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The geoepidemiology of the antiphospholipid antibody syndrome

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ABSTRACT

Antiphospholipid antibodies (aPL) can be detected by functional (lupus anticoagulant) and/or by solid phase assays (anti-cardiolipin and anti-beta2 glycoprotein I). Although detectable in 1–5% of asymptomatic apparently healthy subjects, persistent aPL are significantly associated with recurrent arterial/venous thrombosis and with pregnancy morbidity. Such an association is the formal classification tool for the antiphospholipid syndrome (APS).

The prevalence of the syndrome with no associated systemic connective tissue diseases (primary APS) in the general population is still a matter of debate since there are no sound epidemiological studies in the literature so far. aPL display higher prevalence in systemic lupus erythematosus and rheumatoid arthritis than in other systemic autoimmune diseases. However not all the aPL positive lupus patients display the clinical manifestations. Comparable findings may be found in the paediatric population, although anti-beta2 glycoprotein I antibodies are detected in healthy children more frequently than in adults.

High prevalence of aPL has been also reported in clinical manifestations that are not formal APS classification criteria: heart valve disease, livedo reticular, nephropathy, neurological manifestations, and thrombocytopenia. Antiphospholipid antibodies can be associated with infectious processes, active vaccination, drug administration and malignancies. Their prevalence and titres are lower and the relationship with the APS clinical manifestations are less strong than in the previously mentioned conditions.

Ethnicity was also reported to influence the prevalence of aPL.

Contents

1. Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by the occurrence of recurrent thromboembolic events and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). Antiphospholipid antibodies are formally detected by functional coagulation assay (the so called lupus anticoagulant –

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LAC) and/or by solid phase assays: anti-cardiolipin (aCL), or anti-β2 glycoprotein I (anti-β2GPI) antibody tests.

Classification criteria for APS have been developed at the Sapporo antiphospholipid meeting and then recently updated [1]. APS is defined by the presence of at least one of the clinical criteria and one of the laboratory criteria. The criteria define patients with "primary" APS (PAPS) as those with the diagnosis in the absence of any underlying autoimmune disease, and patients with "secondary" APS (SAPS) as those with autoimmune disorders, aPL and the clinical manifestations of the syndrome [1].

A variant of APS characterized by acute thrombotic microangiopathy with subsequent multiorgan failure and high mortality rate has been also identified: the so called catastrophic APS (CAPS) [2]. Probable and microangiopathic APS are additional disease subsets that have been suggested but not yet formally accepted [2].

The present chapter will address the aPL prevalence in the formal clinical manifestations of the syndrome both in adults and in the paediatric populations as well as their occurrence in association with other systemic autoimmune conditions. The occurrence (and prevalence) of aPL in asymptomatic subjects or in association with other non-autoimmune conditions will also be evaluated.

2. aPL and arterial thrombosis

The cumulative retrospective literature analysis indicates that approximately 30% to 40% of patients with aPL have a history of thrombosis and that 30% of the events are arterial [3].

Cerebral circulation is the most commonly affected arterial district while coronary arteries and additional arterial anatomical localizations are less frequently reported [4].

The Euro-Phospholipid Group analyzed the prevalence of the most relevant clinical and immunological features in a cohort of 1000 APS patients derived from 13 countries. This large multicenter study showed that stroke and transient ischemic attacks were common manifestations (19.8%, 11.1% respectively) [5]. However, several other arterial manifestations were also found: leg ulcers (5.5%), myocardial infarction (MI; 5.5%), and amaurosis fugax (5.4%) [5]. Arterial complications, such as MI and arterial thrombosis in the lower extremities were higher in men than in women (16% vs. 3%, $p<0.001$ and 11% vs. 3%, $p<0.001$, respectively) [5].

A recent large multicenter study showed that β2GPI-dependent aPL can be found in almost 10% of young premenopausal women hospitalized for the first MI. The aPL presence was a risk factor for MI independent on other traditional cardiovascular risk factors [6].

Patients with older onset APS in the Euro Phospholipid Study are also more frequently male and experienced more arterial manifestations of stroke and angina pectoris than the rest of the cohort (30% vs. 18%, $p<0.005$ for stroke and 9% versus 2%, $p<0.001$ for angina pectoris, respectively) [5]. The higher prevalence of arterial events in aPL positive patients of older age has been related to the more frequent presence of concomitant established risk factors for cardiovascular pathology [1].

In agreement with the previous statement, patients with aPL-related cerebral ischemia are younger than the general stroke population and the strongest aPL association with stroke is seen in patients less than 50 years of age, with a prevalence of antibodies reported to be from 4 to 46% in this population [7].

The Antiphospholipid Antibodies and Stroke Study Group (APASS) studied 248 unselected stroke patients and reported aCL positivity in 9.7% of patients and 4.3% of controls, with an odds ratio (OR) of aCL positivity for stroke of 2.3 [8]. The same group subsequently performed a prospective follow-up study of individuals with a first ischemic stroke and IgG aCL positivity, and found the risk of recurrent stroke to be 11.1% over a mean of approximately 3 years [8]. These findings are in agreement with other reports from smaller series [7].

A meta-analysis of case–control, cross-sectional, and ambispective studies on the association between LAC, IgG/IgM aCL and arterial thrombosis reported a strong association with LAC (odds ratio up to 10) while much weaker association was found for aCL. In general only the aCL IgG isotype and medium/high antibody titres (i.e. >40 GPL units) resulted significantly associated with arterial thrombosis (first cerebral stroke or MI) [9]. The same group also performed a similar meta-analysis on the association between anti-β2GPI antibodies and arterial events: 5 out of 17 analyzed studies reported a significant association with arterial thrombosis (odds ratio up to 10). As for the aCL assay, the IgG isotype and the high antibody titre were variables influencing the association. While the presence of systemic lupus erythematosus (SLE) does not affect the association between arterial events and aCL, the number of significant associations between anti-β2GPI antibodies and thrombosis is higher in lupus patients [10].

Arterial events also represent the most frequent recurrences even in already diagnosed and treated APS patients as recently reported by Cervera et al. in the 5 year follow-up of the European series. In particular, strokes (2.4% of the total cohort) and transient ischemic attacks (2.3%) were the most frequent manifestations. Moreover, MI (18.9%) and stroke (13.2%) were also causes of mortality in the same series [11].

3. aPL and venous thrombosis

Venous thrombosis (VT) is the most common APS clinical manifestation, usually deep vein thrombosis (DVT), and occurs in more than 30% of patients [5].

Frequencies of aPL in venous thrombosis have been reported to range from 5.2% to 30% for any aPL, 0.6–16% for LA, and 4–24% for aCL [7].

Galli et al. performed a meta-analysis of case–control, cross-sectional, and ambispective studies to calculate the OR with 95% confidence interval (CI) of LAC and IgG/IgM aCL for venous thrombosis. All the studies reported a significant association between LAC and venous thrombosis independently whether or not patients were suffering from SLE or whether it was the first or a recurrent event (OR up to 16.2). Only one out of 4 studies displayed a significant (95% CI) association between aCL and venous thrombosis and only for IgG aCL titres exceeding the 95th percentile (i.e. 33 GPL units) [9]. In another meta-analysis, twelve out of 21 associations between anti-β2GPI antibodies and venous events were significant; in two studies IgG anti-β2GPI antibodies were also independent risk factors for venous thrombosis. Moreover, the presence of a concomitant SLE was not a significant variable, while the IgG isotype resulted consistently associated with the clinical events [10].

Prospective studies in the general population demonstrated that aPL are predictive of a first DVT, recurrent thromboembolism and death [8,12,13]. In particular, using a cohort of healthy adult men from the Physicians' Health Study, authors found higher aCL titres in physicians with DVT and pulmonary embolism (PE) ($p=0.01$). The same authors also reported that aCL titres greater than the 95th percentile were a relative risk for developing DVT or PE of 5.3 (95% CI 1.55 to 18.3, $p=0.01$) [12].

Elevated anti-β2GPI IgG significantly increased the OR for venous thromboembolism (VTE) by about fivefold (OR 5.2, 95% CI 1.5–18), and displayed a stronger risk association for VTE than elevated aCL IgG [14].

4. aPL and pregnancy morbidity

Multiple cross-sectional studies reported an association between aCL and/or LAC and recurrent foetal loss, with a frequency ranging from 10% to 19%; however some studies failed to confirm such a finding [7]. Foetal losses can occur in any trimester of pregnancy, although their frequency was higher before the 10th week of gestation than after (35.4% vs. 16.9% respectively) in the Euro-phospholipid series. The specificity of recurrent early abortion is still discussed because of the difficulty in excluding other known or suspected causes

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[1]. Premature births (10.6% of live births) were also reported in the same series [5].

In addition to foetal loss, other pregnancy complications have been observed in aPL positive women: preeclampsia (up to 10% of the APS pregnant women [11], 11 to 29% of pre-eclamptic women display aCL [7]), eclampsia (4.4% of pregnant women of the Euro-phospholipid series [5]), intrauterine growth retardation, HELLP syndrome (haemolytic anemia, elevated liver enzymes and low platelet count), oligohydramnios, premature birth related to pregnancy-associated hypertension and uteroplacental insufficiency [5].

Opatrny and colleagues conducted a meta-analysis on the association between aPL and recurrent foetal loss in women without autoimmune disease. LAC was associated with late recurrent foetal loss (OR 7.79, 95% CI 2.30–26.45); this association was stronger than that of any other aPL. IgG aCL, when combining all titres, were associated with both early (OR 3.56, 95% CI 1.48–8.59) and late recurrent foetal loss (OR 3.57, 95% CI 2.26–5.65). Restricting analysis to include only women with moderate to high titres increased the strength of association (OR 4.68, 95% CI 2.96–7.40). Also IgM aCL were associated with late recurrent foetal loss (OR 5.61, 95% CI 1.26–25.03). Otherwise, there was no association between early recurrent foetal loss and anti-β2GPI antibodies (OR 2.12, 95% CI 0.69–6.53) [15].

A recent study investigated the prevalence of LAC and aCL in a large cohort of Indian women with unexplained recurrent foetal losses (median number of abortions: 3). LAC and IgG/IgM aCL were significantly more frequent than in a control group of 100 healthy women who had at least one child and no obstetrical problems (10.6% vs. 1% and 29% vs. 2% in the cases vs. the controls respectively) [16].

In a prospective study, 53.7% of women of fertile age with APS (non-SLE), suffered from foetal loss; previous foetal losses increased the risk of spontaneous abortions [4].

In a recent systematic review, aPL was reported to be one of the most significant risk factors for preeclampsia [7]. However, there are conflicting results on whether women with preeclampsia have a higher prevalence of aPL [17]. By using a population-based hospital dataset, women with elevated aPL had an increased adjusted OR for preeclampsia and eclampsia, (OR = 2.93 $p = 0.0015$), SLE (OR = 61.24 $p < 0.0001$), placental insufficiency (OR = 4.58 $p = 0.0003$), and a prolonged length of stay (OR = 3.93 $p < 0.0001$) [18].

There is more debate about the prevalence and the association between anti-β2GPI antibodies and pregnancy complications. While the recent study of Vora et al. reported a significantly higher prevalence of IgG anti-β2GPI antibodies in women with unexplained recurrent foetal losses so confirming previous studies, other groups failed to report comparable findings [7,18]. In line with the former hypothesis, Faden et al. found a significant increased prevalence of IgG anti-β2GPI antibodies in normal pregnancies complicated by preeclampsia–eclampsia; on the other hand no association was found with aCL [19].

5. aPL and non-classification criterial clinical manifestations

According to the 2006 International consensus statement for classification of definite APS, the following manifestations are not included in the updated criteria: heart valve disease (vegetations, valve thickening and dysfunction), livedo reticularis (LR), nephropathy, neurological manifestations (cognitive dysfunction, migraine, multiple sclerosis, transverse myelopathy, and epilepsy), and thrombocytopenia. Although undoubtedly frequent the above mentioned features are not thought to be specific for APS [1].

Heart valve lesions are frequent in APS, whether or not SLE is present, but data are contradictory because of differences in echocardiography techniques and descriptions for findings, inconsistent associations with aPL, and population heterogeneity [5]. Thrombocytopenia, defined as a plated count less than 100,000, is seen in 20–40% of APS patients and is usually mild and rarely presenting with bleeding complications [5,7]. Livedo reticularis is present in 11–22% of APS patients [7,20]. Both thrombocytopenia and LR are more frequent in APS associated to SLE than in PAPS (43% versus 21%, and 36% versus 16%, respectively) [5].

The prevalence of other clinical features that have occasionally been seen in APS patients include hemolytic anemia (9.7%), arterial thrombosis in the legs (4.3%) and arms (2.7%), venous thrombosis in arms (3.4%), subclavian (1.8%) and jugular (0.8%) vein thrombosis, migraine (20.2%), epilepsy (7%), multi-infarct dementia (2.5%), chorea (1.3%), renal manifestations (2.7%), and pulmonary hypertension (2.2%) [5].

6. aPL and systemic autoimmune diseases

The antiphospholipid syndrome can occur in association with other systemic autoimmune diseases and in particular with SLE: 37% of the patients of the Europhospholipid series was suffering from full blown SLE, while 4% was associated with lupus-like disease [5].

The prevalence of aPL among patients with SLE ranges from 12% to 44% for aCL, from 15% to 34% for LAC, and from 10% to 19% for anti-β2GPI [7]. It has been suggested that fluctuations of the antibody titers because of disease activity and/or therapy may underestimate the true frequency of aPL in SLE [7].

Longitudinal studies show that APS may develop in 50 to 70% of patients with both SLE and aPL after 20 years of follow-up [15]. On the other hand, up to 30% of patients with SLE and aCL were reported to lack any clinical evidence of the APS over an average follow-up of seven years [21].

Thrombotic events occur more often in aPL positive lupus patients compared to aPL positive patients without lupus or with other systemic autoimmune diseases [22]. Similar results have been also shown by another study with a greater frequency of thrombosis and pregnancy loss is in APS associated with SLE than in primary APS [23].

All lupus patients with thrombosis were reported to display anti-β2GPI antibodies in comparison with only 17% of controls ($p < 0.0001$) in one study. On the contrary the prevalence and levels of IgG and IgM aCL were similar in patients with and without thrombosis [24].

Antiphospholipid IgG and/or IgM antibodies detected by aCL assay were found in 18.5% of SLE patients (n.130) before the diagnosis. The mean onset of aCL was 3 years before SLE diagnosis (range 1 month–7.6 years). Additionally, aCL presence early in the disease resulted to be predictive of a more severe clinical outcome [25].

A meta-analysis on the association between aPL and VTE in SLE found that LAC positive patients have a six fold greater risk for VTE than negative patients, whereas aCL positive patients have a twofold greater risk for VTE than the negative ones [26]. Comparable results have been shown in another study on the relationship between LAC and aCL and the incidence of VT among 678 patients with SLE enrolled in the Hopkins Lupus Cohort [27].

In an additional cross-sectional study of 418 consecutive patients with SLE or APS, the prevalence of anti-β2GPI was 44.5%; 15.7% of patients with any anti-β2GPI had venous thrombosis, while 12.4% of patients with any anti-β2GPI had arterial thrombosis [28]. Taking into consideration only the 12-week persistent positivities, the association of IgG anti-β2GPI with VT and IgM anti-β2GPI with arterial thrombosis increased (OR 6.37, 95% CI 1.82–22.31, $p = 0.0125$ and OR 5.63, 95% CI 1.40–22.6, $p = 0.0455$, respectively) [28].

The diagnosis of secondary APS led to a 3.1-fold increase in pregnancy loss, predominantly after 20 weeks of gestation ($p = .004$), and was an independent risk factor for further pregnancy losses in a cohort study of 166 pregnancies at the Hopkins Lupus Centre. However, the presence of aCL and/or LAC without the clinical criteria for secondary APS did not increase the risk for pregnancy loss in the same series [29].

Antiphospholipid antibodies have been reported also in other autoimmune conditions. A high frequency of aPL – up to 28% – was reported in patients suffering from rheumatoid arthritis while lower

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values close to those found in the general population were found in other autoimmune diseases [7].

7. aPL in the general population and in other pathological conditions

Antiphospholipid antibodies can be found in apparently healthy control subjects with a prevalence ranging from 1 to 5% for both aCL and LAC. In most of the cases the antibodies displayed low titres [7]. An increased prevalence of the antibodies detectable with all the assays has been reported with ageing. The highest values were reported in healthy centenarians but without a clear association with the APS clinical manifestations [30].

Since the association of aPL and syphilis was first described, many other viral, bacterial and parasitic infections have been shown to induce aPL. The most common infections associated with aPL include hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus, varicella zoster, Epstein–Barr virus, adenovirus, and parvovirus B19 with prevalences up to 49% in HIV infections. In the majority of the cases the antibodies were β2GPI independent, but with sound exceptions. Concerning bacterial infections, aCL is often present in leprosy (42.7%), where they are frequently displaying an anti-β2GPI activity (44.8%), and in syphilis infections (8 to 67%) [31].

Antiphospholipid antibodies associated with infections are usually transient and followed by APS clinical manifestations only in exceptional cases [31].

Active vaccination may induce the production of autoantibodies including aPL; but the reports are anecdotic and the antibodies usually transient, at low titre and with no relationship with clinical manifestations.

Otherwise, a cause–effect relationship between infections and the development of CAPS or the occurrence of thrombotic events in APS patients was suggested [32].

Several drugs, such as procainamide, phenothiazines, quinine, oral contraceptives, and anti-TNF agents may induce generation of aPL with low prevalence and no clear association with the occurrence of the APS clinical manifestations [33,34].

Furthermore, a higher prevalence of aPL was observed in a large variety of malignancies (solid and haematological) compared to the general population. However, there is no sound evidence that the antibodies are necessarily associated with an increased thrombophilic risk. Conversely, the aPL presence may be a risk factor for haematological malignancies [35].

8. aPL in the paediatric antiphospholipid syndrome

Antiphospholipid antibodies can be found in a high percentage of children without any underlying disorder, with an estimated frequency that ranges from 3 to 28% for aCL and from 3 to 7% for anti-β_2GPI. The reason of such frequent occurrence in comparison with the adults has been related to the frequent infectious processes taking place during childhood [36]. Increased prevalence of anti-β2GPI antibodies (up to 42%) was also detected in children suffering from atopic dermatitis with no APS clinical manifestations. Authors suggested that a repeated exposure to nutritional β2GPI as the consequence of the abnormal intestinal permeability may be responsible for the induction of autoantibodies crossreacting with self and exogenous molecule in susceptible children [37].

It is difficult to estimate the actual prevalence of APS in the paediatric population since there are no validated criteria and the diagnosis rests on extension of adult guidelines and clinical judgment. Although the true prevalence of PAPS in paediatric population is not known, it appears to be less common than in adults [37].

A meta-analysis of the published studies that investigated the prevalence and clinical significance of aPL in paediatric SLE showed a global prevalence of 44% for aCL, 40% for anti-β_2GPI and 22% for LAC [37].

9. aPL and the ethnicity

Environmental and genetic factors contribute to ethnic variation and susceptibility to APS and thus interethnic differences in disease patterns may be due to environmental or genetic factors, or both [38].

Genetic factors are important in the development of APS. This is demonstrated by animal models, by the familial occurrence of this syndrome, and by its association with various HLA alleles. Some HLA alleles carry the risk to produce aPL, and this is independent on the clinical context. In fact, studies reported the same associations between HLA and aPL in primary APS and in APS secondary to SLE. The association of HLA-DR4, -DR7, -DRw53, and -DQB1_0302 with aCL that has been demonstrated in primary APS, can also be found in SLE, a

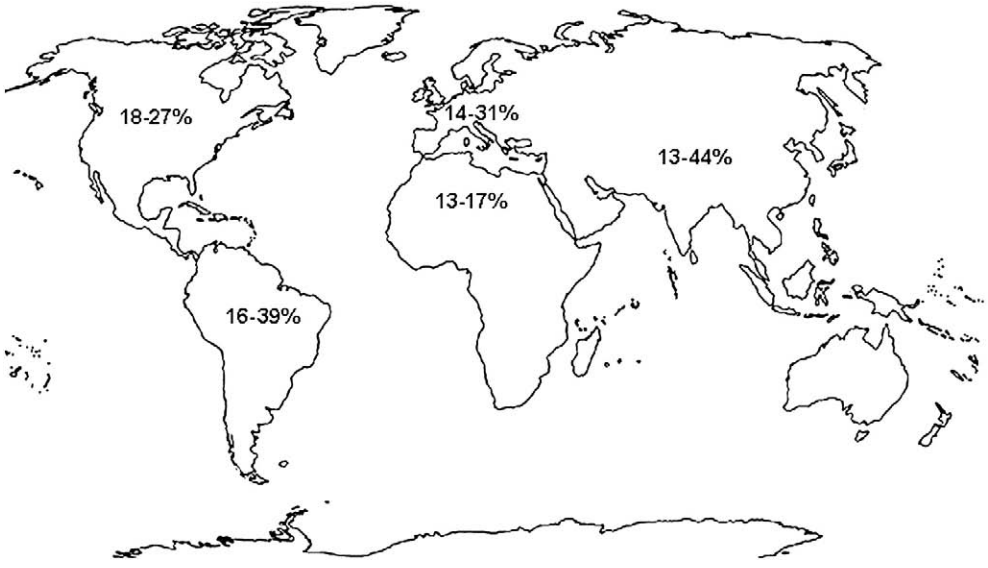

Fig. 1. Prevalence and distribution of aPL in SLE patients.

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disease with a completely different pattern of HLA allele association (DR2, DR3, DRw52). In addition, the various aPL showed similar HLA association, again independent on the clinical context (PAPS or SLE), and across various ethnic groups [39].

This paper does not discuss the treatment of this syndrome and there is only short mention of definition of the epitopes and also the distinction between the catastrophic antiphospholipid syndrome and more conventional discussion of the classic antiphospholipid syndrome. For this, the reader is referred to several recent papers [40–56]. However, we should also emphasize that as with so many other autoimmune syndromes, one should even now consider this syndrome a clinical problem in evolution. We would not be surprised for example to find a complete different definition with individual etiologies, all of whom eventually lead to the clinical entity that we know at the bench as the antiphospholipid antibody syndrome. In this respect, it is not only the autoantibody explosion in the antiphospholipid antibody syndrome, but also the systemic effects, i.e. the cardiovascular effects. We fully expect that such discussion will involve multiple diseases and will be reflective of our common understanding that polyautoimmunity is entirely secondary to unique genetic predispositions with environmental precipitants, but also environmental modifiers. This issue contains discussion of some of those factors, including, for example, infection and nanoparticles.

The prevalence and isotype distribution of aCL and LAC in different populations of patients with primary APS and SLE occur with a high variability (Fig. 1). In general, IgG aCL is the most common isotype and most closely associated with thromboses and foetal losses. IgG aCL prevalence ranged from 2% in Afro-Caribbean population to 51% in a report from India. IgA aCL are rarely present alone, but often coexist with other isotypes. Among Afro-Caribbean SLE patients, the prevalence of IgA aCL is relatively high (21%), but it was not clear whether SLE disease parameters, including disease inactivity, was related to the low frequency of IgG aCL [38].

Chinese patients are generally considered to have lower risk of thrombosis than Caucasian. Mok and colleagues examined the prevalence of LAC, aCL and anti-β2-GPI (22.4, 29, and 7.7%, respectively) and the level of thrombotic risk in a Chinese cohort with SLE. The lifetime and recurrent thrombotic rates in these patients with aPL were not particularly different from those in the literature. However, the lower prevalence of aPL in the cohort may suggest a role for other prothrombotic factors in predisposition to thrombosis [57] (Table 1).

Table 1
Prevalence of antiphospholipid antibodies in different clinical conditions.

Conditions	aPL	Prevalence	Odds ratio	References
Asymptomatic healthy controls	aCL	1–5%	NA	[7]
	anti-β2GPI	3%	NA	[7]
	LAC	1–5%	NA	[7]
Arterial thrombosis	aCL	0.1–9.7%	1–7	[6,8,10]
	anti-β2GPI	0.02–0.3%	10	[6,11]
	LAC	NA	10	[10]
Venous thrombosis	aCL	4–24%	0.4–5	[7,10]
	anti-β2GPI	NA	5.2–10	[7,15]
	LAC	0.6–16%	4–16	[7,10]
Pregnancy losses	aCL	29%	3.57–5.61	[16,17]
	anti-β2GPI	NA	2.12	[16]
	LAC	10.6%	7.79	[16,17]
Preeclampsia–eclampsia	aCL	11–29%	NA	[7]
	anti-β2GPI	NA	NA	
	LAC	NA	NA	
CTDs	aCL	12–44%	NA	[7]
	anti-β2GPI	10–19%	NA	[7]
	LAC	15–34%	NA	[7]

aPL: antiphospholipid antibodies; aCL: anti-cardiolipin antibodies; anti-β2GPI: anti-beta 2 glycoprotein I antibodies; LAC: lupus anticoagulant; NA: not available; CTDs: connective tissue diseases.

Take-home messages

- aPL can be detected in asymptomatic healthy controls (prevalence 1–5%). aPL can be induced by infections, malignancies, vaccinations and drugs. In these cases the autoantibodies are usually transient, at low titre, and with a weak association with the APS clinical manifestations.
- Arterial thrombosis displays a strong association with LAC and anti-β2GPI. Cerebral circulation is the most commonly affected arterial district in APS patients.
- Venous thrombosis is the most frequent APS clinical manifestation and is significantly associated with LAC and anti-β2GPI.
- Pregnancy complications have been observed in aPL positive women. Late recurrent foetal losses have a stronger association with LAC than with aCL and anti-β2GPI. A significant increased prevalence of IgG anti-β2GPI was found in pregnancies complicated by preeclampsia–eclampsia.
- The lack of association between thrombotic events and aCL reported in some meta-analysis studies may be related to the lack of standardization of the assay in the past years.
- APS can occur in association with other systemic autoimmune diseases and in particular with SLE. The prevalence of aPL among patients with SLE ranges from 12% to 44% for aCL, from 15% to 34% for LAC, and from 10% to 19% for anti-β2GPI. Longitudinal studies show that APS may develop in 50 to 70% of patients with both SLE and aPL after 20 years of follow-up.

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