EXTENDED REPORT

Increased carotid artery intima-media thickness may be associated with stroke in primary antiphospholipid syndrome

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Objective: To investigate the prevalence and clinical significance of carotid artery intima-media thickness (IMT) in patients with primary antiphospholipid syndrome (APS).
Methods: 28 patients with primary APS with at least a five year follow up, and 28 healthy subjects, matched by age and sex, were included in the study. Colour Doppler with high resolution B mode carotid ultrasonography and spectral analysis were performed in patients and controls. Information on cardiovascular risk factors and the clinical course were collected.
Results: The mean (SD) age of patients and controls (12 male, 16 female in each group) was 40 (8.5) years; the mean (SD) disease duration 7.7 (3) years. Carotid artery IMT was found in 23/28 patients (2.6 (1.14) mm) and 7/28 controls (1.2 (0.44)) (p=0.0001). A decrease in the lumen diameter was also found in 11/28 patients with primary APS without carotid atherosclerotic plaque, and 2/28 controls (p=0.004). Hyperlipidaemia, diabetes, smoking, obesity, and hypertension were not associated with carotid artery IMT. Patients with carotid artery IMT had arterial vascular disease more often than patients without: 9/23 *v* 0/5 (p<0.009). These patients had stroke (seven patients), myocardial infarction (one), and mesenteric thrombosis (one). Subjects with IMT had a threefold higher risk for stroke than those without IMT (95% CI 0.78 to 14.3).
Conclusions: Patients with primary APS have a high prevalence of carotid artery IMT and a decreased lumen diameter. IMT in primary APS may be associated with stroke. Patients with primary APS with IMT must be considered as carriers of atherosclerosis.

Atherosclerosis is a multifactorial disease that affects the arterial system, with endothelial dysfunction, impaired vascular relaxation, and haemostatic imbalance. It is an inflammatory disease mediated through the action of monocyte/macrophages, complement, and T lymphocytes.[1–3] Recent studies have focused on the inflammatory component of atherosclerosis, supporting the hypothesis that atherosclerosis shares many similarities with other inflammatory and autoimmune diseases, such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).[4 5]

Multiple risk factors have a primary role in promoting premature atherosclerosis in SLE, such as long term corticosteroid use, hypertension, diabetes, obesity, dyslipidaemia, raised homocysteine levels, smoking habit, etc.[6] However, the traditional Framingham risk factors in patients with SLE cannot fully account for the cardiovascular events in these patients.[7] Therefore, the immunological alterations such as antibodies to oxidised low density lipoprotein (LDL), antiphospholipid antibodies (aPL), antibodies to β_2-glycoprotein (anti-β_2GPI), anti-prothrombin antibodies, may play a part in premature atherosclerosis in SLE and APS.[8]

Recently, B mode ultrasound has allowed detection and measurement of the intima-media thickness (IMT) and degree of plaque in the carotid arteries. IMT may be the most sensitive marker for the earliest stages of atherosclerosis and it is considered to be a marker of generalised atherosclerosis.[9–12] B mode ultrasound has been also used to investigate the prevalence of carotid atherosclerosis in women with SLE. Manzi *et al* found a relation between a longer disease evolution and cumulative prednisone dose with a higher prevalence of carotid plaques.[13] However, the evaluation of underlying atherosclerosis has not been widely analysed in patients with primary APS. Studies in humans with primary APS are scarce and have dealt with a relatively small number of patients. In addition, the role of aPL and/or primary APS as independent risk factors for atherosclerosis is unclear because most clinical studies include patients with primary APS and secondary APS. Therefore, the objective of this study was to determine the prevalence and clinical significance of IMT of carotid artery in patients with primary APS.

MATERIALS AND METHODS

We included male and female patients with primary APS, according to the Sapporo criteria, from the Rheumatology and Internal Medicine Departments, Hospital de Especialidades Centro Medico La Raza.[14] Patients aged between 20 and 50 and with at least five years' follow up were included. The protocol was approved by the institutional review board and all eligible patients who agreed to participate signed their informed consent. We did not include patients with secondary APS. Patients without complete charts and who developed SLE criteria during the study were excluded.

Demographic data and clinical manifestations were obtained from patient charts and by direct interview. Cardiovascular risk factors such as arterial hypertension, diabetes mellitus, smoking, obesity, total cholesterol, and triglyceride levels were investigated. Each patient was matched by sex and age with one healthy control subject who underwent a similar protocol.

Abbreviations: aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CCA, common carotid artery; β_2GPI, β_2-glycoprotein I; ICA, internal carotid artery; IMT, intima-media thickness; LDD, lumen diameter decrease; LDL, low density lipoprotein; SLE, systemic lupus erythematosus

Table 1 Distribution of risk factors for patients and controls

Characteristic	Patients (n=28)	Controls (n=28)	p Value
Age (years), mean (SD)	40 (8.5)	41.7 (6.3)	0.97
Diabetes mellitus	0	0	
Smoking	3	4	0.68
BMI*:			
Normal (<26)	13	17	
Overweight (26–30)	8	10	0.98
Obesity (>30)	7	1	0.05
Hypercholesterolaemia	8	8	0.97
High triglyceride levels	7	3	0.06
Hypertension	10	0	0.001

*BMI, body mass index.

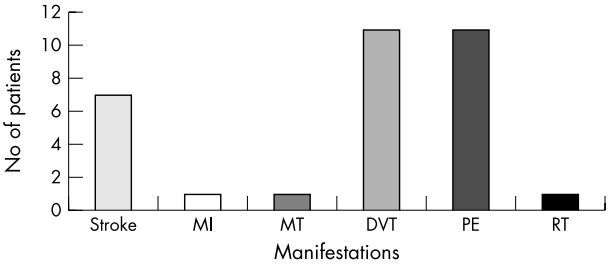

Figure 1 Clinical manifestations of patients with primary APS. MI, myocardial infarction; MT, mesenteric thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism; RT, retinal thrombosis.

Ultrasonographic assessment

The carotid arteries were evaluated in all patients and control subjects, with a high resolution B mode ultrasonography (G E VINGMED) using a 7–10 MHz vascular transducer in multiple projections to optimise detection of atherosclerosis. Colour Doppler and spectral analysis were performed. Microbubble of galactose/palmitic acid (Levovist) was used as a contrast medium to improve the tissue characterisation. The sonographer measured the peak blood flow velocity at the mid-common carotid artery (CCA) and in the internal carotid artery (ICA) at the point of highest velocity distal to the flow divider. If the mid-CCA measurement was abnormal, the sonographer took readings proximal and distal to this point. The ultrasonographic examination was performed by an experienced radiologist (DC) who was "blinded" to different groups. Intrareader reproducibility was assessed by measuring the same carotid IMT three times in 15 patients and yielded correlation coefficients >95%. The ultrasonographic scanning was performed with the subject in the supine position, examining the CCA, bifurcation, and ICA bilaterally in every subject. The carotid arteries were explored with longitudinal (anterior, lateral, posterior) and transverse scans. The end diastolic wall thickness and end diastolic and peak systolic internal diameters were measured on several cycles. The lesions were classified by a standardised scoring system into intimal plus medial thickening (IMT), lumen diameter decrease (LDD), and presence of plaques. If no lesion was detected, the subject was considered normal. The IMT, defined as the distance between the intimal-luminal interface and the medial-adventitial interface, was considered pathological if it was >1 mm.[15] Measurement of the lumen diameter was done from the leading edge of this echo to the leading edge of the echo from the far-wall lumen-intima interface.[16] An LDD >50% was considered abnormal. The atherosclerotic plaque was defined as a distinct area protruding into the vessel lumen.

Table 2 Ultrasonographic findings by group

	Patients (n=28)	Controls (n=28)	p Value
IMT (mm), mean (SD)	2.6 (1.14)	1.2 (0.44)	0.0001
LDD (%)	11 (39)	2 (7)	0.004

IMT, intima media thickness, LDD, lumen diameter decrease.

Statistical analysis

All analyses were performed with SPSS/Windows statistical software (version 10.0). Mean values are reported with 1 SD as the index of dispersion. Mean values of continuous and parametric variables were compared with the Mann-Whitney U test. Categorical variables were compared using the χ^2 statistic. Prediction equations were performed using logistic regression analyses. Statistical significance was considered with an α level of 0.05.

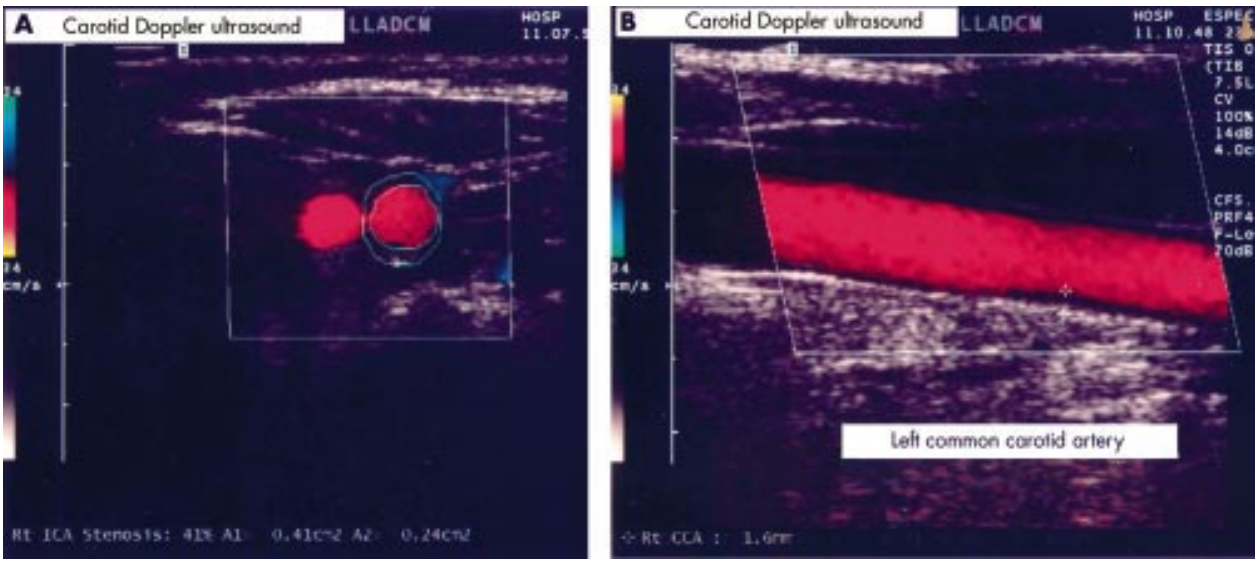

Figure 2 Transverse scan of the left common carotid artery (A) and longitudinal scan of the left common carotid artery (B) showing IMT in a patient with primary APS.

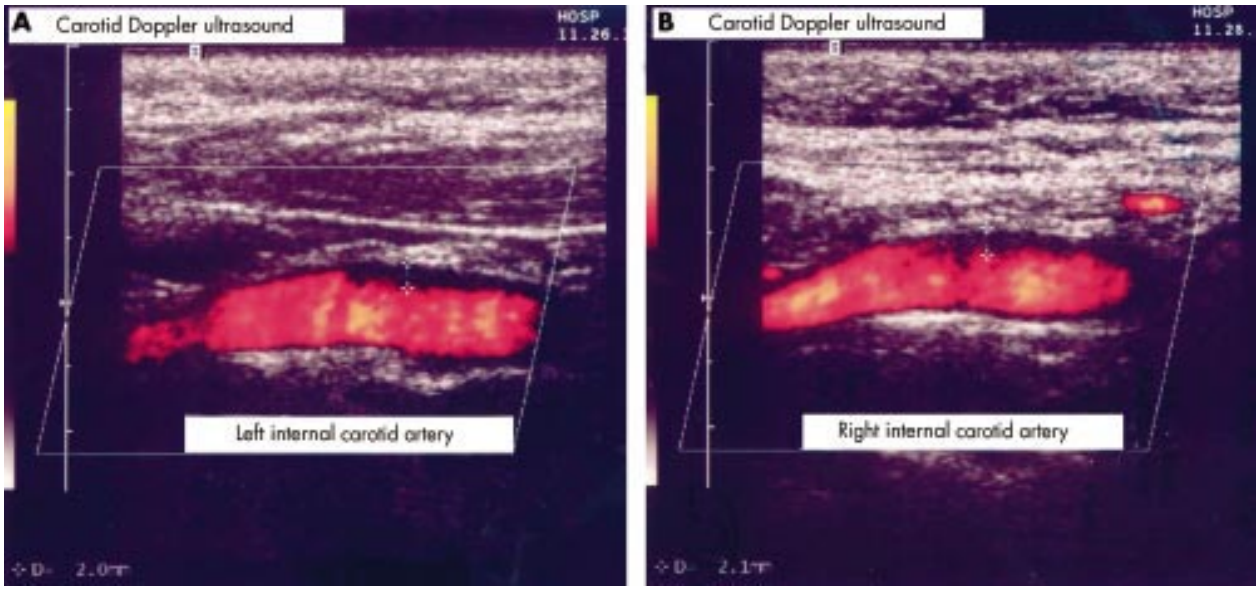

Figure 3 Longitudinal scan showing IMT (+ — +) of the left (A) and right (B) internal carotid artery with indentations in the lumen vessels.

RESULTS

A total of 28 patients with primary APS (12 male, 16 female) with mean (SD) age of 40 (8.5) years (range 22–50) were studied. The mean (SD) disease duration was 7.7 (3) years (range 5–18). These patients were compared with 28 healthy subjects (12 male, 16 female) with a mean age of 41.7 (6.3) (range 22–50).

Table 1 shows the cardiovascular risk factors of patients and controls. We observed a higher prevalence of arterial hypertension (p=0.001) and obesity (p=0.05) in patients than in controls. Figure 1 shows the clinical manifestations of patients with primary APS. Stroke was the principal arterial manifestation and deep venous thrombosis was the most common venous event. All patients with primary APS were treated with oral anticoagulants.

Table 2 gives the ultrasonographic findings. Carotid artery IMT was found in 23/28 patients with primary APS and in 7/28 controls (p=0.0001). A lumen diameter decrease was found in 11/28 patients with primary APS without carotid atherosclerotic plaque and 2/28 controls (p=0.004), one of them with a carotid non-stenotic atherosclerotic plaque. Figures 2 and 3 show examples of IMT. Of 23 patients with IMT, nine patients had a history of arterial complications: seven with stroke, one with myocardial infarction, and one with mesenteric thrombosis. In contrast, the five remaining patients without IMT did not have arterial complications (p=0.009). Comparison of patients with and without hypertension showed no significant differences related to IMT (2.88 mm *v* 2.47 mm respectively, p=NS).

Table 3 shows the relationship between cardiovascular risk factors and IMT. In this analysis we found that patients with IMT had a 3.34-fold greater risk of stroke in comparison with patients without IMT (95% CI 0.78 to 14.3).

Table 3 Logistic regression analysis

Risk factor	OR	95% CI
IMT	3.34	0.78 to 14.3
High cholesterol levels	0.99	0.96 to 1.02
Obesity	0.59	0.33 to 1.05
High triglyceride levels	1.01	0.99 to 1.03
Hypertension	0.83	0.25 to 2.72
Disease duration	1.23	0.69 to 2.1

DISCUSSION

High resolution carotid ultrasonography has been used to obtain measurements of the thickness of the intima and media of the carotid arteries and allows the detection of early atherosclerotic lesions.[11 12] The results of this study demonstrate a significantly increased thickness of the carotid arteries in patients with primary APS in comparison with normal controls. We have also shown that the LDD of these arteries was significantly reduced in patients compared with controls. Of interest, we did not find atherosclerotic plaques in patients with primary APS. In addition, patients with IMT had more arterial events, especially stroke, than patients without IMT. Furthermore, this study suggests that the IMT and LDD are independent of conventional risk factors and they may be a consequence of primary APS itself.

Manzi *et al* studied the IMT in 175 women with SLE[13] and found a mean IMT in these patients of 0.71 (0.14) mm. However, the principal finding of that study was focal carotid plaque in 40% of the lupus population with a direct association with prednisone use, increased IMT, and coronary events without any relationship with anticardiolipin antibodies (aCL) and lupus anticoagulant. Unfortunately, a limitation of the study was the absence of an age matched control group. Roman *et al* reported a similar prevalence of focal plaque.[17] They analysed 18 patients with SLE and four with primary APS. The intima-media thickness of the common carotid artery was similar in patients and control subjects. Despite the lack of significant differences in IMT, there was a striking 4.5-fold increase in the presence of atherosclerosis, defined as the presence of plaques, suggesting that atherosclerosis in patients with SLE develops by formation of atherosclerotic plaque rather than by more generalised thickening of the arterial intima. The small group of patients with primary APS was not analysed separately. In contrast with the aforementioned, our study suggests that atherosclerosis in patients with primary APS develops primarily by generalised IMT rather than by atherosclerotic plaques. These results suggest that in primary APS, other mechanisms participate in the genesis of atherosclerosis. In this regard, indirect data coming from animal studies as well as in vitro observations support the contention that the presence of aCL may be sufficient to increase the propensity to atherosclerosis, regardless of other predisposing factors.[4] In support of our clinical findings, George *et al* have shown that active immunisation with human aCL was followed by the production of mouse aCL and the development of increased early atherosclerosis in LDL receptor

knockout mice.[18] Other studies showed a correlation between the in vitro effect of monoclonal anti-β_2GPI antibodies and induction of an APS-like syndrome in naive mice by passive intravenous transfer of IgG.[19]

In humans with primary APS the process of atherogenicity remains obscure. Premature atherosclerosis of the legs as the first symptom of the APS has been reported. This indicates the possible involvement of aPL in the pathogenesis of progressive atherosclerosis in these patients.[20] Spronk *et al* reported on three patients with severe systemic atherosclerosis in the presence of high levels of aCL and other factors such as hyperhomocysteinaemia without other features of SLE and primary APS.[21] Recently, Ames *et al*, showed that IgG aCL independently predict IMT of carotid arteries in subjects with idiopathic aPL, lending support to the concept of atherosclerosis development in primary APS.[22] All these studies strongly support an atherogenic role for aCL in patients with APS.

In our study, increased IMT, an indicator of subclinical atherosclerotic disease, may reflect past exposure to traditional risk factors. Although most patients with arterial hypertension had IMT, the degree of thickness was similar to that of patients without arterial hypertension. Other risk factors were not associated with IMT. Long term exposure to aCL may itself produce IMT in patients with primary APS. In this regard, histological findings in primary APS showed proliferation and increased thickness of the intimal-medial complex with little evidence of thrombosis.[23]

The relative association between arterial events, particularly stroke and IMT, observed in our patients suggests that IMT may be a risk factor for cardiovascular events. In support of this hypothesis, O'Leary *et al* showed that IMT of the common carotid artery and the internal carotid artery was strongly associated with the risk of myocardial infarction and stroke in asymptomatic older adults.[24]

We found that most patients had IMT and they were young adults. Therefore, the measurement of IMT in patients with primary APS may help identify patients with early atherosclerosis, who would benefit from aggressive preventive measures.

Limitations of our study include the relatively small group of patients with primary APS, the design of the study, and no inclusion of other risk factors for atherosclerosis such as high density lipoprotein and LDL cholesterol, homocysteine, plasma fibrinogen, etc.

In conclusion our study suggests:

- Doppler carotid ultrasound is a useful method to detect atherosclerosis in primary APS
- Patients with primary APS have a high prevalence of carotid artery IMT and lumen diameter decrease, without atherosclerotic plaques
- The IMT in primary APS may be associated with stroke.
- Patients with primary APS with IMT should be considered as carriers of atherosclerosis. Therapeutic strategies, including early control of primary APS and other risk factors may be desirable.

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