The Clinical Significance of IgA Antiphospholipid Antibodies

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 in healthy subjects\(^1,2\). The “antiphospholipid syndrome” is characterized by the association of raised levels of circulating aPL with a spectrum of clinical manifestations such as arterial and venous thrombosis, recurrent fetal loss, and thrombocytopenia\(^3\).

Interest in aPL was renewed by the recognition of the role played by plasma proteins such as \(\beta_2\)-glycoprotein I (\(\beta_2\)-GPI) and prothrombin in the binding of aPL to their respective phospholipid antigens. Initially, aPL were thought to be directed against negatively charged phospholipids, but this view has now changed. The prevailing view is that in patients with autoimmune disease, serum aPL do not bind directly to phospholipid antigens alone, but to epitopes on plasma proteins, such as \(\beta_2\)-GPI or prothrombin, or to a complex of phospholipid and one of these proteins\(^4\).

As a consequence of these findings, new ELISA have been developed for the estimation of anti-\(\beta_2\)-GPI and antiprothrombin antibodies. These new aPL assays are now proving very useful in research, especially in patients with APS, where anti-\(\beta_2\)-GPI antibodies have now been shown to be strongly associated with some of the clinical complications found in the APS\(^5\).

Most studies on aPL have focused mainly on the estimation of the IgG and IgM isotypes, with only a few studies reporting the prevalence of IgA aPL as well. In studies where IgA aCL and/or anti-\(\beta_2\)-GPI were measured, conflicting findings of their prevalence and clinical significance have been reported; as a consequence, raised levels of the IgA isotype of aPL were not included in the classification criteria for the APS\(^6\). The reasons for these discrepancies could be due to the use of assays that are not yet fully standardized; for anti-\(\beta_2\)-GPI ELISA, the lack or limited availability of appropriate standards, the use of different cutoff values, and differences in the ethnic composition of the populations studied could account for these discrepancies\(^7,8\). These were highlighted in a recent study by Bizzaro, et al, who reported that patients with IgA monoclonal gammopathy gave false positive reactions for IgA aCL and anti-\(\beta_2\)-GPI\(^9\).

Although limited data are currently available, it appears that in patients with systemic lupus erythematosus (SLE), IgA aCL antibodies are similar to IgG aCL regarding their thrombogenicity and \(\beta_2\)-GPI requirements for their binding to the cardiolipin antigen\(^10\). In a mouse model designed to study thrombus formation, injected IgA immunoglobulins from patients with APS were shown to cause thrombosis; the mean times taken for thrombus formation using 2 different IgA immunoglobulin preparations were found to be significantly prolonged compared to the IgG and IgM preparations\(^11\).

In patients with SLE, some studies reported a significant correlation between IgA aCL and anti-\(\beta_2\)-GPI levels\(^12,13\), while others did not find such a correlation, suggesting that IgA aCL and anti-\(\beta_2\)-GPI antibodies represent 2 distinct autoantibody populations\(^14\). Faghiri, et al studied the origins of IgA aPL (mucosal vs nonmucosal) in a group of patients with SLE or human T cell leukemia virus (HTLV-1) related myelopathy, and concluded that IgA anti-\(\beta_2\)-GPI were more often of mucosal origin than IgA aCL\(^15\).

Prevalence of IgA aCL and anti-\(\beta_2\)-GPI antibodies. The consensus from the literature is that elevated IgA aCL in patients with SLE and APS are usually present in patient sera in conjunction with raised IgG and/or IgM aCL, and that IgA aCL are very rarely present as the sole aCL isotype\(^6,17\). In unselected patients with SLE, the prevalence of increased titers of IgA aCL has been reported to vary from 1% to 44%. The lowest reported frequency was that found by Selva-O’Callaghan, et al, who detected IgA aCL in only 2 of their 200 patients with SLE\(^18\). Higher prevalences were reported in the 2 largest SLE patient cohort studies to date; in a recent European study, where the IgG, IgM, and IgA aCL isotypes were estimated in 577 SLE patients, IgA aCL was positive in only 13.9% of patients\(^19\). Alarcon-Segovia, et al, in an earlier study that included 500 patients with SLE, found increased titers of IgA aCL in 16.6% of their patients, using a cutoff point 2 SD above the mean of their healthy control group; positivity dropped to 4.3% when the cutoff was set at the mean plus 6 SD\(^20\). In a recent study, Spadaro, et al found IgA aCL to be positive in 13 (20%) of their 65 SLE patients\(^21\). In contrast, Weidmann, et al found IgA aCL to be positive in 44% of 92 SLE patients, and also...
found IgA to be the most frequent aCL isotype. In this study IgA antibodies to phosphatidic acid, phosphatidylserine, phosphatidylcholine, and phosphatidylinositol, and phosphatidylcholine were also studied, and these aPL were positive in 52%, 26%, 53%, and 53% of their SLE patients, respectively22. A similar percentage prevalence for IgA aCL (42.8%) was also reported by Tajima, et al in a population of 77 SLE patients23. The reported frequency for raised IgA aCL was higher (52.5%) in an earlier study by Gharavi, et al, where patients were preselected for being IgG or IgM aCL positive and/or for having APS associated clinical complications26. A prevalence of 83.3% was reported by Lopez, et al in a group of patients with SLE and thrombocytopenia24. As noted, the ethnic group composition of patients can influence the isotype distribution of aPL. Molina, et al studied African-American, Afro-Caribbean, and Hispanic patients with SLE and found elevated levels of IgA aCL in 16%, 21%, and 14% of them, respectively7. The most important finding was that IgA aCL was the only aCL isotype present in 82% of aCL positive Afro-Caribbean patients7. In contrast, IgA aCL was found to be positive in only 4.4% of Chinese patients with SLE25.

Few studies have been published on the prevalence and clinical associations of IgA anti-ß2-GPI — the reported range of the prevalence of this autoantibody varies from 14% to 60.9%, which again is probably due to differences in methodology and patient selection, as above. Tatsunami, et al reported increased titters of IgA anti-ß2-GPI in 25% of their 124 SLE patients12, while Fanopoulos, et al found 58% of their 48 SLE patients to be positive26. We have found increased titters of IgA anti-ß2-GPI in only 17.7% of 130 SLE patients and in 25.7% of 35 patients with the primary APS (unpublished data). In a prospective blinded study by Greco, et al, 118 previously positive and 73 previously negative aCL patients were retested for aCL and anti-ß2-GPI during routine followup; IgA was the most common isotype found for anti-ß2-GPI in previously (60.9%) aCL positive patients, and this reached 74.1% in previously negative aCL patients27. As stated above for aCL, the prevalence of IgA anti-ß2-GPI could also be influenced by the ethnic composition of the patient group; Cucurul, et al, in a study on African-American patients with SLE, found that 24% of these patients were positive for IgA aCL and 19% were positive for IgA anti-ß2-GPI6, while in a more recent study in European patients with primary APS or SLE, Lacos, et al found 35.7% of their 70 patients were positive for IgA anti-ß2-GPI13.

Association of IgA aPL with clinical manifestations. Numerous studies have investigated possible associations between raised levels of aPL and the clinical manifestations of the APS attributed to these autoantibodies. Several of these studies reported a significant association for IgA aPL (mainly aCL) with one or more of the main clinical manifestations of the APS. In contrast, a small number of well designed studies failed to corroborate these associations18,22. Moreover, as most studies were retrospective and based mainly on the review of medical records, the reported clinical associations could have been overestimated. An association between elevated levels of IgA aCL and thrombotic events has been reported28 and was confirmed 10 years later23; Cucurul, et al, studying both IgA aCL and anti-ß2-GPI antibodies in African-American patients with SLE, found an association between thrombotic events and raised levels of both these autoantibodies. However, the number of their patients with thrombotic events was very small: only 5 of their 100 patients had documented evidence of thrombosis8. An association between raised levels of IgA anti-ß2-GPI and thrombosis has also been reported12,13.

Hemolytic anemia in Hispanic patients with SLE has been reported to be associated with IgA aPL in the prospective study of Alarcon-Segovia, et al20 and in the more recent study by Molina, et al7. An association between raised IgA aCL levels and thrombocytopenia in patients with SLE or other collagen vascular diseases has also been reported20,23,24, and a more recent study found a similar association with positive IgA anti-ß2-GPI and thrombocytopenia in SLE13. Finally, an association between IgA aCL and recurrent fetal loss28 and with unexplained spontaneous abortions29 has been reported in women with SLE.

Associations between raised levels of IgA aCL or anti-ß2-GPI antibodies and some of the less frequently reported clinical complications of the APS, such as skin ulcers23, livedo reticularis13, heart valve disease13, and pulmonary hypertension13, have also been described. In a recent carefully conducted prospective study, an association between persistent IgA aCL positivity and cognitive impairment in patients with SLE has been reported30.

In 3 large patient cohort studies, such as that of Weidmann et al, where IgA positivity was as high (44%), no significant associations could be established between the IgA aCL isotype and the clinical manifestations attributed to aCL22. Two other studies that also examined the frequency of aCL positivity in large numbers of patients found a very low frequency for IgA (~1%), and hence could not establish any clinical associations18,31. Escalante, et al, using rigorous statistical methods, have shown that IgA and IgM aCL lack the diagnostic accuracy shown for the IgG aCL isotype in identifying patients with SLE or primary APS and a history of thrombosis32.

IgA aPL in other disorders. IgA aPL have been detected in a variety of other disorders. In rheumatic diseases, raised IgA aCL have been reported in patients with rheumatoid arthritis33, primary Sjögren’s syndrome34, and progressive systemic sclerosis35, although this was not confirmed by others31. Increased titters of IgA aCL were also reported in 60% of patients with cutaneous leukocytoclastic vasculitis36, in 11.6% of uveitis patients37, and in 35.2% of patients with diabetes mellitus38. Vaarala, et al in 1986
found raised levels of aCL in 32% of patients with various infections, and noted a virtual restriction of the IgA aCL isotype in patients with mumps.

Elevated levels of the IgA aCL isotype have also been found in 2 neurological disorders. Frampton, et al found significantly increased IgA aCL titers in severe Guillain-Barré syndrome and Wilson, et al reported raised levels of aCL in roughly 26% of patients with HTLV-1 associated tropical spastic paraparesis that were mostly restricted to the IgA aCL isotype. These workers also noted that the presence of aCL was not related to a positive fluorescent treponema absorption test (FTA-ABS) in these patients, and that, as shown for infections, the binding of aCL to the cardiolipin antigen on polystyrene plates could be inhibited by ß2-GPI. More recently, Faghiri, et al, studying a similar group of patients, reported that anti-ß2-GPI were not associated with HTLV-1 infection, and that IgA was the most prevalent of anti-ß2-GPI isotypes in these patients.

In conclusion, IgA aPL antibodies appear to be similar to IgG aPL in terms of their ß2-GPI requirements and thrombogenicity. However, controversy has arisen over discrepancies regarding their prevalence and clinical associations, resulting in a dichotomy of opinion on the diagnostic usefulness of IgA aPL measurements in autoimmune and APS patient sera. This probably results from the use of nonstandardized assays, and from the retrospective design of most studies on IgA aPL. Future research on IgA aPL should therefore focus on standardization of the assays used and on performing large multicenter prospective clinical studies to evaluate the true clinical associations and the prognostic and diagnostic potential of IgA aPL.

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