**The clinical relevance of IgA anticardiolipin and IgA anti-β2 glycoprotein I antiphospholipid antibodies: a systematic review.**

# The clinical relevance of IgA anticardiolipin and IgA anti-β2 glycoprotein I antiphospholipid antibodies. A systematic review

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Abstract

The antiphospholipid syndrome (APS) is diagnosed in patients with thromboembolic events and/or pregnancy loss in the presence of persistent laboratory evidence for antiphospholipid antibodies (aPL). Diagnostic tests for the detection of antiphospholipid antibodies include laboratory assays that detect anticardiolipin antibodies, lupus anticoagulants, and anti-β(2)-glycoprotein I antibodies. Most studies on aPL have mainly focused on the estimation of the IgG and IgM isotypes, with only a few studies reporting on the pathogenic significance of IgA aPL

In this review we aimed to summarize and analyse the evidence published in the literature on the prevalence and the clinical significance of IgA aPL.

## Introduction

Antiphospholipid antibodies (aPL) are a heterogeneous Group of circulating autoantibodies that are found in the sera of patients with autoimmune and infectious diseases, the antiphospholipid syndrome (APS), and even in healthy subjects [1, 2]. The APS is characterized by the association of raised levels of circulating aPL with a spectrum of clinical manifestations such as arterial and venous thrombosis, recurrent pregnancy loss, and thrombocytopenia [3].

Testing for APS has traditionally included assays for lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL), and anti-β2 glycoprotein I (anti-β2GPI). However, recent evidence gathered through the last years of work suggests that other aPL specificities can also be play a role in the pathogenesis of the syndrome [4-7].

Most studies on aPL have mainly focused on the estimation of the IgG and IgM isotypes, with only a few studies reporting on the pathogenic significance of IgA aPL. In studies where IgA aCL and/or anti-β2GPI were measured, conflicting findings of their prevalence and clinical relevance have been reported. In fact, in addition to thromboembolic manifestations and intrauterine foetal loss, other symptoms such as livedo reticularis, skin ulcers, headaches, cognitive disfunction, transient isquemic atacks or heart valve disease have also been found in association with IgA aPL, [8-11].

Raised levels of IgA aPL have not been included in the classification criteria for the APS [12, 13], being the main reason for their exclusion that these particular assays are not yet fully standardized. This issue also makes it very difficult to compare studies from different laboratories [14-16]. Secondly, there is limited availability of appropriate standards tests and no universal cut-off level accepted despite attempts at International standardization of results. Inter-laboratory variation of results using commercial kits helps to create significant confusion for physicians where tests may be positive in one laboratory

and negative in another. And finally, differences in the ethnic composition of the populations studied could also play an important role in the overall confusion [17].

Generally speaking, the aCL test is positive in about 80% of patients with APS, being the LAC the only positive test in about 20%. Around 60% of the APS cases are positive for both. Anti-β2GPI is associated with thrombosis and other features of APS. Indeed, in few patients with clinical features of APS, IgA anti-β2GPI has been reported as the sole antibody detected. Several authors have suggested that testing for new specifities may help to identify additional patients with clinical suspicion of APS who do not meet the current criteria for APS [18, 19].

The purpose of this review is to try to summarize and analyse the evidence published in the literature on the prevalence and the clinical significance of IgA aPL.

## Methods

Using MEDLINE, Cochrane and OVID databases, we systematically reviewed all publications from January 1990 until April 2012, using the MESH strategy for the term “Immunoglobulin A” with the AND function and “antiphospholipid” and all the heading. In a second step we added the term “stroke” and “cardiovascular disease” to analyse the relationship with these antibodies. All articles referred to pediatric medicine and those were only the abstract was available were excluded. The search was amplified by a manual review of the selected article references.

## Results

Thirty-one relevant articles were selected. These were then divided into 3 subgroups: (1) studies which were performed in an autoimmune population and showed usefulness of IgA aPL testing; (2) studies in which their authors showed no usefulness for IgA testing, and (3) studies of IgA aPL in other non-autoimmune disorders. We analysed the prevalence of IgA aCL and anti-β2GPI, and the association with clinical manifestations, as the sole antibody or in combination with other aPL.

The studies that reported positive results in autoimmune population are shown in Table 1. Excluding case-reports, a highly variable prevalence of IgA aPL has been reported, being the highest of 78% for IgA aCL in a series of 33 APS patients [20], and 72% for IgA anti-β2GPI in a cohort of 67 APS patients [21].

In addition to thrombosis and pregnancy morbidity, associations between high titers of IgA APL and skin ulcers [22], cognitive impairment [23], Raynaud [24], trombocitopenia[20], heart valve disease [20], livedo [20], and epilepsia [20], celiac disease [25], as well as with autoimmune hepatitis [26] were also reported.

Only 6 studies found a statistically significant association between different APS-related clinical manifestations and IgA aPL in the absence of other antibodies/isotypes. Kumar et al [22] showed IgA anti-β2GPI alone in 4/5 cases with pregnancy morbidity. Similarly, Lee et al [18] showed that 44% had IgA anti-β2GPI without other aPL, in a series of patients with unexplained pregnancy loss. Shen et al[25] highlighted that 7% of patients with connective tissue disorders had IgA anti-β2GPI in the absence of other markers of APS, and their presence was significantly associated with arterial thrombosis. Diri et al [27] showed IgA anti-β2GPI as the sole aPL in 2/8 cases with skin ulcers. Finally, Lakos et al [20] reported a prevalence of 5.7% for isolated IgA anti-β2GPI in patients with APS-related features. More recently, Sweiss et al [28] reported that isolated IgA anti-β2GPI was associated with an increased risk of thromboembolic events in the 56 patients with and

without SLE (p=0.018, OR 2.79 [95%CI 1.263–6.172]). Interestingly, when they restricted their analysis to patients with SLE, isolated IgA anti-β2GPI was still associated with an increased risk of events (p=0.026, OR 4.28 [95%CI 1.33–13.56]). In contrast, among non-SLE patients, isolated IgA anti-β2GPI was not associated with an increased risk of thromboembolic events (p=0.773, OR 1.39 [95%CI 0.45–4.27]). These data suggested that IgA anti-β2GPI may be associated with an increased risk of thromboembolic events in the presence, but not in the absence, of SLE.

When analysing a cohort of 796 SLE patients, Mehrani et al [29] found that a history of venous thrombosis was significantly associated with IgA anti-β2GPI positivity (24.2%) as compared to the IgA anti-β2GPI negative (15.8%) population. For the patients with IgA anti-β2GPI alone, 22.1% had venous thrombosis and 11.9% had arterial thrombosis. For IgA aCL alone, 11.1% had venous thrombosis and 5.35% had arterial thrombosis.

Table 2 depicts negative studies in autoimmune populations. As previously, the prevalence of IgA aPL was very variable, being the lowest prevalence of 0.2% reported by Selva-O´Callaghan et al [30] when studying a large series of 773 patients. Most of the studies even reported an association between IgA aPL and thrombosis and/or pregnancy morbidity; when this was analyzed separately, in the absence of other aPL, the association was lost. In fact, Samarkos et al [31] showed that the addition of IgA aPL for the diagnosis of APS, not only failed to improve, but even decreased the accuracy of the test.

More recently, Holc at al [32] in a follow-up study with carefully selected premenopausal Rheumatoid Arthritis females patients with initially low risk for atherosclerosis failed to confirm their original impression that IgA anti-β2GPI might represent an independent risk factor for atherosclerosis.

Table 3 shows studies on IgA aPL in the general population. Yamada et al [33] studied the prevalence of these antibodies in 36 pregnant women without underlying autoimmune disease and recurrent pregnancy loss, showing IgA anti-β2GPI in 14% of

them. Other studies have highlighted the association between atherosclerotic disease (stroke, acute myocardial infarction and peripheral arterial disease) and the presence of IgA anti-β2GPI alone, in the absence of other aPL, data that needs to be confirmed by larger studies.

Serrano et al [34], following prospectively a total of 148 patients on dialysis for 2 years, reported that IgA anti-β2GPI were an independent risk factor for mortality in hemodialysis patients, suggesting a potential role for IgA anti-β2GPI in evaluating the clinical outcome of hemodialysis patients.

## Discussion

Most of the clinical data that supports testing for IgA aPL is based on retrospective studies, case-report and case-series, making it difficult to compare these studies with each other due to differences in design, population studied, the non-standardised assays used and the different cut-off chosen. As a result and in the absence of well-designed prospective studies, the controversy over the usefulness of IgA aPL testing continues. Several studies failed to prove usefulness of adding IgA aCL and IgA anti-β2GPI testing, either because of low prevalence of these antibodies, in most of the cases because they are found in association with other aPL, and also because of the lack of improvement in diagnostic accuracy when routinely tested.

However, a number of authors reported that some patients who do not meet the criteria for APS could benefit from being tested for IgA aPL. These reports are based on studies with a low level of evidence, predominantly from case-series and case-reports, where different not standardized assays have been used. Although IgA aPL is detected alone, in most of the cases this is linked to skin ulcers, Raynaud's, livedo or cutaneous vasculitis. In most cases were major APS manifestations occur (i.e. thrombosis) IgA aPL are usually found in association with other isotypes (i.e IgG and/or IgM).

Some evidence for the importance of testing for IgA aPL comes from pregnancy morbidity studies, although, again, there are small series with controversial results.

Finally, numerous studies show a high prevalence of IgA anti-β2GPI in the general population with atherosclerotic disease, especially stroke. Interestingly, they did not detect other types of aPL neither other features of APS. The possibility of a different molecule, with a different domain and therefore different targets with respect to those responsible for the APS is still elusive.

## Conclusions

To summarize, based on the data published until now, there is not enough evidence to recommend testing for IgA aCL and/or IgA anti-β2GPI to increase the diagnostic accuracy of the APS. Prospective studies assessing the clinical significance of these antibodies are crucial to establish their clinical value.

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Table 1: Studies that reported positive association in autoimmune population

| Reference | Study design | Population | IgA prevalence | | Clinical manifestations | % Isolated IgA |
|---|---|---|---|---|---|---|
| | | | aCL | anti-β2GPI | | |
| Fanopoulos 1998 [35] | R | 48 SLE | 2% | 58% | Thrombosis<br>PM | N/A |
| Tsutsumi 1998 [36] | R | 124 SLE | ND | 25% | Thrombosis | N/A |
| Lewis 1998 [16] | CS | 43 APS | ND | 74% | N/A | N/A |
| Lakos 1999 [20] | R | 37 SLE<br>33 APS | 38%<br>78% | 16%<br>49% | Deep VT<br>Thrombocytopenia<br>Heart Valve Disease<br>Epilepsy<br>Livedo | 5.7% anti-β2GPI |
| Diri 1999 [27] | CR | 8 APS | 87% | 50% | Stroke/TIA<br>Transverse myelitis | 25% aCL |
| Sebastiani 1999 [24] | R | 574 SLE | 13.9% | ND | Raynaud's<br>Livedo | N/A |
| Hanly 1999 [23] | P | 51 SLE | 55% | ND | Cognitive dysfunction | N/A |
| Greco 2000 [17] | P | 118 aPL<br>73 no aPL | 12.7%<br>12% | 35.5%<br>27% | APS<br>Thrombosis<br>Recurrent PL | 5% aCL<br>19% anti-β2GPI |
| Lee 2001 [21] | R | 133 PL<br>48 FD<br>67 APS | 11%<br>2%<br>16% | 44%<br>38%<br>72% | PL<br>FD<br>APS | 100% anti-β2GPI |
| Lee 2001 [37] | R | 270 SLE | ND | 34.8% | Thrombosis | N/A |
| Lopez 2004 [38] | CS | 50 SLE<br>140 APS | N/A† | N/A† | AT<br>VT | 0% |
| Gabeta 2008 [26] | R | 192 | 19% | 33% | Autoimmune hepatitis | N/A |
| Shen 2008 [39] | R | 472 CTD | 5.5% | 19.2% | AT | 7% anti-β2GPI |
| Kumar 2009 [22] | CR | 5 (3 SLE) | ND | 100% | PM<br>Skin ulcers | 80% |
| Sweiss 2010 [28] | R | 56 (31 SLE) | ND | 100% | Thrombosis<br>MIC | 100% anti-β2GPI |
| Mankai 2011 [25] | R | 63 CD | 6.3% | 14.3% | CD diagnosis | 0% aCL<br>7.9% anti-β2GPI |
| Mehrani 2011 [29] | CS | 796 SLE | 8.5% | 20.2% | Venous Thrombosis | 2.4% aCL<br>13.1% anti-β2GPI |

Under study design: R: retrospective, CS: cross-sectional, CR: case report, P: prospective. SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome, aPL: antiphospholipid antibodies; CTD: connective tissue disease, CD: Celiac Disease; PM: pregnancy morbidity; PL: pregnancy loss; FD: fetal death; ND: not done; VT: venous thrombosis; AT: arterial thrombosis; N/A: not available; †OR=6 for IgA aCL and OR=14 for IgA anti-β2GPI reported; MIC: mucosal immune system, mainly gastrointestinal and pulmonary system and skin.

TABLE 2: Studies that reported no association in autoimmune populations

| Reference | Study design | Population | IgA prevalence | | Non-associated clinical manifestations | % isolated IgA |
|---|---|---|---|---|---|---|
| | | | aCL | anti-β2GPI | | |
| Escalante 1995 [40] | R | 113 SLE<br>4 PAPS | N/A | ND | Thrombosis | N/A |
| Selva 1998 [30] | CS | 225 CTD<br>153 DVT<br>108 TIA<br>196 PM | 0.25% | ND | None | 0% |
| Tajima 1998 [41] | R | 77 CTD | 61% | ND | Thrombocytopenia<br>Skin ulcers | 11.6% |
| Cucurull 1999 [42] | R | 100 SLE | 24% | 19% | Thrombosis | 0% |
| Bruce 2000 [43] | R | 133 SLE | ND | 11% | None | 4.5% |
| Bertolaccini 2001 [44] | CS | 134 SLE | 13% | 6% | None | 3.7% aCL<br>0.7% anti-β2GPI |
| Carmo-Pereira 2003 [45] | R | 28 PAPS<br>28 PM<br>28 SLE | 38% | 3.5% | PAPS<br>PM<br>SLE | 2.3% aCL |
| Samarkos 2005 [31] | R | 130 SLE<br>35 PAPS | 8.5%<br>40% | 17.7%<br>25% | DVT<br>Foetal loss<br>Thrombocytopenia | 0% |
| Aslanidis 2010 [46] | R | 36 UCTD<br>20 SLE<br>24 RA<br>19 APS<br>43 (Other) | N/A | N/A | Thrombosis | N/A |
| Holc 2011 [32] | CS | 68 RA | ND | 29.4% | Atherosclerosis progression | N/A |

Under study design: R: retrospective, CS: cross-sectional, P: prospective. SLE: systemic lupus erythematosus; PAPS: primary antiphospholipid syndrome, CTD: connective tissue disease; DVT: deep vein thrombosis; TIA: transient ischemic attack; PM: pregnancy morbidity; UCTD: undifferentiated CTD; RA: rheumatoid arthritis. ND: not done; N/A: not available.

Table 3: Studies on IgA aPL in the general population

| Reference | Study design | Population | Prevalence IgA | | Clinical manifestations | % Isolated IgA |
|---|---|---|---|---|---|---|
| | | | aCL | anti–β2GPI | | |
| Yamada 1999 [33] | R | 36 RSA | ND | 14% | RSA | 100% anti-β2GPI |
| Ahmed 2000 [47] | CC | 123 Stroke | 4% | ND | None | 0% |
| Gonzalez-Portillo 2001 [48] | R | 185 CVD | 6.4% | ND | Stroke<br>TIA | N/A |
| Hsieh 2003 [49] | R | 503 VTE | ND | 5.3% | No thrombosis | N/A |
| Palomo 2004 [50] | R | 226 Thrombosis | 10% | 3% | DVT<br>AT | N/A |
| Veres 2004 [51] | CS | 111 ACS | ND | 7.2% | Unstable angina<br>STEMI<br>Previous stroke | 3.6% anti-β2GPI |
| Kahles 2005 [52] | R | 31 cryptic CVA<br>104 known CVA | 1.6% | 20.8% | Stroke | N/A |
| Staub 2006 [53] | R | 93 stroke<br>82 AMI<br>73 PAD | ND | 21%<br>26%<br>N/A | Stroke<br>AMI<br>PAD | N/A |
| Iverson 2006 [54] | CS | 129 APS<br>382 Atherosclerosis | 9%<br>48% | 1%<br>33% | Atherosclerosis | N/A |
| Serrano 2012 [34] | P | 124 haemodialysis | 1.6% | 33.1% | Mortality | N/A |

Under study design: R: retrospective, CC: case control, CS: cross-sectional, P: prospective. RSA: recurrent spontaneous abortion; CVD: cardiovascular disease; VTE: venous thromboembolism; ACS: acute coronary syndrome; CVA: cerebrovascular accident; AMI: acute myocardial infarction; PAD: peripheral artery disease; TIA: transient ischemic attack; AT: arterial thrombosis; ND: not done; N/A: not available.