Anti-beta 2 Glycoprotein I IgA in the SLICC Classification Criteria Dataset

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SLICC

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ABSTRACT

Objective. Anti-beta 2 glycoprotein I IgA is a common isotype of anti-beta 2 glycoprotein I in SLE. Anti-beta 2 glycoprotein I was not included in the American College of Rheumatology (ACR) SLE classification criteria, but was included in the Systemic Lupus International Collaborating Clinics (SLICC) criteria. We aimed to evaluate the prevalence of anti-beta 2-glycoprotein I IgA in SLE versus other rheumatic diseases. In addition, we examined the association between anti-beta 2 glycoprotein I IgA and disease manifestations in SLE.

Methods. The dataset consisted of 1384 patients, 657 with a consensus physician diagnosis of SLE and 727 controls with other rheumatic diseases. Anti-beta 2 glycoprotein I isotypes were measured by ELISA. Patients with a consensus diagnosis of SLE were compared to controls with respect to presence of anti-beta 2 glycoprotein I. Among patients with SLE, we assessed the association between anti-beta 2 glycoprotein I IgA and clinical manifestations.

Results. The prevalence of anti-beta 2 glycoprotein I IgA was 14% in SLE patients and 7% in rheumatic disease controls (odds ratio, OR 2.3, 95% CI: 1.6, 3.3). It was more common in SLE patients who were younger patients and of African descent (p=0.019). Eleven percent of SLE patients had anti-beta 2 glycoprotein I IgA alone (no anti-beta 2 glycoprotein I IgG or IgM). There was a significant association between anti-beta 2 glycoprotein I IgA and anti-dsDNA (p=0.001) and the other antiphospholipid antibodies (p=0.0004). There was no significant correlation of anti-beta 2 glycoprotein I IgA with any of the other ACR or SLICC clinical criteria for SLE. Those with anti-beta 2 glycoprotein I IgA tended to have a history of thrombosis (12% vs 6%, p=0.071), but the difference was not statistically significant.

Conclusion. We found the anti-beta 2 glycoprotein I IgA isotype to be more common in patients with SLE and in particular, with African descent. It could occur alone without other isotypes.

Introduction

The IgA isotype of anti-beta 2 glycoprotein I (anti-ß2-GPI) is the most common isotype in systemic lupus erythematosus (SLE) ranging between 20% and 59 %. (1–5) African-American SLE patients have a higher prevalence compared to other ethnic groups. (6,7)

Anti-beta 2 glycoprotein I IgA has been associated with thrombosis, particularly venous thrombosis, in SLE patients with secondary antiphospholipid syndrome (APS), as well as in patients with primary APS. (1,8–11) It has also been associated with pregnancy related morbidity. (12,13) However, IgA anti-ß2-GPI is not included in the classification criteria of APS, partially due to the lack of uniform guidelines for the method of measurement and clinical cutoffs. (14)

Anti-beta 2 glycoprotein I IgA has been associated with clinical manifestations other than thrombosis, such as pulmonary hypertension and pulmonary fibrosis. (1) Anti-beta 2 glycoprotein I IgA was correlated with low complement C3, anti-Smith antibodies and a high erythrocyte sedimentation rate (ESR) in one SLE study. (1)

Anti-beta 2 glycoprotein I IgA is not included in the immunological criteria of the American College of Rheumatology (ACR) classification criteria for SLE (15), but it was included in the Systemic Lupus International Collaborating Clinics (SLICC) criteria. (16) Our aim was to assess the prevalence of anti-ß2-GPI IgA in the dataset that was used to derive and validate the SLICC SLE classification criteria. We also evaluated the sensitivity and specificity of anti-ß2-GPI IgA to differentiate between those with SLE versus other rheumatic diseases, and to assess correlations of anti-ß2-GPI IgA with clinical and laboratory associations in SLE.

Methods

The SLICC dataset consisted of clinical information on 1406 patients with rheumatic diseases from 25 international centers. These patient histories were collected in two phases: the "derivation" phase (n=716), and the "validation" phase (n=690). Lupus anticoagulant was determined by the individual sites. Sera for each patient from both phases were sent to RDL Reference Laboratory (Los Angeles, CA, USA) for measurement of immunologic markers. Anticardiolipin isotypes were measured by RDL Reference Laboratory using an enzyme immunoassay. The laboratory reference values were used for the cutoff. Anti-beta 2 glycoprotein I isotypes (IgG, IgM, IgA) were measured on the same samples as the other immunologic markers by ELISA assay at the laboratory of Joan Merrill, M.D. (Oklahoma Medical Research Foundation) for both phases. (17) The ELISA assay used beta 2 glycoprotein I as the antigen (Meridian Life Sciences, Memphis, TN, USA) and anti-human IgG, IgM or IgA alkaline phosphatase conjugate for detection (MilliporeSigma, St. Louis, MO, USA) The reference value was <15 with values 16-100 considered positive. The reference value was set as 2 standard deviations above the mean of 30 healthy controls.

Using the clinical and laboratory data in the histories, patients from the derivation and validation phases were given a diagnosis of SLE or not based on a consensus process described previously. (16) Information on a patient's history of anti-ß2-GPI and information on anti-ß2-GPI results from the reference laboratory were included in the patient histories, if available. If either value was positive, anti-ß2-GPI was scored as positive. Non-SLE patients consisted of rheumatoid arthritis, undifferentiated connective tissue disease, primary antiphospholipid antibody syndrome, vasculitis, chronic cutaneous lupus, scleroderma, Sjogren's syndrome, myositis, psoriasis, fibromyalgia, alopecia areata, and sarcoidosis.

The research was reviewed and approved by the Johns Hopkins University School of Medicine Institutional Review Board (approval number NA_00039294). All study participants provided written informed consent.

Statistical Methods

Subgroups of patients were compared with respect to the presence of anti-ß2-GPI and its isotypes. The statistical significance of observed differences was assessed using a Pearson Chi Square test. The associations between anti-ß2-GPI IgA and SLE disease manifestations, after adjusting for age and ethnicity, were assessed using multiple logistic regression.

Results

Of the 1406 patient histories, a consensus classification could not be reached for 14 histories, and information on anti-ß2-GPI was missing on 8 patients. This analysis was based on the remaining 1384 patients (657 classified as SLE and 727 classified as non-SLE).

Of the 657 patients with SLE, 599 (91%) were female, 394 (60%) were Caucasian, 134 (20%) were of African descent, and 76 (12%) were Asian. Their mean age (years) at the time of assessment was 37.9 (SD=13.3). Of the 727 classified as not having SLE, 588 (81%) were female, 530 (73%) were Caucasian, 86 (12%) were of African descent, and 48 (7%) were Asian. Their mean age (years) at the time of assessment was 46.5 (SD=14.7)

The prevalence of anti-ß2-GPI IgA in the central laboratory was 14% (94/657) in SLE patients and 7% (49/727) in controls ($p<0.0001$). (Table 1) Considering those positive for anti-ß2-GPI IgA the median titer was somewhat higher among patients with SLE (median=29.5) than among controls (median=23.0, $p=0.15$ for difference).

In contrast, there was no difference in the prevalence in anti-ß2-GPI IgM or IgG in SLE patients versus controls (Table 1) vs. controls. Eleven percent (73/657) of SLE patients had anti-ß2-GPI IgA alone (no anti-ß2-GPI IgG or IgM).

The association between demographic characteristics and anti-ß2-GPI IgA in patients with SLE is shown in Table 2. The highest prevalence of anti-ß2-GPI IgA was found in African American SLE patients (21.6%), compared to other ethnic groups ($p = 0.019$). There was no difference in the prevalence of anti-ß2-GPI IgA by sex. However, it was significantly more common in the younger age group ($p = 0.0048$).

The association between the disease manifestations as defined in the ACR or SLICC classification criteria for SLE and anti-ß2-GPI IgA in patients with SLE is shown in Table 3. There was a significant association between anti-ß2-GPI IgA and anti-dsDNA ($p=0.0001$) and the other antiphospholipid antibodies ($p=0.0016$). There was no significant correlation of anti-ß2-GPI IgA with any of the other ACR or SLICC clinical criteria for SLE.

We were able to evaluate the association between anti-ß2-GPI isotype with thrombosis and pregnancy morbidity in only half of the SLICC dataset patients (the derivation dataset). Those with anti-beta 2 glycoprotein I IgA tended to have a history of thrombosis (12% vs 6%, $p=0.071$), but the difference was not statistically significant. Twenty-three patients had anti-beta 2 glycoprotein I IgA alone with no other antiphospholipid antibodies. Of those 1/23 (4%) had a history of thrombosis. Of those in the derivation data set who did not have isolated anti-beta 2 glycoprotein I IgA, 28/285 (10%) had a history of thrombosis. We did not have enough patients with adverse pregnancy outcomes to address an association with pregnancy loss.

If we removed anti-ß2-GPI from the SLICC classification rule, the sensitivity of the rule (relative to physician classification) declined from 95.6% to 95.5%, and the specificity changed

from 88.3% to 88.4%. The lack of change was due to the fact that it is only one component of antiphospholipid antibodies, which in turn is one component of the SLICC immunologic score.

Discussion

In the SLICC classification criteria dataset, only anti-ß2-GPI IgA was significantly more prevalent in SLE patients compared to other rheumatic disease patients. Anti-ß2-GPI IgG and IgM were not significantly more prevalent in SLE patients than in those with other rheumatic diseases. The IgA isotype was the most frequent isotype, with 11% of SLE patients having IgA alone without IgM and/or IgG isotypes.

Only the IgA isotype of SLE was associated statistically with the physician consensus diagnosis of SLE. Thus, the IgA isotype has particular relevance in SLE, but did not affect the overall sensitivity or specificity of the classification rule in any important way.

The variability in the prevalence studies of anti-ß2-GPI IgA in SLE patients may be partly attributed to the different ethnic composition of the studied population. The highest prevalence of anti-ß2-GPI IgA is in African American SLE patients. (1,6,7) In our study, 22% of the African descent patients had anti-ß2-GPI compared to 11% in patients of other ethnicities. Some variability might be due to different assays. A recent study by Tebo et al, found that the overall diagnostic and predictive value of anti-ß2-GPI IgA were dependent on the assays used. Assays were similar in predicting venous thrombosis, while there was a variable predictive result for pregnancy related morbidity. (13) Our study benefited from the use of only one central laboratory.

We found no significant association between anti-ß2-GPI IgA with ACR or SLICC classification criteria except for anti-dsDNA and other antiphospholipid antibodies. The association between anti-ß2-GPI IgA and anticardiolipin antibodies has also been confirmed in

other reports. (3,4) In contrast, Lakos et al, found a significant correlation between anti-ß2-GPI IgA and thrombocytopenia and epilepsy. (5)

Mehrani et al, in a study based in the Hopkins Lupus Cohort, found a significant association of anti-ß2-GPI IgA isotype with pulmonary hypertension and pulmonary fibrosis. The IgA isotype of anti-ß2-GPI was the only isotype to be significantly associated with anti-Smith antibodies and elevated erythrocyte sedimentation rate in Hopkins SLE patients. (1)

In other studies, the IgA isotype of anti-ß2-GPI has been found to be associated with venous thrombosis. (1,4,5) We did find an odds ratio of 2.5 in the SLICC dataset with an adjusted p-value of 0.065.

Strengths of the study include that all assays were done in a central laboratory using the same assay, and that the international patient sample increased the generalizability of our findings. A limitation is the cross-sectional nature of the study. In conclusion, anti-ß2-GPI IgA is twice as frequent in SLE as in rheumatic disease controls and appears in 11% as the sole isotype. Thus, it could be missed if only IgG and IgM isotypes were checked; particularly important given the growing data that the IgA isotype is associated with thrombosis (13).

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Table 1: Number (%) with Anti-ß2-GPI by Diagnosis of SLE vs Non-SLE

Anti-ß2-GPI subtype	SLE (n=657)	Non-SLE (n=727)	p- value
IgA	94 (14%)	49 (7%)	<0.0001
IgM	47 (7%)	38 (5%)	0.14
IgG	42 (6%)	40 (6%)	0.48

Table 2. Demographic characteristics and anti-ß2-GPI IgA in patients with SLE.

		Proportion (%) with Anti-ß2-GPI IgA	p-value
Ethnicity	African descent	29/134 (21.6)	0.019
	Caucasian	45/394 (11.4)	
	Asian	14/76 (18.4)	
	Other	6/53 (11.3)	
Gender	Female	85/599 (14.2)	0.78
	Male	9/58 (15.5)	
Age (years)	≤30	40/200 (20.0)	0.0048
	>30	53/455 (11.7)	

Table 3. Number (Percent) of patients with a history of various SLE manifestations (as defined by the American College of Rheumatology (ACR) classification criteria for SLE) by anti-ß2-GPI IgA in patients with SLE

Clinical and serologic variables	Anti-ß2-GPI IgA (%) PRESENT (n=94)	Anti-ß2-GPI IgA (%) ABSENT (n=563)	P-value	Odds Ratio (95% CI)	Adjusted P-value[4]
Malar Rash	49 (52.1%)	245 (43.5%)	0.12	1.4 (0.9, 2.2)	0.16
Discoid Rash	19 (20.2%)	101 (17.9%)	0.60	1.3 (0.7, 2.2)	0.42
Photosensitivity	46 (48.9%)	287 (51.0%)	0.71	1.0 (0.6, 1.5)	0.91
Oral Ulcers	36 (38.3%)	234 (41.6%)	0.55	0.9 (0.6, 1.4)	0.57
Arthritis	62 (66.0%)	371 (65.9%)	0.99	1.0 (0.6, 1.6)	0.93
Pleurisy	32 (34.0%)	143 (25.4%)	0.079	1.4 (0.9, 2.3)	0.16
Pericarditis	12 (12.8%)	61 (10.8%)	0.58	0.9 (0.5, 1.9)	0.86
Proteinuria	35 (37.2%)	169 (30.0%)	0.16	1.1 (0.7, 1.8)	0.71
Seizure	5 (5.3%)	31 (5.5%)	0.94	1.0 (0.4, 2.6)	0.92
Psychosis	3 (3.2%)	11 (2.0%)	0.44	1.5 (0.4, 5.8)	0.54
Hemolytic Anemia	8 (8.5%)	34 (6.0%)	0.36	1.3 (0.53,2.9)	0.59
Leukopenia	33 (35.1%)	160 (28.4%)	0.19	1.2 (0.7, 1.9)	0.56

Clinical and serologic variables	Anti-ß2-GPI IgA (%) PRESENT (n=94)	Anti-ß2-GPI IgA (%) ABSENT (n=563)	P-value	Odds Ratio (95% CI)	Adjusted P-value[4]
Lymphopenia	28 (29.8%)	174 (30.9%)	0.83	0.9 (0.6, 1.5)	0.72
Thrombocytopenia	17 (18.1%)	79 (14.0%)	0.30	1.2 (0.7, 2.3)	0.46
Anti-dsDNA[1]	77 (81.9%)	334 (59.3%)	<0.0001	3.0 (1.7, 5.4)	0.0001
Anti-Smith[1]	37 (39.4%)	140 (24.9%)	0.0034	1.5 (0.9, 2.5)	0.085
Antiphospholipid Antibodies[1]	71 (75.5%)	315 (56.0%)	0.0004	2.3 (1.4, 3.8)	0.0016
Anticardiolipin IgG[1]	42 (44.7%)	157 (26.1%)	0.0002	2.2 (1.4, 3.5)	0.0009
Anticardiolipin IgM[1]	35 (37.2%)	105 (18.7%)	<0.0001	2.6 (1.6, 4.2)	0.0001
Anticardiolipin IgA[1]	10 (10.6%)	13 (2.3%)	<0.0001	5.8 (2.3, 14.9)	0.0002
Lupus Anticoagulant[2]	26 (28.6%)	72 (13.2%)	0.0002	2.5 (1.4, 4.3)	0.0012
Anti-ß2-GPI IgG[2]	11 (11.7%)	31 (5.5%)	0.023	3.2 (1.5, 7.0)	0.0034
Anti-ß2-GPI IgM[2]	14 (14.9%)	33 (5.9%)	0.0017	3.3 (1.6, 6.8)	0.0011
History of thrombosis[3]	9 (12.3%)	14 (6.0%)	0.071	2.5 (0.9, 6.4)	0.065

1 For these variables, the patients were considered positive if they had a clinical history of the serologic marker, or if a serologic specimen collected specifically for the parent study was positive for the marker.

[2] For these variables patients were considered positive based only on the serologic specimen collected specifically for the parent study.

[3]Based only on the patients in the derivation data set (73 positive for Anti-ß2-GPI IgA, and 235 negative for Anti-ß2-GPI IGA)

[4] P-value adjusted for Ethnicity and Age