Comparison of the 1999 Sapporo and 2006 revised criteria for the classification of the antiphospholipid syndrome

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Abstract

Objective

The 2006 revised criteria for antiphospholipid syndrome (APS) provide a new classification challenge, and studies validating the updated criteria against the older ones are still scanty. We compared the 1999 preliminary with the 2006 revised classification criteria for APS, and evaluated if the revised criteria provide an added value over the original ones.

Methods

A laboratory-based registry population was obtained on the basis of the positivity of antiphospholipid (aPL) antibodies. Patients were analysed for fulfillment of the 1999 and 2006 classification criteria for APS, non-criteria features of APS, and autoantibody profile.

Results

Of 144 aPL-positive identified patients, 119 had at least 2 aPL tests on separated occasions, and were included in this study. According to the 1999 criteria, 23 patients had APS (15 had thrombosis alone, 4 pregnancy morbidity, and 4 both); while 26 fulfilled the 2006 revised criteria (15 had thrombosis alone, 5 pregnancy morbidity, and 6 both). One patient with isolated thrombosis who met 1999 criteria did not meet those of 2006 (aCL positivity but not >12 weeks apart). One patient with thrombosis, other with pregnancy morbidity, and 2 with both only fulfilled the 2006 criteria because they had isolated anti-β_2GPI antibody-positivity. High concordance between criteria was found, with κ index of 0.87 (95% CI, 0.76-0.98).

Conclusion

The 2006 revised criteria represent a step-forward since it allows the inclusion of patients with anti-β_2GPI antibodies as an isolated serological feature. However, a wider time interval between serologic tests seems unlikely to make differences.

Key words

Antiphospholipid syndrome, antiphospholipid antibodies, lupus anticoagulant, classification criteria, anticardiolipin antibodies.

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Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder with a wide array of clinical manifestations and serologic features. Due to the variability in its clinical presentation, different sets of criteria have been formulated attempting to homogenise patients for research purposes. In 1999, preliminary classification criteria were formulated in a post-conference workshop in Sapporo, Japan (1). Since then, these have been widely used in clinical research, but major clinical and laboratory insights have come to emerge (2). In 2004, a revised version was developed in Sydney, Australia, and published as a consensus statement in 2006 (3).

In the 2006 consensus, clinical criteria remained mostly unchanged, while laboratory criteria were substantially modified. First, anti-β_2 glycoprotein-I (anti-β_2GPI) IgG/M antibodies were added as a laboratory criterion. Second, antiphospholipid antibodies (aPL) have to be positive on ≥2 occasions at least 12 weeks apart in titers ≥40 U or ≥99th percentile, instead of ≥6 weeks at "medium-to-high titer" as stated in the Sapporo criteria. Additionally, the 2006 revised criteria introduce a stratification of APS patients into four categories according to the type of aPL positivity, and provide specific definitions for clinical features associated with APS, but not accepted as criteria (3).

Based on the importance of criteria for research purposes, the American College of Rheumatology Quality Measures Committee encourages the development and validation of new and improved classification criteria for different rheumatic diseases (4). In APS, studies validating the updated classification criteria against the older ones are still scanty, and there is no conclusive evidence whether the revised criteria confer an advantage over the Sapporo ones (5-8).

Updated criteria provide a new classification challenge, but any proposed classification criteria must show superiority over the older ones before they are generally accepted. Therefore, we decided to compare the 1999 with the 2006 revised classification criteria for APS, and to evaluate if the revised criteria provide an added value over the original ones, using our own data from a single outpatient rheumatology clinic.

Material and methods

Patients

We selected all subjects (irrespectively of the APS diagnosis) who had at least one (whichever) positive aPL test between September 2006 and August 2007 in a local laboratory-based registry. Afterwards, a retrospective medical record review was performed, in which patients' demographics, aPL profile (results and testing dates of anticardiolipin (aCL), anti-β_2GPI, and lupus anticoagulant (LA) tests), APS features outlined in the classification criteria (type of thrombosis and pregnancy morbidity), and other clinical manifestations not included in the criteria (namely, cardiac valve disease, cutaneous manifestations (*livedo reticularis* and skin ulcerations), thrombocytopenia, aPL-associated nephropathy, and neurological manifestations (migraine and epilepsy)) were systematically recorded. To be included in the analysis, all patients needed to have aPL measurements in at least two separate occasions. Protocols were approved by our local ethics committee and each patient signed an informed consent.

Patients were classified according to the 1999 and 2006 classification criteria (in those meeting only one set of criteria, the reason why they did not meet the other one was registered) (1, 3). Additionally, we analysed the presence of isolated thrombosis, pregnancy morbidity, or both. Patients with thrombotic and/or obstetrical events who did not meet the laboratory criterion (that is, those with only one positive aPL determination) were denominated as "APS-like syndrome". Finally, patients without clinical APS features in which at least one aPL has been found were defined as "isolated aPL positivity". In accordance with the 2006 classification criteria, patients with coexisting inherited or acquired factors for thrombosis were not excluded from the study.

Definitions

Clinical episodes of vascular thrombosis were included only when confirmed by an appropriate imaging technique (ultrasonography, computed tomography, and/or magnetic resonance imaging). Cardiac valve disease was defined on echocardiography as the presence of valve thickness (>3 mm in the aortic and pulmonary leaflets, or >5 mm in the mitral and tricuspid leaflets), regurgitation and/or stenosis of the mitral or aortic valves, as well as the presence of nodules in the atrial side of the mitral valve, or in the vascular side of the aortic valve. The aPL-associated nephropathy was diagnosed if thrombotic microangiopathy was demonstrated (involving arterioles and glomerular capillaries) in the absence of inflammatory infiltration by renal histology. Thrombocytopenia was defined as platelet count <150 x 10^9 L^{-1} in at least two occasions. Clinical manifestations and aPL positivity were not more than 5 years apart.

Laboratory tests

Since their introduction at our centre in September 2006, anti-β_2GPI (QuantaLite β_2GPI Screening ELISA, INOVA Diagnostics, San Diego, CA) and aCL (QuantaLite ACA Screen III, INOVA Diagnostics) antibodies have been detected by commercial qualitative enzyme-linked immunosorbent assays. According to the manufacturer, serum samples are compared versus known positive and negative reference sera included in the kit, and results are expressed as positive (cut-off, >99th percentile from a reference population) or negative. In accordance with the International Society on Thrombosis and Haemostasis guidelines (9), LA is detected in a step-wise approach: a prolonged activated partial thromboplastin time assay, a non-correction in a mix with pooled normal plasma, and finally a confirmation throughout the Russell's viper venom time test (Licon, Mexico City, MX).

Routinely, in our laboratory all serum samples are tested in duplicate.

Statistics

Categorical data were expressed as proportions, and its differences measured by χ^2 tests. Continuous variables were expressed as mean ± 1 standard deviation (SD), and Student's *t*-tests were used for comparisons. Odd ratios (OR) and their 95% confidence intervals (95%CI) were also obtained. Concordance between criteria was evaluated by the Cohen's unweighted kappa (κ) test. All tests were two-tailed and a $p<0.05$ was regarded as significant. Data were analysed with the GraphPad Prism 4.0 software (GraphPad Inc, San Diego, CA).

Table I. Demographic and clinical data of patients according to the 2006 revised classification criteria for APS.

	With APS n=26 (%)	Without APS n=93 (%)	Odds ratio (95% CI)	*p*-value
Age (mean ± SD)	38.5 ± 14.3	36.1 ± 12.4	–	0.4
Female	19 (73)	80 (86)	–	0.11
Systemic autoimmune disease				
SLE	10 (38)	44 (47)	–	0.42
Other	2 (8)	14 (15)	–	0.33
None	14 (54)	35 (38)	–	0.13
Cardiovascular risk factors				
Hypertension	9 (34)	33 (35)	–	0.93
Smoking	1 (4)	8 (8)	–	0.65
Diabetes mellitus	1 (4)	4 (4)	–	0.91
Dyslipidemia	8 (30)	15 (16)	–	0.09
Clinical features				
Arterial thrombosis	20 (77)	26 (28)	8.5 (3.1-23.8)	<0.0001
Venous thrombosis	9 (34)	9 (10)	4.9 (1.7-14.3)	0.003
Pregnancy morbidity	11 (42)	10 (11)	6 (2.2-16.9)	0.0002
aPL nephropathy	3 (11)	2 (2)	5.9 (0.9-37.6)	0.034
Neurological involvement	10 (38)	11 (12)	4.6 (1.7-12.8)	0.001
Cardiac valve disease	2 (7)	2 (2)	3.8 (0.5-28)	0.16
Skin involvement	7 (27)	6 (6)	5.3 (1.6-17.7)	0.003
Thrombocytopenia	7 (27)	19 (20)	1.4 (0.5-3.9)	0.47

Results

One hundred and forty-four patients with aPL-positive tests were detected. Of these, 119 (83%) had sufficient data for analysis and were included in the study. Ninety-nine (83%) patients were female, with a mean age of 36.6±12.8 years, and 53% of patients had other coexisting autoimmune disease, mainly systemic lupus erythematosus. For comparison, the cohort was first divided into patients who fulfilled the 2006 criteria and those who did not (Table I). Demographics, coexistence of other systemic autoimmune diseases, and traditional cardiovascular risk factors were similar in patients fulfilling the 2006 criteria than in those who did not. Regarding the presence of selected clinical manifestations, significant differences were found on arterial thrombosis (77 *vs*. 28%, $p<0.0001$), venous thrombosis (34 *vs*. 10%, $p=0.001$), pregnancy morbidity (42 *vs*. 11%, $p=0.0002$), aPL-associated nephropathy (11 *vs*. 2%, $p=0.03$), as well as neurological (38 *vs*. 12%, $p=0.001$) and cutaneous (27 *vs*. 6%, $p=0.003$) involvement. The clinical manifestations conferring risk to be classified as APS according to the 2006 revised criteria were arterial thrombosis (OR 8.5, 95%CI 3.1–23.8), pregnancy morbidity (6, 2.2–16.9), venous thrombosis (4.9, 1.7–14.3), as well as cutaneous (5.3, 1.6–17.7) and neurological (4.6, 1.7–12.8) involvement.

Each patient was then analysed for fulfillment of the 1999 and/or 2006 classification criteria (Table II). According to the 1999 criteria, 23 patients had a definite APS diagnosis (15 with thrombosis alone, 4 with pregnancy morbidity, and 4 with both), 38 patients were classified as APS-like syndrome, and the remaining 58 were asymptomatic. On the other hand, according to the 2006 revised criteria, 26 patients had definite APS diagnosis (15 with isolated

thrombosis, 5 with pregnancy morbidity, and 6 with both), 35 patients were catalogued as APS-like syndrome, and 58 were asymptomatic. Of note, a patient with isolated thrombosis who met the 1999 criteria did not meet those of the 2006 because of two positive aCL tests but not within the recommended time frame of >12 weeks apart (subsequent tests were negative). One patient with thrombosis, other with pregnancy morbidity, and two additional patients with both clinical features met only the 2006 criteria because of isolated anti-β_2GPI antibody-positivity. In the group referred as "isolated aPL positivity" there were no changes by either set of criteria. Given these data, κ index of 0.87 (95% CI, 0.76–0.98) between both classification criteria was found.

Finally, according to the aPL profile in the group classified as having APS by the 2006 revised criteria, 14 patients showed >1 aPL, eight patients were positive for aCL alone, and four for anti-β_2GPI alone (Table III). Although 11 patients were positive for LA, no patient had this as a unique antibody. Fifteen patients had only thrombosis (either arterial, venous, or both), five only obstetric morbidity, while the remaining six had both.

The reasons for having requested aPL tests in patients with APS-like syndrome were: isolated thrombosis (72%), pregnancy morbidity (14%), or both (14%). Meanwhile, in asymptomatic patients catalogued as "isolated aPL positivity" these were: systemic lupus erythematosus (36%), thrombocytopenia (14%), other coexistent rheumatic disease (12%), migraine or epilepsy (12%), cardiac valve disease (9%), renal thrombotic microangiopathy (3%), *livedo reticularis* or skin ulcers (3%), pulmonary hypertension (2%), and unknown (9%).

Table II. Distribution of 119 aPL-positive patients according to the 1999 and 2006 classification criteria for APS.

	APS			APS-like	Isolated
	Thrombotic	Obstetrical	Both	syndrome	aPL
1999 criteria *n* (%)	15 (13)	4 (3)	4 (3)	38 (32)	58 (49)
2006 criteria *n* (%)	15 (13)	5 (4)	6 (5)	35 (29)	58 (49)

Table III. Distribution of APS patients (2006 classification criteria) according to the aPL profile.

Subgroup	Thrombotic	Obstetrical	Both
I: >1 aPL (any combination)	7	3	4
IIa: LA alone	0	0	0
IIb: aCL alone	7	1	0
IIc: anti-β_2GPI alone	1	1	2

Discussion

This descriptive study based on a registry of aPL-positive patients supports that the APS revised criteria show tightly superiority than the original ones.

Vascular thrombosis and pregnancy morbidity have long been recognised as indisputable features of APS, so that, these were included as criteria since the first proposed APS classification system by Harris in 1987, and have remained almost unchanged until now (10). As expected, in our study both conditions were the strongest clinical features discriminating between patients with or without APS according to the 2006 revised criteria; while this may seen tautological, both manifestations are the major medical conditions to request aPL tests. Regarding non-criteria APS features, cutaneous and neurological involvement were also suitable discriminators, with a 3- to 4-fold more prevalence in APS patients; however, cardiac valve disease, aPL-associated nephropathy, and thrombocytopenia only showed trends for association with APS, perhaps due to small sample size for those manifestations (type II error). With respect to these non-criteria APS features, similar trends were found by Kaul *et al*. in a retrospective study on 200 aPL-positive patients (6). In this study, *livedo reticularis* was found more frequently in APS patients (17 *vs*. 4%), although cardiac valve disease (22 *vs*. 7%), and nephropathy (5 *vs*. 1%) were also found more frequently in APS patients than in those who did not fulfill the 2006 revised criteria. These results suggest that the inclusion of thrombocytopenia and perhaps cardiac valve disease or aPL-associated nephropathy as APS criteria might decrease the diagnostic specificity, even though their associations with APS are well-recognised (11-13).

Persistence of aPL positivity through time seems to be important, and there are concerns that transient presence of epiphenomenal aPL – for instance, aPL induced by infections – could risk misclassification (14, 15), regardless of their potential pathogenic or epiphenomenal role (16, 17). In the 2006 criteria, it was proposed that an increase in the interval of positive tests to 12 weeks would unlikely affect sensitivity. However, since this interval was based on experts' opinion, studies validating this time frame are needed (3, 8). We found that among 23 patients who met the 1999 criteria, 22 also fulfilled the 2006 criteria, but the remainder did not because aCL antibodies were positive with more than six but less than twelve weeks apart. In the study by Kaul *et al*., 2 of 144 patients which met the laboratory requirement for the 1999 classification criteria did not fulfill the 2006 revised ones because the two positive aPL were not within the recommended time frame of >12 weeks apart (6). Thus, increasing the interval for aPL positivity seems to result in a more selective screening for APS patients. However, it is doubtful that this tight difference really represents a discriminating step-forward in the improvement of classification criteria.

Reactivity against β_2 glycoprotein-I plays a critical role in the pathogenesis of APS, and anti-β_2GPI antibodies have been found to be an independent risk factor for vascular thrombosis and pregnancy morbidity (18, 19). In our study, four patients who did not meet

the 1999 original criteria met the 2006 revised criteria because of isolated anti-β_2GPI positivity; that is, in our patients the addition of anti-β_2GPI antibodies increased the detection of patients with APS in ~4%. This figure is in accordance with previous reports. In a retrospective study including 107 obstetric patients, six newly cases of APS were found when persistent isolated positivity to anti-β_2GPI antibodies was taken into account (5%) (5). Similarly, Kaul, *et al*. found that 5 of 39 patients who did not meet the 1999 criteria met the 2006 revised criteria because of isolated anti-β_2GPI positivity (13%) (6). Recently, Swadzba, *et al*. analysed the association between clinical complications and laboratory tests for APS in 336 patients with diverse autoimmune diseases, based on the 2006 revised classification criteria. The inclusion of anti-β_2GPI antibody positivity changed the number of patients classified with APS from 112 to 117 (4.5%) (7). All, these results are in agreement with evidence pointing towards the fact that the single positivity for anti-β_2GPI antibodies explains 3 to 9% of the thrombotic events in the absence of LA or aCL (20-22).

Given that the 1999 and 2006 revised criteria share the majority of the clinical and laboratory items, high concordance between both classifications could be expected. The observed concordance in our study tends to be high, with κ index of 0.87. In the same direction, Pourrat, *et al*. described a high agreement between both classification criteria; again, the updated criteria resulting in some new cases classified as APS, especially in patients with obstetric morbidity (5). Nevertheless, discrepancies have been reported by Kaul *et al*.; from 81 patients with APS according to the 1999 classification criteria, only 47 (58%) also met the 2006 revised criteria (6). Thus, even when no conclusive data can be drawn, it is possible that the degree of concordance between criteria depends on the type of patients included or even be due to different ethnical/genetical background (Mexican/mestizo ethnicity in the present study).

Our study is limited by the retrospective data analysis, and a selection bias cannot be excluded, since the study population was exclusively composed of aPL-positive patients. Inclusion of asymptomatic aPL-positive patients who did not meet the APS criteria could be viewed as a limitation; however, even though the explicit purpose of the criteria is classification of individuals for research purposes, many clinicians have used them as a guideline for diagnostic and therapeutic purposes. So that, we believe that this heterogeneous population is more representative of what happens in "real life". Moreover, previous reports have selected patients from previously-generated databases for other studies (each with their own set of inclusion criteria) (6), obstetric medicine clinics (5), or internet medical articles researches (8), limiting their applicability in general rheumatology clinics.

In conclusion, the 2006 revised criteria seem to represent a step forward in the development of classification criteria by expanding the inclusion of some APS patients through the addition of anti-β_2GPI antibodies as an isolated serological item, and add valuable information by including definitions of associated clinical manifestations. The use of a wider time interval between serologic tests resulted in only slight differences. If this is clinically relevant must be further elucidated.

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