Clinical manifestations of the anti-phospholipid syndrome as defined by the updated Sapporo classification criteria

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The antiphospholipid syndrome (APS) is characterised by thrombosis and recurrent fetal loss accompanied by the presence of lupus anticoagulant (LA) and/or anti-cardiolipin antibodies (aCLA).^{1,2} Anti-phospholipid (aPL) antibodies require a protein cofactor, β_2 -glycoprotein 1 (β_2 -GP1) or prothrombin, for proper binding.^{3–5} Patients may also present with antibodies to β_2 -GP1, but not LA or aCLA. Originally, they were classified as having the anti-phospholipid/cofactor syndrome,^{6,7} but recently the Sapporo classification criteria have been updated by including the β_2 -GP1-antibodies.⁸

We retrospectively evaluated the clinical manifestations of APS in 105 consecutive patients that presented with the suspicion of APS and/or systemic lupus erythematosus, and tested positive for aPL antibodies twice at least 6 weeks apart. LA was assessed by performing the LA-screen/confirm (Gradipore dRVVT, Australia). IgM and IgG aCLA, as well as IgG antibodies to β_2 -GP1, were determined by ELISA (Varelisa, Phadia, Germany).

Sixty-eight patients (65%) fulfilled the clinical APS classification criteria; 33 patients (31%) did not. In four patients, insufficient clinical information was available. The 33 non-APS patients were tested for aPL antibodies, because they were diagnosed as having systemic autoimmune diseases (n = 19), because they exhibited only minor APS criteria (n = 5), or for miscellaneous reasons (n = 7). According to the adjusted criteria,⁸ aPL-antibody presence is categorised as follows: I, more than one aPL-antibody; IIa, only LA; IIb, only aCLA; IIc, only anti- β_2 -GP1 antibodies. The aPL-antibody distribution of the 68 APS patients and 33 patients not having APS are shown in table 1. Six APS patients (categories IIb/IIc) were not tested for LA and therefore were possibly erroneously categorised. Surprisingly, 13 APS patients (19.1%) were in category IIc. This is not due to the anti- β_2 -GP1 ELISA being too sensitive, since only two non-APS patients (6.1%) were in category IIc. That these anti- β_2 -GP1 antibodies are not detected in the β_2 -GP1 dependent aCLA assay can be explained by the finding that these antibodies bind close to the phospholipids-binding site in domain V of β_2 -GP1,⁷ and so this epitope is blocked once β_2 -GP1 has bound to cardiolipin.

Clinical manifestations were scored from symptom onset until the end of inclusion. The most common events were DVT (37%), fetal loss >10 weeks of pregnancy (25%), stroke/transient ischaemic attack (21%), fetal loss <10 weeks of pregnancy (19%), pulmonary embolism (15%) and arterial thrombosis in the legs (12%). Other common findings were thrombocytopenia (28%), arthralgia (10%), epilepsy (9%) and myocardial infarction (7%). Our data are in agreement with the multicentre study of Cervera *et al*.⁹ Clinical manifestations of patients categorised based on their antibody profile hardly differed between categories (table 1). Both category IIa patients had DVT, whereas a substantial proportion of category IIc patients had stroke/transient ischaemic attack (TIA) (38%). These associations were, however, not statistically significant (p = 0.12 and p = 0.06, respectively).

Altogether, inclusion of anti- β_2 -GP1 antibodies results in a 20% increase in patients classified with APS. Clinical manifestations in APS as defined by the updated laboratory criteria⁸ are not different from patients with APS defined by the original Sapporo criteria.¹ In addition, clinical manifestations are not predictive of a typical autoantibody profile.

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Abbreviations: aCLA, anti-cardiolipin antibodies; aPL, anti-phospholipid; APS, antiphospholipid syndrome; LA, lupus anticoagulant

Table 1 Laboratory characteristics in relation to clinical characteristics

	Category I* (%)	Category IIa (%)	Category IIb (%)	Category IIc (%)
APS patients (n = 68)	25 (36.8)†	2 (2.9)	28 (41.2)	13 (19.1)
DVT (n = 25)‡	10 (40.0)§	2 (100.0)	10 (35.7)	3 (23.1)
Stroke/transient ischaemic attack (n = 14)‡	4 (16.0)	0 (0.0)	5 (17.9)	5 (38.5)
Obstetric complications (n = 24)‡	11 (44.0)	0 (0.0)	10 (35.7)	3 (23.1)
Other manifestations¶ (n = 10)‡	4 (16.0)	0 (0.0)	4 (14.3)	2 (15.4)
Patients without APS (n = 33)	8 (24.2)†	2 (6.1)	21 (63.6)	2 (6.1)

*I: More than one laboratory criterion present (any combination); IIa: LA present alone; IIb: aCLA present alone; IIc: anti- β_2 -GP1 antibody present alone; † percentage of total of APS patients (n = 68) or patients without APS (n = 33), respectively; ‡ note that only most common events are specified and that some patients may have exhibited more than one of these major clinical manifestations; therefore, the number of patients may sum up to >100% of the patients in the respective antibody category (I and IIb); §Number of patients (percentage of total patients in respective category); ¶ 10 patients presented with other manifestations than those specified above; these patients presented with: pulmonary embolism (n = 6), claudication/ischaemia of limbs (n = 2), renal artery thrombosis (n = 1), or retinal vein thrombosis (n = 1).

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FORTHCOMING EVENTS

VI Meeting of the European Forum on Antiphospholipid Antibodies

12–13 October 2007, Ljubljana, Slovenia

Informal meeting of the clinicians, scientists that are active in the field of antiphospholipid antibodies and antiphospholipid syndrome

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CORRECTION

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There was an error in an author name in a letter published in the July issue (Tsavaris N, Mavragani CP, Dimitrios P. Rheumatoid arthritis: correlation between rheumatoid factor levels and CA-125 tumour marker elevation. *Ann Rheum Dis* 2007;**66**:980.) The correct author list is as follows: Tsavaris N, Mavragani CP, Pikazis D.