotype, in medium or high titre (>the 99th percentile), on ≥2 occasions, at least 12 weeks apart.

aPL can be found in healthy subjects with an increased prevalence in older populations, as outlined in Table 2.1. Generally, aCL and the LA have a prevalence of 1–5% in young healthy controls [9]. There is some heterogeneity in the earlier studies, which were limited by a lack of uniformity in assay methods. For the most part, in normal control populations, these antibodies were identified at low titres without an association with APS manifestation. In large population-based studies involving older individuals, such as the Honolulu Heart study, aPL (anticardiolipin and anti-β2 glycoprotein I) were demonstrated in up to 12% of normal controls [10].

Viral, bacterial, and parasitic infections have been found to be associated with aPL positivity. These include hepatitis C, cytomegalovirus, Epstein–Barr, human immunodeficiency virus, adenovirus, and parvovirus B 19 [11]. Regarding bacterial infections in particular, aPL positivity is commonly associated with leprosy and syphilis infections [12]. A higher rate of aPL positivity has also been observed in patients with malignancies [13,14]. It is unknown whether aPL play a role in the increased rate of thrombosis observed in this population.

There appears to be a higher prevalence of aPL positivity in children. The syndrome is diagnosed based on the adult classification criteria, with the exception of the obstetric components, which generally do not apply to this population. The estimated frequency of positive aPL in children without any underlying disorder ranges widely, from 3% to 28% for aCL and from 3% to 7% for anti-β2 glycoprotein I [11]. This is thought to be due to the high rate of infections in children [15]. In children, aPL from infection are often transient [16–18]. In children with paediatric APS, the rate of SLE is in the range of 9–14% [19,20]. A meta-analysis by Kenet et al. [21] evaluated 16 case-controlled studies [22–36] comparing aPL in children with and without a history of thrombosis. They demonstrated a strong association between aPL and both venous and arterial thrombosis with an odds ratio of 5.9.

Without underlying autoimmune disease, those who have multiple positive aPL have been shown to have the highest rate of thrombosis. This was particularly true in those with ‘triple positivity’ (ie, a positive LA, anticardiolipin, and anti-β2 glycoprotein I). These individuals were shown to have a 9.8% risk of thrombosis after 2 years, which increased to 37% after a decade [37]. Mustonen et al. evaluated a large Finnish population with positive aPL who did not have a history of thrombosis at inception. They also demonstrated that double or triple positivity carried a higher risk of future thrombotic events. The rate of thrombotic events was lower in those who were taking aspirin as a prophylaxis [38]. In the Hopkins Lupus Cohort, LA was strongly related to lifetime thrombosis. After controlling for the LA, aCL were not predictive of thrombosis. This is in keeping with other SLE literature demonstrating that, of the aPL, the LA is the strongest predictor of thrombotic events [39].

The titre of aPL is also important in the risk stratification of those who have not had a thrombosis. Multiple studies have reported a higher rate of thrombosis
<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Number</th>
<th>Source</th>
<th>LA</th>
<th>aCL</th>
<th>IgG-aCL</th>
<th>IgM-aCL</th>
<th>IgA-aCL</th>
<th>β2GP-IgM</th>
<th>β2GP-IgG</th>
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<tbody>
<tr>
<td>Vaarala et al. (1986) [64]</td>
<td>380</td>
<td>P + NP</td>
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<td>Manoussakis et al. (1987) [65]</td>
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<td>El-Roei et al. (1988) [66]</td>
<td>400</td>
<td>50% M</td>
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<td>1.8%</td>
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<td>Briley et al. (1989) [67]</td>
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<td>Fields et al. (1989) [68]</td>
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<tr>
<td>Lockwood et al. (1989) [69]</td>
<td>737</td>
<td>P</td>
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<td>2.7%</td>
<td>2.2%</td>
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<td>Shi et al. (1990) [70]</td>
<td>499</td>
<td>BD</td>
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<td>3.6%</td>
<td>5.6%</td>
<td>1.8%</td>
<td>4.3%</td>
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<tr>
<td>Infante-Rivard et al. (1991) [71]</td>
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<tr>
<td>Perez et al. (1991) [72]</td>
<td>1200</td>
<td>P</td>
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<tr>
<td>Pattison et al. (1993) [73]</td>
<td>933</td>
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<td>1%</td>
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<tr>
<td>Phadke et al. (1993) [74]</td>
<td>504</td>
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<td>4.2%</td>
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<td>Juby et al. (1998) [75]</td>
<td>250</td>
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<td>1.2%</td>
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<td>12.3%</td>
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<tr>
<td>Study and Year</td>
<td>Number</td>
<td>Source</td>
<td>LA</td>
<td>aCL</td>
<td>IgG-aCL</td>
<td>IgM-aCL</td>
<td>IgA-aCL</td>
<td>β2GP-IgM</td>
<td>β2GP-IgG</td>
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<td>Avcin et al. (2001) [76]</td>
<td>113</td>
<td>61 Ch</td>
<td>11.4%</td>
<td>11.4%</td>
<td>9.6%</td>
<td>5.7%</td>
<td>3.8%</td>
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<tr>
<td></td>
<td></td>
<td>52 BD</td>
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<td>Brey et al. (2001) [10]</td>
<td>1360</td>
<td>Controls</td>
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<td>12.1%</td>
<td>4.4%</td>
<td>0.8%</td>
<td>9.0%</td>
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<td>Harrison et al. (2002) [77]</td>
<td>268</td>
<td>68 ET</td>
<td>23%</td>
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<td>10.2%</td>
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<td></td>
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<td>200 H</td>
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<tr>
<td>Pusterla et al. (2004) [13]</td>
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<td>100 L</td>
<td>7%</td>
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<td>24%</td>
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<td>100 H</td>
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<td>7%</td>
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<td>Meroni et al. (2004) [78]</td>
<td>77</td>
<td>Centenarians</td>
<td></td>
<td></td>
<td>20%</td>
<td>2.5%</td>
<td></td>
<td>8.6%</td>
<td>54%</td>
</tr>
</tbody>
</table>

P, pregnancy; NP, not pregnant; M, male; HE, healthy elderly; E, elderly; ET, essential thrombocytosis; H, healthy controls; Ch, children; BD, blood donors; L, lymphoma. *β2-Glycoprotein I dependent and independent results.*
in those who have high-titre aPL and in those with and without underlying autoimmune disease [40,41]. The presence of the LA has been found to be a particularly strong predictor of future thrombosis in both normal populations and in those with SLE [39,41,42]. A total of 50% of SLE patients with a positive LA will develop a thrombosis over 20 years [41].

Other cardiovascular risk factors, such as smoking and hypertension, have also been found to contribute to the rate of thrombotic events in patients with positive aPL [38,39,41]. In particular, hypertriglyceridemia has been shown to be predictive of venous thrombotic events and hypertension is a strong predictor of arterial thrombosis [43]. These are particularly notable, as they are modifiable.

2.3 aPL AND VENOUS THROMBOSIS

Venous thrombosis, usually DVT, is the most common APS clinical manifestation. The frequency of positive aPL in DVT has been reported in the range of 5.2–30% [77,80, 81–83,85]. In those with DVTs, the prevalence of the LA in the reported literature is 0.6–5.5%, with aCL in 4–24%. In venous sinus thrombosis, the rate of aPL positivity is 8–53% [78,79,84]. This is a rare condition; hence, the numbers in these studies were small (Table 2.2).

A meta-analysis performed by Galli et al. [42] evaluated studies involving 4184 patients and 3151 controls. They found that the LA was most

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Number</th>
<th>Any aPL Positive</th>
<th>LA</th>
<th>aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mateo et al. (1997) [79]</td>
<td>2132</td>
<td>5.2%</td>
<td>0.6%</td>
<td>4%</td>
</tr>
<tr>
<td>Deschiens et al. (1996) [80]</td>
<td>40 (VST)</td>
<td>8%</td>
<td></td>
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<tr>
<td>Carhuapoma et al. (1997) [81]</td>
<td>15 (VST)</td>
<td>53%</td>
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<tr>
<td>Bick et al. (1999) [82]</td>
<td>100</td>
<td>4%</td>
<td>24%</td>
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<tr>
<td>Eschwège et al. (1998) [83]</td>
<td>122</td>
<td>15%</td>
<td>16%</td>
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<tr>
<td>Salomon et al. (1999) [84]</td>
<td>109</td>
<td>5.5%</td>
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<tr>
<td>Zanon et al. (1999) [85]</td>
<td>227</td>
<td>30%</td>
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<tr>
<td>Saasatnia et al. (2004) [86]</td>
<td>30 (VST)</td>
<td>23.5%</td>
<td>20%</td>
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<tr>
<td>Roldan et al. (2009) [87]</td>
<td>597 (first) 326 (recurrent)</td>
<td>24% 28%</td>
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</tbody>
</table>

VST, venous sinus thrombosis; aPL, antiphospholipid; LA, lupus anticoagulant; aCL, anticardiolipin antibody.
strongly predictive of thrombosis. This has also been the finding in the SLE literature [44]. aCL, particularly at high titres, have also been shown to be predictive of thrombotic events and recurrences with the cessation of anticoagulation [45].

2.4 aPL AND ARTERIAL THROMBOSIS

In contrast with thromboses associated with many of the congenital thrombophilias, any vascular bed can be affected with APS. In the arterial system, the central nervous system is the most commonly affected site. Stroke is the most frequent arterial clinical manifestation. There is evidence that subclinical disease may also occur in the form of white mater changes on magnetic resonance imaging, the clinical significance of which is unknown [46]. The strongest association of aPL with stroke is in those who are less than 50 years old; 10% of the total stroke population are in that category. Sciascia et al. [47] performed a meta-analysis evaluating the prevalence of aPL in young people with stroke. A total of 43 studies demonstrated positive aPL in 17.4% of the 5217 participants. In older individuals, the relationship is less clear. A recent study by Arvanitakis et al. [48] included the postmortem evaluation of 607 brains for infarction, 23% of whom had at least one positive aPL. There was no relationship found between the prevalence of positive aPL and cerebral infarcts. In infants presenting with stroke, 12 of 62 (about 19%) were found to have positive aPL of unclear clinical significance [49].

An association has been found between myocardial infarction and aPL. This is thought to be due to both thrombotic and atherosclerotic mechanisms. aPL have been reported to play an important role in the development and progression of atherosclerosis, representing a nontraditional cardiovascular risk factor [50–52]. However, aPL have been associated with atherosclerosis mainly on the basis of animal models, whereas passive infusion of aPL or active induction of antibodies cross-reacting with murine anti-β2 glycoprotein I showed an enhanced formation of atherosclerotic plaque [53]. Belizna et al. [54] evaluated carotid intimal medial thickness and found that this increased, in both primary and secondary APS, regardless of the other disease features. Contrarily, comparing APS to normal controls, Ames et al. found that there were no differences in carotid intimal medial thickness between young patients with APS and controls. However, there were some differences found in older populations [55]. In SLE, LA positivity has been found to be associated with cardiovascular events, but not with the development of atherosclerosis; this points toward thrombotic, rather than predominantly atherosclerotic, mechanisms [56,57].

2.5 aPL AND PREGNANCY MORBIDITY

There is some association between aPL and pregnancy morbidity. Recurrent miscarriage occurs in about 1% of the female population trying to have children
Approximately 10–15% of women with recurrent miscarriages are found to have positive aPL and are diagnosed with obstetric APS [59,60]. However, the association between pregnancy morbidity and aPL has not been consistently demonstrated [61]. Most studies, although not all were evaluated in a meta-analysis by the APS action group [61], point toward a higher incidence of pregnancy loss with positive aPL. When studies were pooled, there was no association found between aPL and preeclampsia or the HELLP syndrome, although there was a significant relationship demonstrated between those with severe preeclampsia and aPL. The PROMISSE study found that LA is the primary predictor of adverse pregnancy outcomes after 12 weeks of gestation and that aCL and anti-β2 glycoprotein I, in the absence of a positive LA, did not predict adverse pregnancy outcomes [62].

### 2.6 aPL AND SLE

aPL are common in SLE, as outlined in Table 2.3. They are among the most frequent autoantibodies in SLE and were first described in this population [1]. These antibodies can fluctuate with time, which makes it difficult to firmly establish a point prevalence. In the Hopkins Lupus Cohort, a longitudinal study

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Number</th>
<th>LA</th>
<th>aCL</th>
<th>ANTI β2GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alarcón-Segovia et al. (1989) [88]</td>
<td>500</td>
<td>39%</td>
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<tr>
<td>Buchanan et al. (1989) [89]</td>
<td>117</td>
<td>30%</td>
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<tr>
<td>Worrall et al. (1990) [90]</td>
<td>100</td>
<td>38%</td>
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<tr>
<td>Mayumi et al. (1991) [91]</td>
<td>106</td>
<td>16%</td>
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<tr>
<td>Wong et al. (1991) [92]</td>
<td>91</td>
<td>11%</td>
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<tr>
<td>Jones et al. (1991) [93]</td>
<td>200</td>
<td>17%</td>
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<tr>
<td>Picillo et al. (1992) [94]</td>
<td>102</td>
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<td>86%</td>
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<tr>
<td>Cervera et al. (1993) [8]</td>
<td>1000</td>
<td>15%</td>
<td>24%</td>
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<tr>
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<tr>
<td>Axtens et al. (1994) [96]</td>
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<td>Somers et al. (2002) [41]</td>
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<td>27%</td>
<td>48%</td>
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<td>Petri (2010) [63]</td>
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<td>26%</td>
<td>47%</td>
<td>32.5%</td>
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<tr>
<td>Woo et al. (2010) [97]</td>
<td>88</td>
<td>34%</td>
<td>31.8%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

LA, lupus anticoagulant; aCL, anticardiolipin antibody; ANTI β2GP, anti-β2 glycoprotein I.
in which aPL are measured quarterly, the prevalence of aCL positivity was 46% and that of the LA was 26% [63]. In the setting of LA positivity in SLE, the 20-year risk of thrombosis is 50% [11]. Neither aCL nor LA are associated with carotid intimal medial thickness, carotid plaque or coronary calcium score by helical computed tomography in SLE [57].

2.7 CONCLUSIONS

aPL occur at a low frequency in the general population. Longitudinal studies have shown that they are a risk factor for thrombosis. In the general population, the risk of thrombosis increases with the number of positive antibodies. In SLE, only the LA is an independent risk factor for thrombosis. The relationship between aPL and stroke is strongest in those who are young. The association with stroke weakens with advancing age (although the incidence of antibodies is highest in those who are elderly). The exact role played by these antibodies in the pathogenesis of thrombi and mechanisms of possibly enhanced atherosclerosis in this population is presently unknown.

ACKNOWLEDGEMENTS

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