

# Significance of Persistent Antiphospholipid Antibodies in the Elderly

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**ABSTRACT.** *Objective.* The prevalence of anticardiolipin antibodies (aCL) and of vascular diseases increases with age, and aCL may be associated with various diseases in the elderly. So the significance of aCL in the elderly remains difficult to determine. We sought to determine the significance of persistent antiphospholipid antibodies (aPL) in the elderly.

*Methods.* We retrospectively analyzed the files of 327 patients [149 patients with antiphospholipid syndrome (APS); 64 patients age  $\geq 65$  yrs] with 2 positive aPL [lupus anticoagulant (LAC) and/or aCL].

*Results.* The frequency of APS was 40.8% ( $n = 134$ ) in our 263 young patients ( $< 65$  yrs) and 23.4% ( $n = 15$ ) in our 64 elderly patients ( $\geq 65$  yrs). The clinical characteristics of patients with persistent aPL were the same in those under and over 65 years. LAC was positive in all but one elderly patient with APS, and occurred in this group more frequently than in the young patients (93.3% vs 44.6%;  $p < 0.006$ ). The presence of LAC allowed to discriminate APS patients in our elderly population (93.3% in APS vs 48.9% in non-APS patients;  $p < 0.009$ ).

*Conclusion.* Interpretation of a positive determination of APL is difficult in the elderly; persistent LAC may be the most valuable biological marker of APS in the elderly. (First Release July 1 2006; J Rheumatol 2006;33:1559–62)

## Key Indexing Terms:

LUPUS ANTICOAGULANT

AGED

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial and/or venous thrombosis, recurrent fetal loss, and thrombocytopenia, associated with high levels of antiphospholipid antibodies (aPL)<sup>1</sup>.

APS usually affects young patients<sup>1,2</sup>. However, the prevalence of anticardiolipin antibodies (aCL) and thrombotic events increases with age<sup>3,4</sup>. Therefore an association between aPL and thromboembolic disease is not rare in elderly populations<sup>5</sup>.

We investigated a population of patients with persistent aPL to determine the significance of persistent aPL in an elderly population.

## MATERIALS AND METHODS

We retrospectively studied 327 consecutive patients with persistent aPL. Patients were followed in a tertiary care internal medicine department between January 1999 and December 2003. The population consists of rheumatology inpatients and outpatients. In our medical department it is routine to test all rheumatology inpatients and outpatients for aPL. Persistent aPL were defined as aPL seen as positive twice with an interval of at least 6 weeks [positive determination of lupus anticoagulant (LAC) and/or aCL].

Clinical data were evaluated at the time of the second aPL determination.

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APS was diagnosed under the Sapporo criteria<sup>1</sup>. Patients aged 65 years and over were considered as “elderly,” and 64 years or less were considered as “young” patients. aCL and anti- $\beta_2$ -GPI antibodies (anti- $\beta_2$ -GPI) were measured using a commercial kit: Inova-Quantalite™ (Menarini, France), with quantification of both IgG and IgM subfractions. Samples above 15 standardized units for aCL and above 20 for anti- $\beta_2$ -GPI were regarded as positive.

LAC was determined according to the revised criteria proposed by the Subcommittee for Standardization of Lupus Anticoagulants<sup>6</sup>. Standardized procedures were used to detect LAC in patients treated with an oral anticoagulant<sup>7</sup>.

To determine differences between patients' subgroups, statistical analyses were performed using Student's T test and nonparametric tests (Mann-Whitney test). Differences between proportions were estimated using chi-square tests. Fisher's exact test (2-tailed) was used for  $2 \times 2$  tables with one or more cells with an expected frequency  $< 5$ . Statistical significance was set at  $p < 0.05$ .

## RESULTS

Three hundred twenty-seven patients with persistent aPL were analyzed (260 women, 67 men, mean age  $45.3 \pm 17.9$  yrs). APS was diagnosed in 149 patients and considered as primary in 116 patients (78% of APS patients). Sixty-four patients with persistent aPL were  $\geq 65$  years old (47 women, 17 men, mean age  $71.4 \pm 5.4$  yrs). APS was diagnosed in 15 of these 64 patients (8 women, 7 men, mean age  $69.1 \pm 3.6$  yrs).

The prevalence of APS was significantly lower in patients older than 65 years versus those younger than 65 years ( $p < 0.002$ ). However, the frequency of clinical manifestations was not statistically different between the 2 groups. LAC was more frequent in the older group versus the younger (60% vs 28.1%;  $p < 0.0001$ ). aCL IgG and IgM were more frequent in

the younger than in the elderly group (73% vs 50.7%,  $p = 0.0004$ , and 33.5% vs 14%,  $p = 0.004$ ), but mean aCL IgG and IgM levels were similar in both groups (Table 1).

In patients with APS, the sex ratio showed a higher prevalence of male patients over 65 years (46.6% vs 18.6%;  $p = 0.046$ ) and LAC was positive for all but one of the patients

over 65 years (93.3% vs 43.3%;  $p = 0.0006$ ) (Table 2). In patients over 65, only the presence of LAC was associated with existence of APS (93.3% vs 48.9%;  $p = 0.0095$ ).

The 15 elderly APS patients are presented in Table 3. The 49 patients with persistent aPL and over 65 years had the following diagnoses: 14 connective tissue diseases, 12 temporal

*Table 1.* Characteristics of patients with persistent antiphospholipid antibodies. Values are mean  $\pm$  SD or percentage (no.) of patients.

Patients	Global Population, n = 327	< 65 yrs, n = 263	$\geq$ 65 yrs, n = 64	p*
Mean age, yrs	45.3 $\pm$ 17.9	38.8 $\pm$ 13.5	71.4 $\pm$ 5.4	
Antiphospholipid syndrome	45.6 (149)	50.9 (134)	23.4 (15)	< 0.002
Clinical manifestations				
Arterial thrombosis	26.3 (86)	28.5 (75)	17.2 (11)	NS
Venous thrombosis	21.1 (69)	23.2 (61)	12.5 (8)	NS
Valvular disease	4.9 (16)	5.7 (15)	1.5 (1)	NS
Livedo	8.2 (27)	9.5 (25)	3 (2)	NS
Immunological markers				
LAC	34.5 (113)	28.1 (74)	60.9 (39)	< 0.0001
aCL				
IgG > 15 U PL	68.8 (225)	73 (192)	51.5 (33)	< 0.0004
Mean titer	33.0 $\pm$ 50.7	35.3 $\pm$ 53.4	24.0 $\pm$ 36.7	NS
IgM > 15 U PL	29.6 (97)	33.5 (88)	14 (9)	0.004
Mean titer	24.7 $\pm$ 81.4	21.1 $\pm$ 54.6	38.9 $\pm$ 144.9	NS
Anti- $\beta_2$ -GPI				
IgG > 20 U PL	19.5 (64)	20.9 (55)	14 (9)	NS
Mean titer	25.1 $\pm$ 175.2	30.1 $\pm$ 188.8	5.2 $\pm$ 15.2	NS
IgM > 20 U PL	25.9 (85)	26.2 (69)	25 (16)	NS
Mean titer	24.1 $\pm$ 78.2	21.7 $\pm$ 78.8	33.9 $\pm$ 75.8	NS

\* Comparison according to age. LAC: lupus anticoagulant; aCL: anticardiolipin antibody; anti- $\beta_2$ -GPI: anti- $\beta_2$ -glycoprotein I antibody; NS: not significant.  $p < 0.05$  is considered statistically significant; PL: phospholipids.

*Table 2.* Characteristics of patients with antiphospholipid syndrome. Values are mean  $\pm$  SD or percentage (no.) of patients.

Patients	< 65 yrs, n = 134	$\geq$ 65 yrs, n = 15	p*
Mean age, yrs	38.3 $\pm$ 12.9	69.4 $\pm$ 4.2	
Male patients	18.6 (25)	46.6 (7)	0.046
Clinical manifestations			
Arterial thrombosis	56 (75)	73.3 (11)	NS
Venous thrombosis	45.5 (61)	53.3 (8)	NS
Valvular disease	9.8 (13)	0	NS
Livedo	15.7 (21)	0	NS
Immunological markers			
LAC	43.3 (58)	93.3 (14)	0.0006
aCL			
IgG > 15 U PL	73.1 (98)	26.6 (4)	0.0003
Mean titer	38.3 $\pm$ 46.4	14.5 $\pm$ 22.6	0.045
IgM > 15 U PL	35 (47)	26.6 (4)	NS
Mean titer	22.2 $\pm$ 47.4	82.7 $\pm$ 273.3	NS
Anti- $\beta_2$ -GPI			
IgG > 20 U PL	26.8 (36)	13.3 (2)	NS
Mean titer	45 $\pm$ 257.3	46 $\pm$ 72	NS
IgM > 20 U PL	30.6 (41)	26.6 (4)	NS
Mean titer	24.3 $\pm$ 72.6	37.7 $\pm$ 70.4	NS

\* Comparison according to age. For abbreviations see Table 1.  $p < 0.05$  is considered statistically significant.

Table 3. Characteristics of “elderly” patients with antiphospholipid antibody syndrome.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age at APS diagnosis, yrs/sex	66/M	73/M	73/M	70/F	65/M	74/M	74/F	68/F	67/M	74/F	66/F	67/M	65/F	66/F	68/F
Cardiovascular diseases	ICA, PAD, abnormal MRI	ICA, TIA, abnormal MRI	DVT with PE	AMI	ICA, PAD	2 DVT, PAD	DVT with PE	DVT	ICA, DVT	2 SVT, ICA	2 DVT, ICA	AMI	3 DVT, AMI	ICA	2 DVT
Risk factors for cardiovascular disease	Tobac, HTA	HTA	None	Tobac, HTA, dyslipid	Tobac, HTA	FVL	HTA, dyslipid, diabetes	Dyslipid	Tobac	None	None	Tobac, dyslipid	HTA	HTA	none
LAC	No. 1	+	+	+	+	+	+	+	+	+	+	+	+	+	0
	No. 2	+	+	+	+	+	+	+	+	+	+	+	+	+	0
aCL	No.1	49 MPL, 26 GPL	1098 MPL	17 MPL	0	87 GPL	58 GPL	50 MPL	0	0	0	324 GPL, 0 MPL	0	11 GPL, 22 MPL	60 GPL, 0 MPL
	No.2	37 MPL, 41 GPL	907 MPL	20 MPL	0	ND	24 GPL	69 MPL	0	0	0	83 GPL, 0 MPL	0	9 GPL, 26 MPL	40 GPL, 0 MPL
Anti-β <sub>2</sub> GPI	No. 1	1+	466 IgM	0	0	144 IgM	ND	114 IgM 40 IgG	0	0	0	150 IgG 0 IgM	0	0 IgG, 85 IgM	23 IgG 14 IgM
	No. 2	1+	240 IgM	0	0	ND	ND	148 IgM	0	0	0	54 IgG 0 IgM	0	0 IgG 69 IgM	28 IgG 10 IgM
SLE	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
Regimen	OA, aspirin	OA, aspirin, vitamin E	OA	OA, aspirin, vitamin E, statins	Aspirin	OA	OA	OA	Aspirin OA	OA	Aspirin OA	Aspirin	OA	Aspirin	OA
Followup, mo	60	25	47	15	43	29	45	20	19	26	24	13	80	20	8

APS: antiphospholipid syndrome, LAC: lupus anticoagulant, aCL: anticardiolipin antibody, anti-β<sub>2</sub> GPI: anti-β<sub>2</sub> glycoprotein I antibody, SLE: systemic lupus erythematosus, HTA: arterial hypertension, ICA: Ischemic cerebrovascular accident, PAD: Peripheral artery disease, abnormal MRI: vascular abnormalities on cerebral magnetic resonance imaging, DVT: deep venous thrombosis, SVT: superficial venous thrombosis, PE: pulmonary embolism, AMI: acute myocardial infarction. ND: not done, 0: negative, +: positive determination; OA: oral anticoagulant; Tobac: tobacco; Dyslip: dyslipidemia; FVL: factor V Leiden.

arteritis, 10 isolated aPL, 8 aPL associated with manifestations of atherosclerosis, 3 infections, and 2 neoplasia. None of them declared a thrombotic event during the followup.

## DISCUSSION

Although few studies have tried to determine the significance of aPL in elderly patients, aCL are present in 12% to 51.6% of the healthy elderly population<sup>3-5</sup>. However, these studies took into account only one aCL measurement. Therefore we investigated patients over 65 years based on 2 measurements of aPL and APS diagnosis according to the Sapporo criteria<sup>1</sup>. Fortunately, all our rheumatology inpatients and outpatients are tested for aPL. As expected, the prevalence of APS was lower in our elderly population: only 23.4% of our patients over 65 versus 51% of our younger patients with persistent aPL. However, the frequency of APS manifestations was similar between young and elderly patients with persistent aPL. aCL were more frequent in young patients but showed similar levels in young and elderly patients. LAC was more frequent in elderly patients.

Our elderly APS group presented 2 characteristics unusual for patients with APS. First, 7/15 of our patients were male.

The increase of the prevalence of men in the older APS patients has already been described by Cervera, *et al*<sup>8</sup>. Second, the presence of LAC in patients with APS is about 50%, similar to our experience (50% in our global APS population)<sup>8</sup>. But our elderly APS population is remarkable for the prevalence of positive LAC of 93.3% (14/15 patients). Therefore, our data would suggest considering LAC as the most valuable biological marker of APS in the elderly. In retrospect, current explorations of the coagulation pathway (activated cephalin time) might have disclosed the presence of LAC in elderly patients. This bias may explain the increasing prevalence of LAC in our elderly population with persistent aPL (60.9% vs 28.1%;  $p < 0.0001$ ), but not in elderly APS patients. Indeed, in those patients, LAC was discovered because of unexplained thrombotic events.

Whether aPL should be measured in elderly subjects to diagnose APS needs to be determined. Our study clearly shows that the diagnosis of APS in the elderly presenting with persistent aPL is difficult. aPL in elderly patients with vascular disease could be interpreted as an immunological marker of true APS or as potential marker and/or co-factor of atherosclerosis<sup>9</sup>. Our study also shows that elderly patients with

APS are remarkable for being more frequently male, and more frequently associated with LAC. Additional prospective studies are needed to determine the role of aPL and particularly the role of persistent LAC in the occurrence of thrombosis or atherosclerosis in elderly patients, and to help us in the management of such patients.

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