

## Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder

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**SUMMARY** Raised levels of serum antiphospholipid antibodies have most commonly been reported in patients with systemic lupus erythematosus (SLE). There remains, however, a group of patients with raised antiphospholipid antibody levels who do not have any other well defined disease, but do have clinical features associated with these raised antibodies. The clinical, haematological, and serological features of 20 such patients are reported. Antiphospholipid antibody levels were measured by a solid phase assay for anticardiolipin activity. Fourteen patients had raised IgG antiphospholipid antibodies, 12 had raised IgM, and six had both. Nine out of 19 had raised antinuclear antibody levels; however, none fulfilled criteria for the diagnosis of SLE. Seven patients had a history of venous thrombosis and five of definite or presumed arterial thrombosis—for example, stroke. Of the 15 female patients who underwent pregnancy, 12 experienced fetal loss with up to eight abortions each (mean 3.6). Six individuals had thrombocytopenia and four others had migraines. Other clinical features included livedo reticularis, cardiac and neuropsychiatric disorders, arthralgias, and Raynaud's phenomenon. These findings confirm that the clinical features of individuals with what may be called the 'primary antiphospholipid syndrome' are similar to those in patients with other diagnoses who have raised antiphospholipid antibodies. They indicate that the antiphospholipid syndrome may be related to SLE and other autoimmune diseases, but that, although it frequently overlaps with these disorders, it also exists as a distinct entity.

**Key words:** antiphospholipid antibody, connective tissue disease.

In recent years a distinct clinical syndrome has been delineated, consisting typically of one or more of thrombosis, thrombocytopenia, and recurrent fetal loss, together with raised levels of antibodies to negatively charged phospholipids (reviewed in refs 1 and 2). Although these clinical features had been associated with the presence of the lupus anticoagulant (subsequently shown to be mediated by antiphospholipid antibodies), it was the development of a solid phase radioimmunoassay for anticardiolipin antibodies which allowed the easy and sensitive detection of antiphospholipid antibodies and made possible a large number of studies on the clinical and other associations of these antibodies.<sup>3</sup>

Most reports concentrate on systemic lupus erythematosus (SLE). Antiphospholipid antibodies have, however, been described in a number of different conditions, including Sjögren's syndrome,<sup>4</sup> systemic sclerosis,<sup>5</sup> Behçet's syndrome,<sup>6</sup> Lyme disease,<sup>7</sup> and syphilis.<sup>8,9</sup> Some patients appear to have no underlying disorder: although there is an extremely low incidence of raised antiphospholipid antibodies in normal individuals,<sup>2</sup> some patients with an uncomplicated history of thrombosis or recurrent abortion have been shown to have raised antiphospholipid antibody levels.<sup>2</sup> These individuals may be regarded as having a 'primary antiphospholipid syndrome'.

We therefore performed a retrospective study on a cohort of patients attending the Hammersmith Hospital, who had raised antiphospholipid antibodies as detected by an enzyme linked immunosorbent

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assay (ELISA) for anticardiolipin antibodies (cardiolipin is a negatively charged phospholipid), and who did not have SLE, according to American Rheumatism Association criteria, or any other well defined disease. We report the clinical and serological findings on 20 such patients with primary antiphospholipid syndrome.

### Patients and methods

#### PATIENTS

Patients were selected who were attending the department of medicine (rheumatology unit) or the department of obstetrics and gynaecology at the Hammersmith Hospital. Individuals attending both departments are routinely tested for serum anticardiolipin antibodies if the clinical features suggest that these may be raised. For the present study patients were identified who had raised levels of anticardiolipin antibodies (IgM or IgG class, or both), but who did not have SLE according to the 1983 revised American Rheumatism Association criteria,<sup>10</sup> and in whom it was not possible to make another substantive diagnosis to account for their clinical findings. A retrospective examination of their clinical, haematological, serological, and other features was then carried out.

#### SEROLOGICAL TESTS

Serum anticardiolipin antibody levels were measured by ELISA as previously described.<sup>11</sup> The results are expressed in units, the normal range being <9 units for IgG and <8 units for IgM. These values represent five standard deviations (SD) above the mean for a cohort of 150 normal controls. Antinuclear antibody titres,<sup>12</sup> Venereal Disease Research Laboratory tests,<sup>13</sup> *Treponema pallidum* immobilisation tests,<sup>14</sup> Coombs' tests,<sup>15</sup> and antibodies to extractable nuclear antigens<sup>16</sup> were all determined by standard methods. Tests to detect the lupus anticoagulant were not routinely performed.

### Results

#### ANTICARDIOLIPIN ANTIBODIES

Twenty patients (18 female, two male) were identified and studied who had raised levels of anticardiolipin antibodies but who did not have SLE and in whom no other substantive diagnosis was possible. The age range was 17–53 years (mean 32.7, median 30.0). Fourteen patients had raised IgG anticardiolipin antibody titres, while 12 had raised IgM; six had both (Table 1). For each patient the titres of anticardiolipin antibodies varied with time; the figures in Table 1 represent the highest recorded

Table 1 Serological and clinical data for 20 patients with raised anticardiolipin antibodies

Patient No	Age (years)	ACA†‡		ANA†	VDRL†	Thrombosis		Abortion§	Thrombocytopenia	Livedo	Migraine
		IgG	IgM			Venous	Arterial				
1	34	250	–	+	–	+		+			+
2	47	160	–	+	–			–	+		
3	31	130	–	+	+		+	+		+	
4	46	130	–	+	+	+		()			+
5	35	80	–	–	–	+		+			
6	36	48	–	+	+			+	+		
7	28	25	–	–	+			+			
8	19	15	–	NT	–			(+)			
9	27	200	50	+	–		+	+			
10	28	105	35	+	–	+		()			+
11	53	97	25	–	–	+		+			
12	29	38	12	+	–		+	+	+		
13	52	15	130	–	+	+		–			
14*	17	105	22	–	–	+		()	+		
15	40	–	29	+	–			+	+		
16	34	–	21	–	–			+			
17	28	–	11	–	–			+			
18	25	–	11	–	–	?	+	()			
19	27	–	10	–	–			+			
20*	17	–	15	–	–		+	()	+		

\*Patients 14 and 20 were the only male patients.

†ACA=anticardiolipin antibodies; ANA=antinuclear antibodies; VDRL=Venereal Disease Research Laboratory test.

‡ACA levels are expressed in units (see 'Patients and methods'), and each figure represents the highest IgG and IgM value recorded for the individual. The age of a patient refers to the time at which that highest level was recorded. –=normal level. NT=not tested.

§(+)=threatened abortion; ()=not applicable because of lack of any known pregnancies (patients 10 and 18), gynaecological underdevelopment (patient 4), or male sex (patients 14 and 20).

titres for each individual. The range of raised IgG anticardiolipin antibody titres (patients 1–14) was 15–250 units (mean 99.9, median 101), while the range for raised IgM titres (patients 9–20) was 10–130 (mean 30.9, median 21.5).

#### OTHER SEROLOGICAL FINDINGS

Nine out of 19 patients (47%) tested had a positive antinuclear antibody test, up to a serum dilution of 1:64 (patient No 6), 1:80 (No 12), 1:160 (Nos 1, 2, 3, 9, and 15), 1:320 (No 4), and 1:10 000 (No 10). The pattern of immunofluorescence was typically homogeneous or speckled. Despite this, none of our patients fulfilled sufficient criteria for a diagnosis of SLE to be made.

Five patients tested had biological false positive serological tests for syphilis—that is, had positive Venereal Disease Research Laboratory tests but negative *Treponema pallidum* immobilisation tests. Of 11 patients tested for anti-extractable nuclear antigen antibodies, patient No 14 with an antinuclear antibody negative test had antibodies to Ro, and another patient (No 15) had antibodies to an unidentified protein. A direct Coombs' test was performed in four cases (patients 1, 12, 14, and 17); it was weakly positive only in No 1, for C3d.

#### CLINICAL FINDINGS

Seven patients had a history of definite venous thrombosis; all of these had raised IgG anticardiolipin antibodies; in addition, four had raised IgM anticardiolipin antibodies. Four had deep venous thromboses confined to the leg veins, one (No 14) had an iliofemoral vein thrombosis, and another (No 5) developed thrombophlebitis of the right foot during pregnancy. The remaining patient (No 10) had a history of recurrent widespread venous thrombosis, involving brachial and calf veins, and the inferior vena cava. Venous thrombosis was confirmed in three patients (Nos 1, 10, and 14) by venography, and in patient 11 by ultrasound. Four patients had pulmonary emboli, two of them on two occasions. Ventilation/perfusion lung scans confirmed pulmonary embolism in all four. A seventh patient (No 18) had an episode of swelling of the calf and foot for three weeks, which was thought to be a probable deep venous thrombosis. She had raised IgM anticardiolipin antibodies only. Table 2 summarises all of these features.

Five patients had features suggestive of arterial thrombosis, three of whom had raised IgG anticardiolipin antibodies. Two had transient ischaemic attacks, one of whom (No 12) also had hepatic infarction. Two had cerebrovascular accidents. A fifth patient (No 18) had swelling and intermittent

Table 2 Venous thrombosis: details of patients affected

Patient No	ACA*†		Details of venous thrombosis	
	IgG	IgM	Age (years)	Event
1	250	—	28	DVT*
			33	DVT
			34	DVT+PE×2*
4	130	—	42	DVT
			44	DVT
5	80	—	25	Thrombophlebitis of the foot
10	105	35	14	Bilateral DVT
			15	thrombophlebitis of right arm
			17	Recurrent DVT+PE
			21	IVC* thrombosis
11	97	25	42	PE
13	15	130	50	DVT
			52	Probable PE
14	105	22	17	Iliofemoral vein thrombosis+PE×2
18	—	11	24	?DVT

\*ACA=anticardiolipin antibodies; DVT=deep venous thrombosis of the calf; PE=pulmonary embolus; IVC=inferior vena cava.

†ACA values represent the highest IgG levels recorded (as in Table 1).

Table 3 Details of probable arterial thrombosis in the five patients affected

Patient No	ACA*†		Details of arterial events	
	IgG	IgM	Age (years)	Event
3	130	—	31	CVA*
9	200	50	26–27	Eight episodes of transient partial visual loss
			26	Hepatic infarction
12	38	12	29	Transient ischaemic attacks
			22	Probable subclavian artery thrombosis—several episodes
20	—	15	17	CVA

\*ACA=anticardiolipin antibodies; CVA=cerebrovascular accident.

†ACA levels as in Table 1.

loss of pulses in the left arm, thought to be due to thrombosis in the region of a cervical rib. She had previously been taking an oral contraceptive (Table 3).

Of the 15 female patients who had undergone pregnancy, only three had not experienced fetal loss. Two of these had had only one pregnancy, one of which had been threatened with abortion at seven

Table 4 Details of all pregnancies

Patient No	ACA*§		No of pregnancies	No of lost fetuses	Details of fetal loss and other events†
	IgG	IgM			
1	250	—	3	3	28 (9); 30 (22); 31 (23)
2	160	—	1	0	—
3	130	—	3	3	23 (34 pre-eclampsia); 30 (12); 31 (28)
5	80	—	8	8	18 (20); 20 (20); 22 (18); 23 (18); 25 (20); 28 (12); 31 (16); 35 (8)
6	48	—	6	6	30 (12); 31 (16); 33 (20); 34 (22); 35 (28 – twins). Aged 37: LSCS* at 28 weeks for IUGR*: Down's syndrome – neonatal death. Aged 39: normal pregnancy
7	25	—	2	2	18 (7); 19 (10)
8	15	—	1	0	18 (7 – threatened)
9	200	50	4	4	21 (6); 23 (12); 24 (17); 25 (15)
11	97	25	1	1	29 (12)
12	38	12	3	2	20 (24); 28 (24); 3rd pregnancy normal
13	15	130	2	0	
15	—	29	8	4	38 (8); 39 (11 and 6); 40 (24). (Normal pregnancies aged 26, 29 and 32; aged 42, LSCS at 34 weeks for IUGR‡)
16	—	21	4	5	27 (12); 31 (18); 32 (9); 33 (11 – twins)
17	—	11	5	3	24 (8); 26 (13); 27 (16). (Normal pregnancy aged 25; currently pregnant)
19	—	10	7	5	20 (13 and 17); 24 (8); 25 (21); 26 (14). (Aged 22 delivered at 37 weeks because of threatened abortion; currently pregnant after threatened abortion at 5 weeks)

\*ACA=anticardiolipin antibody; LSCS=lower segment caesarean section; IUGR=intrauterine growth retardation.

†Age at which fetal loss occurred (weeks from beginning of last menstruation).

‡Intrauterine death following intercurrent hepatic infarction.

§ACA values as in Table 1.

weeks' gestation. The remaining 12 patients showed a wide range of episodes of fetal loss (range 1–8 (two twin abortions), mean 3.7, median 3.5). Of the total number of pregnancies for the whole group of 15 patients (58, mean 3.9, median 3.0), 44 (76%) resulted in fetal loss; one of them ended in intrauterine death following hepatic infarction. A further three pregnancies (5%) were complicated by threatened abortion and one (2%) by intrauterine growth retardation. Eighteen episodes of spontaneous fetal loss occurred during the first trimester, 24 during the second, and two during the third; twin abortions counted as one event (Table 4). In the case of one abortion (patient 5) a placental infarct was demonstrated.

Six patients had thrombocytopenia (patients 12 and 20 only transiently) and four had migraine; no patient had both. One individual had livedo reticularis. Two patients had neurological disorders. One (No 20), in addition to a right parietal lobe stroke, had a chronic psychiatric illness, characterised by behavioural problems, delusions, and auditory hallucinations; he also had one episode of acute confusion. The other (No 12, who had severe migraines and transient ischaemic attacks) noticed two episodes of difficulty in speaking associated with paraesthesia and a feeling of 'heaviness' in the lower limbs, lasting for a few minutes; in addition, she reported transient partial visual field loss on several occasions, unaccompanied by headache. A further patient (No 18) had anorexia nervosa at the age of 21.

Three patients had cardiac abnormalities. One (No 9) developed aortic incompetence, which required aortic valve replacement; there was no past history of rheumatic fever. Patient No 2 developed a dilated cardiomyopathy, which is currently reasonably controlled by medical treatment. A third (No 8) was found to have Wolff-Parkinson-White syndrome type B, with recurrent episodes of atrial flutter. In addition, a fourth individual (No 6) had an unexplained sinus bradycardia.

A few subjects had clinical features suggestive of another connective tissue disease. Three patients (Nos 1, 3, and 9) had recurrent attacks of arthralgia, and two of these (3 and 9) also had Raynaud's phenomenon. One individual (No 20) had a vasculitic rash, and serum from another (No 1) produced a heavy cryoprecipitate at 4°C. Seven individuals (Nos 5, 7, 11, 16, 17, 18, and 19), however, were entirely lacking in features which are typical of other disorders and which are not associated with raised antiphospholipid antibodies (including antinuclear activity).

Patient 10 had a past history of another autoimmune condition, myxoedema. Family histories were relevant in two cases. Patient 10, whose predominant clinical feature was widespread venous thrombosis, had a paternal uncle and a paternal great uncle who had deep venous thrombosis of the leg. The father of patient No 18 had suffered a myocardial infarction at the age of 47 followed by a cerebrovascular accident at age 48.

## Discussion

This paper reports the clinical and serological findings for a series of 20 patients with raised anticardiolipin antibodies, in whom a diagnosis of SLE was excluded according to the American Rheumatism Association revised criteria and in whom no other substantive diagnosis was possible. They may be regarded as having a primary antiphospholipid syndrome.

The composition of the patient group is not random as it consists chiefly of patients seen in the rheumatology unit at the Hammersmith Hospital, or referred to the department of obstetrics and gynaecology because of obstetric problems. The former were referred either because of a clinical problem which suggested a connective tissue disease, or because of the presence of raised anticardiolipin antibodies; the latter were identified by the routine anticardiolipin antibody testing of women with a history of multiple abortions. As a consequence there is likely to be an ascertainment bias; patients are currently tested for anticardiolipin antibody levels because of a clinical suspicion that these may be raised. Thus although a number of studies have shown an extremely low incidence of raised anticardiolipin antibody titres among normal individuals and patients with a wide range of medical conditions, it is probable that our patient cohort is not wholly representative of all individuals with raised titres, in that it may exclude some otherwise normal individuals and patients with other as yet unassociated conditions. It is likely, therefore, that the manifestations described here overestimate the severity of the clinical syndrome associated with these autoantibodies.

Nine out of 20 (47%) of our patients had a positive antinuclear antibody test at some stage in their illness; six of these (67%) were individuals with multiple abortions. In most cases the test was positive at a low titre. One patient with a negative antinuclear antibody test had antibodies to the extractable nuclear antigen Ro. These findings suggest that many of these patients have a condition which is related to SLE. The sex ratio (nine women to one man) and age range of our patients (17–53 years, median 30) are also similar to those found in SLE. There is also clearly an overlap between the clinical features seen in some of our patients—for example, arthralgias, Raynaud's phenomenon, migraine, livedo reticularis, and vasculitic rash—and lupus.

Our patients are, however, more striking for the presence of clinical features previously associated with raised anticardiolipin antibody levels: thrombosis (both venous and arterial),<sup>3</sup> fetal loss,<sup>17</sup> and

thrombocytopenia.<sup>18</sup> In those individuals with venous thrombosis and fetal loss there was a relatively high incidence of raised anticardiolipin antibodies of the IgG class, a finding which accords with previous reports. In addition, some of our patients had features described but less clearly associated with raised serum anticardiolipin antibodies: livedo reticularis,<sup>19</sup> neurological disorders other than stroke,<sup>3</sup> and aortic and mitral valve disease.<sup>20</sup> Thus it appears that our patients display a range of clinical features similar to those of subjects with raised anticardiolipin antibodies in the presence of other disorders; and, although some have features of SLE, others do not. At least seven of our patients had features of the antiphospholipid syndrome but no other abnormalities.

These findings are consistent with the idea that the antiphospholipid syndrome may exist as a distinct clinical entity.<sup>1</sup> It seems to show considerable overlap with other connective tissue disorders but does not appear to be merely a subset. It is possible that the clinical abnormalities are due to pathophysiological activities of antiphospholipid antibodies themselves, though no direct causal link has been established. There is, however, considerable *in vitro* evidence for their ability to interfere with clotting mechanisms,<sup>21 22</sup> and this contrasts with other non-organ specific autoantibodies such as anti-DNA antibodies, which are thought to cause tissue damage by immune complex formation. It may be that further study of primary cases of the antiphospholipid syndrome, such as those described in this report, will lead to a better understanding of its pathogenesis.

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