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Anti-annexin II Antibodies in Systemic Autoimmune Diseases and Antiphospholipid Syndrome

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Abstract
Objectives The objective of this study were (1) to evaluate the prevalence of anti-annexin II antibodies in patients with various autoimmune diseases and antiphospholipid syndrome and (2) to correlate anti-annexin II antibodies with antiphospholipid antibodies.
Materials and Methods Anti-annexin II antibodies and antiphospholipid were detected, using an enzyme-linked immunosorbent assay, in the serum of patients with primary antiphospholipid syndrome (n=16), systemic lupus erythematosus (n=53), primary Sjögren syndrome (n=71), systemic sclerosis (n=17), systemic vasculitis (n=18), and rheumatoid arthritis (n=119). Healthy blood donors (n=99) were used as controls.
Results Anti-annexin II antibodies were significantly more prevalent in patients with connective tissue diseases (8.5%), especially antiphospholipid syndrome (14.8%) and rheumatoid arthritis (10%), than in controls (2%). An inverse correlation was observed between anti-annexin II antibodies and antiphospholipid antibodies.
Conclusion Annexin II can be recognized by antibodies in serum from patients with systemic autoimmune disorders. Further studies are required to determine the clinical significance of anti-annexin II antibodies in rheumatoid arthritis and to determine their diagnostic value in discriminating clinical subgroups of patients with antiphospholipid syndrome.

Keywords Systemic autoimmune diseases · antiphospholipid syndrome · anti-annexin II antibodies

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Introduction

Impaired fibrinolysis has been described in association with antiphospholipid antibodies (APL) and could represent one of the pathogenic mechanisms in antiphospholipid syndrome (APS) [1–4]. Fibrinolytic abnormalities have also been reported in patients with connective tissue diseases [5]. APL represent a heterogenous family of distinct antibodies directed against phospholipids and phospholipid-binding protein cofactors mainly β2 glycoprotein I (β2GPI) [6]. APL may interact with coagulation factors, fibrinolytic proteins, or cells involved in hemostatic reactions such as endothelial cells, monocytes, and platelets.

Annexin II (ANXII), a 36-kD protein, belongs to the family of annexins, which are calcium-dependent, phospholipid-binding proteins. ANXII exists as a monomer and can form a heterotetramer with protein p11. ANXII has been found on

various cell types including endothelial cells, smooth muscle cells, monocytes, keratinocytes, syncytiotrophoblast cells, and lymphoma cells [7–9]. ANXII is involved in several biological processes such as exocytic and endocytic mechanisms, immunoglobulin transport in the placenta, and signal transduction [9]. It has also been identified to be an endothelial cell receptor for plasminogen and tissue plasminogen activator [10]. ANXII also mediates the binding of β2GPI to endothelial cells and plays also a pivotal role in endothelial cell activation by anti-β2GPI antibodies (aB2GPI) [11, 12]. Cesarman-Maus and coworkers [13] recently identified anti-annexin II antibodies (aANXII) in patients with lupus and APS. aANXII were found to be significantly more prevalent in patients with APS than in healthy individuals or in patients with lupus without thrombosis. According to these various studies, ANXII appears to be a new target antigen in APS. However, the prevalence of aANXII in other systemic autoimmune diseases remains unknown. In this study, we therefore evaluated the prevalence of aANXII IgG in patients with various connective tissue diseases and APS and investigated the relationship between these antibodies and other APL such as anticardiolipin antibodies (ACL) and aB2GPI.

Materials and Methods

Patients

Two hundred ninety-four patients with systemic autoimmune diseases were retrospectively included in this study. Patients were followed at the Department of Internal Medicine and Nephrology of Amiens University Hospital, Amiens, France and at the Department of Rheumatology of Rouen University Hospital, Rouen, France. Patients were divided into six groups of systemic autoimmune disorders: 53 patients with systemic lupus erythematosus (SLE) meeting the American College of Rheumatology (ACR) revised criteria for SLE [14, 15]; 16 patients with primary antiphospholipid syndrome (PAPS), 11 of whom had PAPS according to the Sapporo criteria [16], while the other 5 had 'equivocal' APS with either low titers of ACL or other APL [17]; 17 patients with systemic sclerosis (SSc), 7 with the diffuse form of the disease and satisfied the ACR criteria [18] and 10 with the limited form according to the criteria of LeRoy et al. [19]; 18 patients with systemic vasculitis (SV), most of whom had Wegener's granulomatosis and polyarteritis nodosa and satisfied the ACR criteria [20, 21]; 71 patients with primary Sjögren syndrome (pSS) as defined by the American–European consensus group criteria [22]; and 119 patients with rheumatoid arthritis (RA) who satisfied the ACR criteria [23], including 85 patients with RA less than 5 years duration and 34 patients who presented RA with structural damage and high disease activity. A control group consisted of 99 healthy blood donors.

Serum samples were obtained from patients at diagnosis or during follow-up of the disease and were stored at −80°C. Sera from healthy individuals were collected at the time of blood donation. Demographic data were collected for all patients except for RA patients. Patient characteristics are reported in Table I. Clinical data in SLE population and patients with PAPS were recorded.

Anti-annexin II Antibody Assay

aANXII IgG antibodies were detected by an enzyme-linked immunosorbent assay (ELISA) using 96-well plates (Nunc

Table I Patient Characteristics

	Number of patients	Mean age, years (range)	Female/male
Blood donors	99	42.7 (18–64)	43/53 (3 undetermined)
Patients	294	–	–
PAPS	16	48.6 (29–75)	14/2
SLE	53	37.2 (14–68)	52/1
SLE with SAPL	11		
SSc	17	50.5 (23–77)	16/1
SV	18	59.9 (20–79)	11/7
Wegener's granulomatosis	10	–	–
Polyarteritis nodosa	4	–	–
Microscopic polyangiitis	2	–	–
Churg–Strauss syndrome	1	–	–
Isolated cerebral angiitis	1	–	–
pSS	71	57.9 (26–85)	63/8
RA	119	NA	NA
Erosive and active RA	34	NA	NA
Early RA evolving for < 5 years	85	NA	NA

NA indicates not available

Maxisorp, Nunc A/S, Roskilde, Denmark). Wells were coated overnight at 4°C with 100 µl of either recombinant annexin II [full-length human annexin II expressed in *Escherichia coli* which contains a 7 kD tag (6xHis included) at its N terminus; AmProx, Carlsbad, CA, USA; 0.5 µg/ml in phosphate-buffered saline (PBS)] or PBS alone. To avoid an edge effect of microplates, peripheral wells were not used. After three washes with PBS containing 0.1% Tween 20 (PBST), the wells were blocked for 90 min at room temperature with 200 µl of solution containing PBST and 5% powdered milk. After three washes with PBST, the wells were incubated for 1 h at room temperature with 100 µl of patient serum diluted in blocking buffer (1:50). Serum was added twice to duplicate wells. Mouse monoclonal aANXII (Zymed laboratories, San Francisco, CA, USA) was used as a positive control, and a highly positive serum from a patient with PAPS was used as reference serum. The plates were washed three times with PBST and were incubated with 100 µl of peroxidase-conjugated antibodies, either goat anti-human IgG (Sigma, St. Louis, MO, USA) or goat anti-mouse IgG (Sigma), diluted in blocking buffer (1:2,000) for 1 h at room temperature. After three washes with PBST, the bound peroxidase was then revealed with 100 µl of tetramethyl-benzidine solution (Sigma) for 10 min at room temperature, and color development was stopped by addition of 50 µl of H_2SO_4 for 5 min. Absorbance was measured at 405 nm in a microplate reader (V_{max}, Molecular Devices, USA). Optical density (OD) was calculated by subtracting the OD measured in uncoated wells from that measured in coated wells. A calibration curve was generated with the positive reference serum, which was added to wells at serial dilutions (1:50, 1:100, 1:200, 1:400, 1:800, and 1:1,600). Serum autoantibody titers were expressed as arbitrary units (AU) relative to the positive reference serum, whose OD at a dilution of 1:50 was equal to 320 AU. Patients' sera were considered to be positive for aANXII when they exceeded the cutoff value defined as 3 standard deviations (SD) above the mean value observed with a serum panel from 99 healthy blood donors and corresponding to 17 AU.

Antiphospholipid Antibody Assays

ACL IgG and aB2GPI IgG were detected by a commercial ELISA kit purchased from Pharmacia. Values>15 GPL units were considered positive.

Statistical Analysis

The frequency of aANXII in patients and controls was compared by the Fisher exact test. The Spearman's correlation coefficient was used to analyze the relationship between aANXII and APL. A p value<0.05 was considered statistically significant.

Results

Patient Characteristics

Sex ratio was different between the patients and healthy individuals, but no statistically significant difference was observed between males and females in healthy blood donors in terms of the prevalence of aANXII. Thrombosis occurred in 43.3% of SLE patients, and 20.7% of SLE patients presented APS. The prevalence of APS in SLE was nearly the same as that observed in other published series of SLE [24]. All patients with PAPS had a history of episodes of venous thrombosis, arterial thrombosis, or pregnancy losses.

Prevalence of Anti-annexin II Antibodies

aANXII were detected in the serum of 25 patients (8.5%) and were statistically more prevalent in patients with systemic autoimmune diseases than in healthy individuals (2%; p=0.036; Table II). The prevalence of aANXII in healthy individuals was similar to that observed for ACL and aB2GPI. The frequency of aANXII was higher in APS and RA compared to that observed in patients with SLE, pSS, and SV. aANXII were detected in any of the patients with SSc. aANXII were significantly more prevalent in RA patients and erosive and active RA than in controls (Table II). In patients with APS including both PAPS and secondary APS related to SLE, the prevalence of aANXII (14.8%) was statistically greater than in control group (2%; p=0.019). Three patients with RA and one patient with PAPS had aANXII levels >100 AU (Fig. 1). However, the highest levels of aANXII IgG (>400 AU) were observed in serum from a patient with PAPS presenting recurrent thrombotic events (arterial and venous thrombosis, recurrent pregnancy losses). The main clinical and laboratory data of patients positive for aANXII in SLE and PAPS population are shown in Table III.

Correlation Between Anti-annexin II Antibodies and Antiphospholipid Antibodies

No significant correlation was observed between aANXII and APL such as ACL and aB2GPI, but we found an inverse correlation between aANXII and ACL (r=−0.099; p=0.05) or aB2GPI (r=−0.147; p=0.004). Relation between aANXII and APL is shown in Figs. 2 and 3. In patients with APS, the prevalence of ACL IgG and aB2GPI IgG was 48% and 33%, respectively (Table II). The

Table II Prevalence of aANXII IgG, ACL IgG, and aB2GPI IgG in Patients and Healthy Individuals

	Positive anti-annexin II (%)	Positive ACL (%)	Positive anti-β2 GPI (%)
Blood donors (n=99)	2	2	1
Patients (n=294)	8.5*	11.3	5.5
PAPS (n=16)	12.5	31.2	18.7
SLE (n=53)	7.5	41.5	20.7
APS (PAPS and secondary APS related to SLE; n=27)	14.8**	48.1	33.3
SSc (n=17)	0	0	0
SV (n=18)	5.5	0	0
pSS (n=71)	8.4	1.4	0
RA (n=119)	10***	4.2	1.7
Erosive and active RA (n=34)	14.7****	5.8	0
Early RA evolving for < 5 years (n=85)	8.2	3.6	2.4

*p=0.036 as compared to positive controls
**p=0.019 as compared to positive controls
***p=0.023 as compared to positive controls
****p=0.012 as compared to positive controls

prevalence of APL was therefore unexpectedly low but can be explained by the absence of detection of ACL IgM or aB2GPI IgM. Some patients were therefore positive for APL and became negative, and some patients presented 'equivocal' APS. In RA patients, the prevalence of ACL IgG and aB2GPI IgG, 4.2% and 1.7%, respectively, was nearly the same compared as that reported by Vittecoq and coworkers [25], and only one sample had high titers of ACL IgG (>500 U/ml).

Discussion

Annexin II, a receptor on the endothelial cell surface for both plasminogen and tissue plasminogen activator has recently been identified as a new autoantigen in APS [13]. Human anti-annexin II IgG could also activate endothelial cells and may inhibit plasmin generation [13]. Thus, in APS, aANXII could play a pathogenic role in the development of thrombosis. The prevalence of aANXII in other systemic autoimmune diseases has not been previously evaluated. The present study shows that annexin II may be targeted by autoantibodies present in serum of 294 patients with various systemic rheumatic diseases. A statistically significant difference was observed between patients with systemic autoimmune diseases and healthy individuals with regard to the presence of aANXII. In healthy blood donors, the prevalence of aANXII IgG was the same (2%) as that reported by Cesarman-Maus and coworkers (1.4%) [13]. SLE is a systemic autoimmune disease characterized by the excessive production of autoantibodies [26]. Other annexins, such as annexins IV, V, and XI, have been identified as target antigens in SLE patients [26]. aANXII IgG were detected in our series of SLE patients with a low frequency (7.5%), which is not very different from that observed in a series of 206 SLE patients without thrombosis (3.4%) [13]. aANXII IgG were detected in APS, including PAPS and secondary APS related to SLE, with the same frequency (14.8%) as that observed in a series of 62 patients with APS (11.3%) [13]. In our series of 27 patients with APS, aANXII were significantly more prevalent than in healthy individuals. The prevalence of aANXII in serum from 119 patients with RA was significantly higher than that reported in serum from healthy controls. Furthermore, high levels of aANXII (>100 AU) were observed in three patients with RA. Among these patients with high aANXII levels, only one had positive ACL IgG at low levels (18 GPL units). Unfortunately, no clinical data were available in these patients to determine whether or not they had developed venous or arterial thrombosis. ANXII (p11 subunit) has

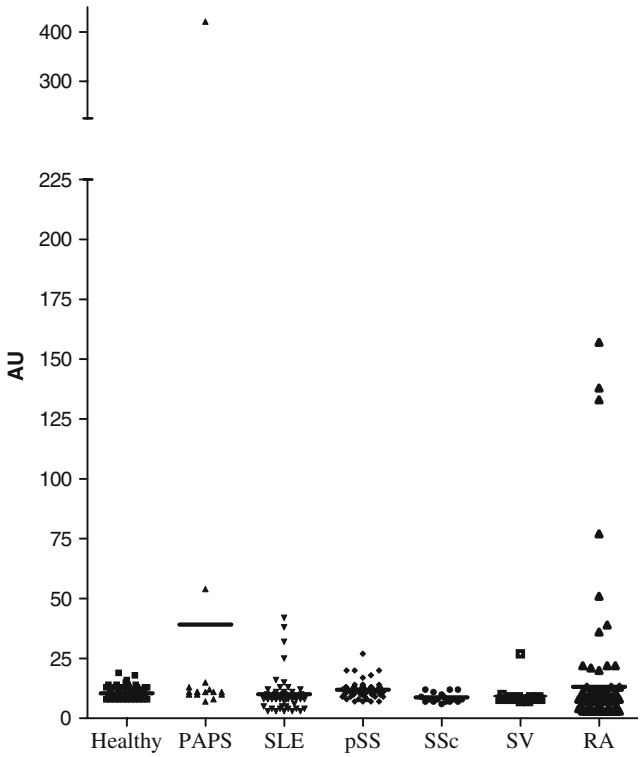

Fig. 1 Levels of aANXII IgG in patients and healthy individuals

Table III Clinical and Laboratory Data of Patients with Positive Anti-annexin II Antibodies in SLE and PAPS Population

	Sex	Age (years)	Clinical history	aANXII (AU)	ACL (GPL)	aB2GPI (GPL)	LA
SLE patients							
Patient 1	Female	66	Arthralgia, rash malar, serositis, nephritis, pancytopenia, APS, deep vein thrombosis	32	96	37	Negative
Patient 2	Female	26	Arthritis, serositis, meningoencephalitis, Raynaud's phenomenon	42	10	17	Negative
Patient 3	Female	68	APS, deep vein thrombosis, serositis	25	10	10	NA
Patient 4	Female	59	Arthritis, myalgia, photosensitivity	38	10	10	Negative
PAPS patients							
Patient 1	Female	46	Ischemic stroke, recurrent venous thrombosis, recurrent pregnancy losses, endocarditis	421	18	10	Negative
Patient 2	Female	58	Recurrent venous thrombosis, recurrent pulmonary embolism, recurrent pregnancy losses	54	5	1	NA

Normal ranges: aANXII, AU less than 17; ACL, GPL less than 15; aB2GPI, GPL less than 15. NA indicates not available

been detected in synovial tissue from patients with RA and osteoarthritis [27]. Significant staining of ANXII in RA synovium was observed in the lining layer and around blood vessels. ANXII gene overexpression has been identified in RA synovium [28]. Annexin II gene was upregulated in RA synovium and less intensely expressed in synovial tissue from patients with osteoarthritis. Therefore, ANXII could represent a new antigenic target for antibodies in RA patients. Annexin V, a potent anticoagulant protein, which also belongs to the annexin family, plays a role in the pathology of APS, particularly in pregnancy-related morbidity. High levels of anti-annexin V antibodies were found in RA and were correlated to RA activity [29]. Prospective studies are required to determine the clinical significance of aANXII in RA patients.

All sera from the 294 patients and 99 healthy blood donors were tested for ACL IgG and aB2GPI IgG. β2GPI, a major antigenic target for APL, can bind to annexin II with a high affinity. The binding of β2GPI to ANXII, therefore, raised the question of whether aANXII are associated with APL such as ACL and aBGPI. No correlation was observed between aANXII and APL. However, aANXII were inversely correlated with APL. Thus, in most patients and blood donors, when aANXII are present, ACL and aBGPI are low or absent. Lupus anticoagulant assays were performed in 71% of SLE patients and 62.5% of patients with PAPS. The prevalence of LA was 29% in SLE patients and 30% in patients with PAPS. In most of patients with SLE or PAPS who were positive for aANXII, none of them had positive LA (Table III).

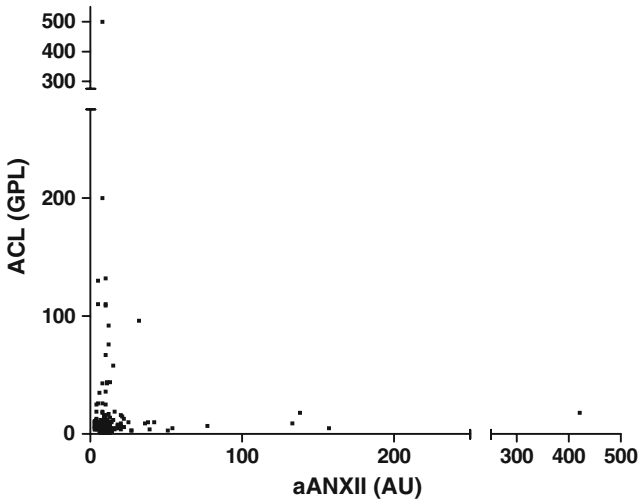

Fig. 2 Relation between ACL IgG and aANXII IgG in patients with systemic autoimmune diseases and blood donors controls

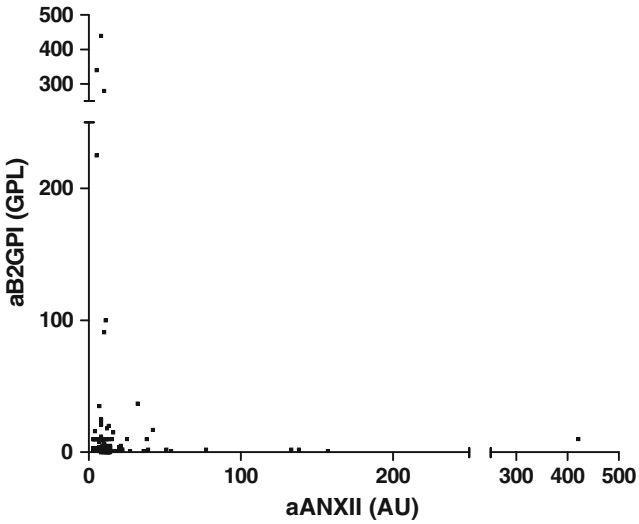

Fig. 3 Relation between aB2GPI IgG and aANXII IgG in patients with systemic autoimmune diseases and blood donors controls

High levels of aANXII (>100 AU) were found in serum from a patient with PAPS presenting recurrent venous thrombosis, recurrent pregnancy losses, endocarditis, and ischemic stroke. This patients had positive ACL IgG (18 GPL units) without LA. In APS, recurrent thrombotic events may occur after the first thrombotic event, and some patients with APS present multiple occlusions, which occur simultaneously in vessels of different organs, known by the name of "catastrophic antiphospholipid syndrome" [6]. It was recently demonstrated that annexin II null mice displayed microvascular fibrin accumulation in multiple organs [30]. The diagnostic value of aANXII in relation to recurrence of thrombotic events in APS or the occurrence of multiple vascular occlusions in "catastrophic antiphospholipid syndrome" should therefore be investigated in a longitudinal study on patients with PAPS and SLE.

In conclusion, ANXII represents a new autoantigen in systemic autoimmune disorders and APS. aANXII are present in serum from patients and blood donors independently of ACL and aB2GPI. Further studies are required to determine the clinical significance of these antibodies in RA and their diagnostic value to discriminate clinical subgroups of APS patients.

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