Relation of Immunoglobulin A Isotype of Anti-β2 Glycoprotein I to Clinical and Laboratory Features of Antiphospholipid Syndrome and Systemic Lupus Erythematosus

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies to components of the cell nucleus. Antiphospholipid syndrome (APS) is the most common type of acquired thrombophilias. The diagnosis of APS should be made on the presence of the characteristic clinical manifestations of thrombosis/pregnancy morbidity and the presence persistently positive antiphospholipid antibodies [aPL] (anticardiolipin [aCL] IgM/IgG or anti-β2 glycoprotein I [anti-β2GPI] IgM/IgG), lupus anticoagulant [LA] or both.

Aim of the Work: Clarifying the significance of anti-β2GPI of IgA isotype among Egyptian lupus patients with and without APS regarding clinical and laboratory features of both diseases.

Patients and Methods: The study included 54 SLE patients. Twenty seven (50%) of those patients had no APS while the other half had secondary APS. Patients with other known causes of thrombophilia were excluded. Twenty seven apparently normal age and sex-matched Egyptian control persons were included. Patients were subjected to clinical assessment and routine laboratory tests. Both patients and controls were evaluated for the presence of lupus anticoagulant, anti-β2GPI of IgM, IgG and IgA isotype as well as aCL of IgM, IgG and IgA isotypes.

Results: Dural sinus thrombosis and autoimmune thrombocytopenia were significantly more common in patients with positive anti-β2GPI IgA (p-value: 0.025 and 0.03 respectively).

Conclusion: Anti-β2GPI of IgA isotype seems to contribute to the pathogenesis of thrombotic and non thrombotic manifestations of SLE and APS i.e. dural sinus thrombosis and autoimmune thrombocytopenia.


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Introduction

SYSTEMIC lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies to components of the cell nucleus. It can affect almost all organ systems with a pattern of remissions and exacerbations [1].

Antiphospholipid syndrome (APS) is the most common type of acquired thrombophilias [2]. The most common manifestation of arterial thrombosis is stroke while the most frequent type of venous thrombosis is deep venous thrombosis. Pregnancy losses in patients with APS typically occur after the 10th week of gestation. The diagnosis of APS should be made on the presence of the characteristic clinical manifestations and the presence of persistently positive antiphospholipid antibodies (aPL) (anticardiolipin [aCL] IgM/IgG or anti-β2 glycoprotein I [anti-β2GPI] IgM/IgG), lupus anticoagulant [LA] or both. APS may occur in isolated form or in association with other rheumatic diseases, most commonly SLE [3].

Anti-β2 glycoprotein I antibodies are directed against the phospholipid-binding plasma protein, β2-glycoprotein I or apolipoprotein H [4]. The association between anti-β2GPI and manifestations of APS is stronger than that of aCL [5] and the determination of anti-β2GPI is necessary in patients with features of APS who test negative for aCL and LA [6].

Although IgA isotype of anti-β2GPI antibodies is not included in the classification criteria of APS, it was found to be very frequent among SLE patients [7,8]. Many of lupus patients and patients experiencing pregnancy loss or thrombosis without
satisfying the classification criteria for APS are positive for IgA aPL alone or with other aPL isotypes [9-12]. Hence, many researchers kept the enthusiasm evaluating the role of aPL IgA isotype. They thought that aPL IgA could help classification of patients experiencing manifestations highly suggestive of APS but they have aPL IgA as the only positive aPL. However, their work provided controversial results [6,8,10,13-19].

It was reported that there was a significantly higher frequency and level of IgA anti-ß2GPI in patients with SLE who have APS compared to those without [14]. Furthermore, other researchers found that measuring IgA anti-ß2GPI may be important for assessing the risk of thrombosis, especially venous thrombosis, in patients with SLE [6,20]. Mehrani and Petri’s work concluded that the classification criteria for APS should be revised to include IgA anti-ß2GPI [21]. Recently, IgA anti-ß2GPI positivity was added to the Systemic Lupus International Collaborating Clinics (SLICC) Revision of the American College of Rheumatology (ACR) Classification Criteria for SLE [22].

Our study aimed at clarifying the significance of the anti-ß2GPI of IgA isotype among Egyptian lupus patients with and without APS regarding clinical and laboratory features of both diseases.

Patients and Methods

The study included 54 Egyptian SLE patients. Age of the patients ranged from 13-46 years. The age of the control persons ranged from 14-45 years. Four of the patients, all with APS, were males. Ten of the enrolled patients, five with APS, had juvenile-onset SLE while the others developed lupus during adulthood. Age of onset ranged from 12-42 years. The range of disease duration was 0.6-23.3 years. SLE was diagnosed based on fulfilling the 1997 update of the 1982 American College of Rheumatology revised criteria for SLE [23,24]. Half of our patients were selected to have secondary antiphospholipid syndrome (SAPS) based on fulfilling the Revised preliminary Sapporo classification criteria of APS [25]. Lupus patients having no APS were referred to as group 1 patients while those suffering from APS were referred to as group 2 patients. The patients were enrolled from the Rheumatology and Rehabilitation Department, Cairo University Hospital.

Exclusion criteria:

Known risk factors of arterial and venous thrombosis as history of smoking, diabetes mellitus, uncontrolled systemic hypertension, dyslipidemia, nephrotic syndrome and use of estrogen containing contraceptive drugs or hormone replacement therapy were excluded.

Twenty seven age- and sex-matched Egyptian Healthy volunteers served as controls. Approval of the local ethical committee was obtained. All patients were subjected to full history taking, thorough clinical examination in addition to routine laboratory investigations. Other investigations were done when indicated.

Both patients and controls were subjected to testing for aPL:

- Measurement of lupus anticoagulant: Screening was done using the dilute Russell viper venom time (dRVVT) which followed by a confirmatory step. The screen ratio, the ratio of screen clotting time of the tested plasma to that of the reference pool, was calculated. The confirm ratio, the ratio of confirm clotting time of the tested plasma to that of the reference pool, was calculated. The presence of lupus anticoagulant was confirmed when the normalized ratio, the ratio of the screen ratio to confirm ratio, was equal to or more than 1.2. The assay was performed using kits purchased from DIAGNOSTICA STAGO, 9, rue des Frères Chausson 92600 ASNIERES, France and analyzer of the STA® line.

- Measurement of anticardiolipin antibodies (aCL) IgA, G and M levels by ELISA using kits purchased from Demeditec Diagnostics GmbH, Lise-Meitner-Straβe 2, D-24145 kiel (Germany). This assay was considered positive when Ig A/G level was greater than 10U/ml and IgM level was greater than 7U/ml.

- Measurement of anti-ß2GPI IgA, G and M levels by ELISA using kits purchased from Demeditec Diagnostics GmbH, Lise-Meitner-Straβe 2, D-24145 kiel (Germany). This assay was considered positive when the level of antibodies was greater than 8U/ml.

Assessment of SLE activity and damage:

Disease activity was assessed using Systemic Lupus Erythematosus Disease activity Index (SLE-DAI) [26] and damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/SDI) [27]. Both scores were recorded at the time of testing for aPL.

Statistical methods:

Data were statistically described in terms of mean ± standard deviation (±SD), range, or frequencies (number of cases) and percentages when appropriate. For comparing categorical data, Chi square
\( (\chi^2) \) test was performed. Exact test was used instead when the expected frequency is less than 5. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

Demographic features and obstetric history of the patient groups and controls are shown in Table (1).

Comparison between the two patient groups regarding Clinical manifestations and disease indices revealed the presence of statistically significant differences concerning APS nephropathy, venous thromboses, DVT, superficial thrombophlebitis, arterial thrombosis, digital gangrene / threatened digital ischemia and Lymphopenia where these manifestations were more common in group 2 patients (\( p \)-value: 0.038, 0.002, 0.002, 0.038, 0.002, 0.038 and 0.043 respectively). Dry mouth, discoid rash and cutaneous vasculitis were more common in group 1 patients than group 2 patients (\( p \)-value: 0.038, 0.017 and 0.026 respectively). SLICC-SDI was higher in group 2 patients than group 1 patients (\( p \)-value: 0.028) while there was no significant difference concerning SLE-DAI.

Comparison between the two patient groups regarding the routine laboratory features revealed that serum albumin was lower in group 1 patients than group 2 (\( p \)-value: 0.006).

Comparison between SLE Patients and controls regarding aPL levels and positivity revealed that prolonged LA was more common in the patients than the controls (\( p \)-value: 0.006) and the normalized ratio was significantly higher in the patients than in the control group (\( p \)-value: 0.001). Positivity and level of aCL IgG were significantly higher in the patients than the control group (\( p \)-value: 0.026 and 0.021 respectively). The level, but not the positivity, of aCL IgA was significantly higher in the control group than the patients (\( p \)-value: 0.009). Positivity for anti-\( \beta2 \)GPI, in general, and IgM isotype in particular, was more common in the patients than the control group (\( p \)-value: 0.02 and 0.047 respectively). Moreover, the level of anti-\( \beta2 \)GPI IgA was significantly higher in the patients than the control group (\( p \)-value: 0.048).

The comparison between the two patient groups was performed regarding the immunological laboratory features, including aPL positivity and levels. LA prolongation and isolated anti-\( \beta2 \)GPI positivity tended to be more common in group 2 patients than group 1 patients but these differences could not reach a statistically significant value (\( p \)-value: 0.07 and 0.09 respectively).

Comparison between SLE patients of both groups who are positive for anti-\( \beta2 \)GPI IgA with those who are negative regarding obstetric morbidity and vascular events; other Clinical manifestations and laboratory features; as well as the disease duration and indices is shown in Tables (2,3,4) respectively. Dural sinus thrombosis and autoimmune thrombocytopenia were significantly more common in anti-\( \beta2 \)GPI IgA positive patients.

Anti-\( \beta2 \)GPI IgA isotype existed in an isolated form, without other anti-\( \beta2 \)GPI isotypes or other aPL, in a significant number of SLE patients without APS (18.5%) and with APS (29.6%). Dural sinus thrombosis and leukopenia were more common among patients with isolated anti-\( \beta2 \)GPI IgA positivity compared with other patients.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group 1 patients (SLE)</th>
<th>Group 2 patients (SLE with APS)</th>
<th>Control</th>
<th>( P )-Value</th>
<th>Feature</th>
<th>Group 1 patients (SLE)</th>
<th>Group 2 patients (SLE with APS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=27</td>
<td>N=27</td>
<td>N=27</td>
<td></td>
<td></td>
<td>N=18</td>
<td>N=18</td>
</tr>
<tr>
<td>Sex</td>
<td>Males</td>
<td>0 (0)</td>
<td>4 (14.8)</td>
<td>3 (11.1)</td>
<td>0.1</td>
<td>History of pregnancy ever</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>27 (100)</td>
<td>23 (85.2)</td>
<td>24 (88.9)</td>
<td></td>
<td>Pregnancy morbidity</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Disease onset:</td>
<td>Juvenile onset</td>
<td>5 (18.5)</td>
<td>5 (18.5)</td>
<td>1</td>
<td>Abortion</td>
<td>3 (16.7)</td>
<td>11 (68.75)</td>
</tr>
<tr>
<td></td>
<td>Adult onset</td>
<td>22 (81.5)</td>
<td>22 (81.5)</td>
<td></td>
<td>Stillbirth</td>
<td>3 (16.7)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td></td>
<td>Demographic features Mean (SD)</td>
<td></td>
<td></td>
<td>0.4</td>
<td>Preterm labor</td>
<td>2 (11.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age in years</td>
<td>27.06±5.83</td>
<td>29.09±7.5</td>
<td>27.6±7.3</td>
<td></td>
<td>Pre eclampsia</td>
<td>1 (5.6)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.7±4.05</td>
<td>7.04 ± 5.7</td>
<td>–</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table (2): Comparison between IgA anti-ß2GPI positive patients of both groups with negative patients concerning obstetric morbidity and vascular events.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Positive patients</th>
<th>Negative patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy morbidity</td>
<td>Yes (7/28) 7 (50)</td>
<td>No (10/45) 12 (54.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Yes (6/24) 6 (24)</td>
<td>No (8/27.6) 21 (72.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>DVT</td>
<td>Yes (9/36) 5 (17.2)</td>
<td>No (16/82.8) 24 (82.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>Yes (5/20) 3 (10.3)</td>
<td>No (20/89) 26 (89.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Dural sinus thrombosis</td>
<td>Yes (4/16) 0 (0)</td>
<td>No (21/100) 29 (100)</td>
<td>0.03</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>Yes (2/15.4) 2 (4.9)</td>
<td>No (11/84.6) 39 (95)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Table (3): Comparison between IgA anti-ß2GPI positive patients of both groups with negative patients concerning other clinical manifestations and laboratory features.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Positive patients</th>
<th>Negative patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Yes (18/72) 22/75.9</td>
<td>No (7/28) 7/24.1</td>
<td>0.747</td>
</tr>
<tr>
<td>Musocutaneous</td>
<td>Yes (21/84) 25/86.2</td>
<td>No (4/16) 4/13.8</td>
<td>0.82</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Yes (21/84) 28/96.6</td>
<td>No (4/16) 1/3.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Yes (18/72) 21/72.4</td>
<td>No (7/28) 8/27.6</td>
<td>0.97</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Yes (10/40) 8/27.6</td>
<td>No (15/60) 21/72.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Yes (12/48) 20/69</td>
<td>No (13/52) 9/31</td>
<td>0.12</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Yes (15/60) 1/58.6</td>
<td>No (10/40) 12/41.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Yes (14/56) 13/44.8</td>
<td>No (11/44) 16/55.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Sicca</td>
<td>Yes (2/8) 4/13.8</td>
<td>No (23/92) 25/86.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Other ocular</td>
<td>Yes (2/8) 23/92</td>
<td>No (1/3.4) 28/96.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Yes (19/76) 16 (55.2)</td>
<td>No (6/24) 13 (44.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>Yes (16/64) 10 (34.5)</td>
<td>No (9/36) 19 (65.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Yes (24/96) 28 (96.6)</td>
<td>No (1/3.4) 1 (3.4)</td>
<td>0.92</td>
</tr>
<tr>
<td>Hypo complementemia</td>
<td>Yes (23/92) 23 (79.3)</td>
<td>No (2/8) 6 (20.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>7.06±35.1</td>
<td>6.68±27.6</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Table (4): Comparison between IgA anti-ß2GPI positive patients of both groups with negative patients regarding disease duration and indices.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Positive patients (Mean±SD)</th>
<th>Negative patients (Mean±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>7.1±5.3</td>
<td>6.7±4.6</td>
<td>0.79</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>5.6±6.9</td>
<td>6.2±7.1</td>
<td>0.87</td>
</tr>
<tr>
<td>SLLC</td>
<td>1.2±1.2</td>
<td>1.1±1.4</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Discussion

IgA isotype of aPL were excluded from APS classification criteria based on lacking specificity and providing no additional information to those given by IgM or IgG isotypes [8]. Moreover, they are not fully standardized making it difficult to compare studies from different laboratories [9,28-31]. Furthermore, there is a considerable difference among the studied ethnicities adding difficulty to the interpretation of the results of the different studies [32-35]. Most of the studies supporting the usefulness of IgA aPL are retrospective studies, case-reports and case-series making the comparison between the results of studies of different designs difficult. In addition their benefit could not be verified because they are commonly found in association with other aPL [36].

Our study aimed at clarifying the significance of IgA isotype of anti-ß2GPI among Egyptian lupus patients without or with associated APS regarding clinical and laboratory features of both diseases.

In our study, comparison between anti-ß2GPI IgA positive patients of both groups with negative patients regarding the obstetric morbidity, thrombotic manifestations, other clinical manifestations, disease duration, laboratory features as well as disease indices revealed that Dural sinus thrombosis was significantly more common in patients with positive anti-ß2GPI IgA. Other studies [37-39] reported that IgA aPL do correlate with APS manifestations including cardiovascular disease and thrombotic events. In our study, the anti-ß2GPI isotype having the strongest association with APS and SLE manifestations was IgA; our finding is in agreement with the results obtained by Mehrani and Petri. They reported that venous thrombosis affected a higher percentage of patients with IgA anti-ß2GPI positivity compared with negative patients and the frequency of arterial and venous thromboses was higher in anti-ß2GPI IgA positive patients than aCL IgA positive ones [20]. Many authors suggested that measuring IgA anti-ß2GPI
may be considered in assessing SLE patients for the risk of thrombosis, especially on the venous side \cite{6,21}. In a stepwise multivariate logistic regression analysis of another study, anti-\(\beta 2\)GPI IgA was determined as the strongest risk factor of venous thrombosis \cite{37}.

Although positivity of IgA anti-\(\beta 2\)GPI was significantly associated with thrombosis in the study done by Tsutsumi and his coworkers, their results did not directly prove a relationship between the presence of IgA anti-\(\beta 2\)GPI and thrombosis. They explained this finding by that most patients who had a history of thrombosis with positive IgA anti-\(\beta 2\)GPI were also positive for IgG or IgM anti-\(\beta 2\)GPI \cite{40}.

In our study, autoimmune thrombocytopenia was more common among patients with anti-\(\beta 2\)GPI IgA positivity. Our results are more or less concordant with the results of other studies that linked the association of IgA isotype of anti-\(\beta 2\)GPI antibody to APS manifestations in lupus patients including thrombocytopenia, livedo reticularis, epilepsy and heart valve disease \cite{7,10,14,41}.

In other studies, high titers of IgA aPL were frequently associated with skin ulcers \cite{42}, cognitive impairment \cite{43}, Raynaud’s phenomenon \cite{44}, celiac disease \cite{48}, autoimmune hepatitis \cite{46} and transient ischemic attacks \cite{47}. Many studies have also suggested the possible significance of assessment of IgA anti-\(\beta 2\)GPI \cite{14,48-52}. Being dimeric or trimeric, IgA isotype of anti-\(\beta 2\)GPI could be more efficient in recruiting \(\beta 2\)GPI on the cell surface receptors and so being more efficient in signal transduction \cite{53}.

Furthermore, in a study of SLE patients, it was reported that IgA anti-\(\beta 2\)GPI, among the different anti-\(\beta 2\)GPI isotypes, was significantly associated with laboratory markers as high ESR, low C3 and anti-Smith antibodies; and Clinical parameters as pulmonary hypertension and pulmonary fibrosis \cite{21}; however, this could not be approved in our study.

In addition to the known association of anti-\(\beta 2\)GPI with the various manifestations of APS, Lakos and his colleagues stated that the association of the different anti-\(\beta 2\)GPI antibody isotypes with the different clinical features of APS seems to classify APS patients into distinct subgroups and this may be reflected on therapy \cite{10}.

On the other side, other studies have found no association between IgA anti-\(\beta 2\)GPI and APS manifestations in SLE patients \cite{6,8,9,17,19,54,55}. Kumar and his colleagues stated that most patients positive for IgA aPL are also positive for other aPL isotypes \cite{41} Moreover, Samarkos and his colleagues found that the addition of IgA aPL for the diagnostic tests of APS, even, decreased the accuracy of the test \cite{19}.

Despite of the presumed pathogenic role of anti-\(\beta 2\)GPI IgA, the increased risk of thromboembolism in SLE patients with anti-\(\beta 2\)GPI IgA positivity could be explained by lupus flare itself as stated by many authors \cite{8}. Moreover, in a study of lupus patients and others, Swiss and his colleagues stated that isolated IgA anti-\(\beta 2\)GPI positivity was a risk factor of thromboembolic events. However, this increased risk persisted for lupus patients when they were analyzed separately; but it was not the case with other patients \cite{8}. Isolation of anti-\(\beta 2\)GPI IgA isotype in our APS patients at time of recruitment may be explained by the suggestion that aPL level may fluctuate with disease activity and treatment \cite{56}.

In a study of a cohort of 472 SLE patients, the association between LA and thrombosis has been confirmed. Importantly, both univariate and multivariate analyses showed that elevated IgA of aCL and anti-\(\beta 2\)GPI were significantly associated with a thrombotic event, even in the absence of LA. However, multivariate analysis of the data showed no significant association between thrombosis and elevated IgG aCL and anti-\(\beta 2\)GPI \cite{53}.

In a systematic review done in 2013, it was concluded that there was not enough evidence to recommend testing for neither IgA aCL nor IgA anti-\(\beta 2\)GPI to increase the diagnostic accuracy of the aPL testing. It was also stated that, when the association between IgA aPL and thrombosis and/or pregnancy morbidity was analyzed separately in the absence of other aPL in most of the studies supporting their utility, the association was lost. Moreover, it was found that when aPL IgA present alone in absence of other isotypes, they were usually associated with minor APS manifestations as skin ulcers, Raynaud’s phenomenon, livedo reticularis and cutaneous vasculitis \cite{36}.

Moreover, racial differences were reported to play a role in the prevalence, isotype distribution and clinical significance of aCL and anti-\(\beta 2\)-GPI \cite{33}.

From our findings, we can conclude that evaluating SLE patients with manifestations highly
suggeensive for APS, but lacking all the standardized aPL, for anti \(\beta 2\)-GPI IgA could be valuable. However, the potential benefit of anti \(\beta 2\)-GPI IgA deserves further studies on a larger number of patients with the consideration of exclusion of inherited thrombophlias, although this may not be feasible in anticoagulated patients.

References


