Prevalence of an abnormal ankle-brachial index in patients with primary antiphospholipid syndrome: preliminary data

M A Barón, M A Khamashta, G R V Hughes, D P D’Cruz


Objectives: To evaluate the prevalence of abnormal ankle-brachial indexes (ABIs), their relationship with other cardiovascular risk factors and/or the presence of antiphospholipid antibodies (aPL), and the clinical use of the ABI in patients with primary antiphospholipid syndrome (primary APS).

Methods: An 8 MHz Doppler probe was used in the arms and legs to assess the ABI in 43 patients with primary APS (mean (SD) age 40.2 (7.9) years) and 49 healthy subjects (aged 41.0 (11.7) matched for age and sex. Data on traditional cardiovascular risk factors, such as hypertension, hypercholesterolaemia, presence of diabetes mellitus, nephrotic syndrome or renal failure, smoking, and other variables, were collected at that time for all subjects. A ratio of the highest blood pressure from the posterior tibial or pedal arteries of each leg to the highest blood pressure from the brachial arteries <1.00 was considered abnormal.

Results: Abnormal ABIs were found in 8/43 (19%) patients with primary APS and 2/49 (4%) controls (p=0.026). No correlation between abnormal ABI and traditional cardiovascular risk factors nor with the presence of aPL was found.

Conclusion: Abnormal ABIs are more common in primary APS than in healthy controls, possibly indicating a subclinical atherosclerotic process in these patients.

The antiphospholipid syndrome (APS) or Hughes’ syndrome is characterised by recurrent arterial and venous thrombosis and pregnancy morbidity. Although it has been recognised as a disease secondary to systemic lupus erythematosus (SLE), up to 50% of patients with APS have no other underlying systemic disease and are labelled primary APS. Recent evidence suggests that APS may also result in erythematosus (SLE), up to 50% of patients with APS have not been recognised as a disease secondary to systemic lupus erythematosus (SLE).

The ankle-brachial index (ABI) is a simple, inexpensive, and non-invasive diagnostic test for lower extremity peripheral arterial disease. It was considered useful in assessing the future risk for coronary heart disease by the Group III for the Prevention Conference V. The ABI has a sensitivity of about 90% and specificity of 98% to detect stenosis (≥50%) in the leg arteries of older people.

In this study we performed an ABI test in 43 patients with primary APS to assess the prevalence of early atherosclerosis. We excluded all patients with APS secondary to SLE and other autoimmune conditions.

PATIENTS AND METHODS

Study group

We designed a case-control study of 43 patients with primary APS who attended the lupus unit at St Thomas’ Hospital, London, UK, between October 2002 and March 2003. All fulfilled the preliminary (Sapporo) criteria for the classification of APS. We also included 49 healthy subjects matched for age, sex, and race as a control group. All had negative antinuclear antibodies, anti-dsDNA, and anti-extractable nuclear antigen antibodies. This information was obtained from the patients’ files, a questionnaire, and from the blood tests obtained at the time of the interview and ABI determination.

Study protocol

The ABI was measured with a blood pressure cuff and a Doppler ultrasound sensor. The cuff was applied to both arms and ankles. The Doppler probe was used to determine systolic blood pressure in both brachial arteries in the antecubital fossa, and in the right and left posterior tibial arteries and the right and left dorsalis pedis arteries. A 12 cm cuff was inflated to 20 mm Hg above the systolic arterial pressure and slowly deflated. With an 8 MHz Doppler probe (mod MD200) we obtained the systolic arterial pressure when the first Doppler signal was heard. The ABI for each leg was calculated as the ratio of the higher of the two systolic pressures (posterior tibial or dorsalis pedis) in the leg and the higher systolic pressure of either the left or right arm. The method used was in accordance with a recent consensus statement on measuring the ABI. An ABI <1.00 in either leg was considered abnormal, suggesting peripheral arterial disease; progressively lower ABI values indicate more severe obstruction.

Cardiovascular risk factors, such as arterial hypertension, hypercholesterolaemia, diabetes mellitus, smoking, renal impairment, obesity, and any family history of premature cardiovascular events, were recorded. Physical activity and postmenopausal status were documented. All current treatments, including aspirin, warfarin, antihypertensive agents, statins or hormone replacement therapy, were recorded. We determined the fasting glucose and total cholesterol levels, the renal profile, the full blood cell count, when possible, with the patient’s agreement. Autoantibodies, including antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigen and antiphospholipid antibodies (aCL) (IgM and IgG isotypes), and the lupus anticoagulant (LA), were measured by standardised methods in our laboratory. Approval for the study was given by the hospital ethics committee.

Statistical analysis

Statistical analysis was with the non-parametric Fisher’s exact test, Wilcoxon’s test, and univariate regression analysis.

Abbreviations: ABI, ankle-brachial index; aCL, antiphospholipid antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; b2GPI, b2-glycoprotein I; LA, lupus anticoagulant; LDL, low density lipoprotein; SLE, systemic lupus erythematosus
RESULTS

We included 43 consecutive patients with primary APS and 49 healthy subjects as a control group. They were similar in age, sex, and race without any significant difference (table 1). Hypertension was present in 15/43 (35%) patients with primary APS and in 3/49 (6%) controls, and the difference was significant (p = 0.001). Hypercholesterolaemia was identified in 11/43 (26%) cases and in only 3/49 (6%) controls (p = 0.01). Obesity was significantly more common in the group with primary APS: 14/43 (33%) patients but only 6/49 (12%) controls (p = 0.018). Somewhat surprisingly, physical activity was significantly more common in the group with primary APS (10/43 (23%)) than in the healthy group (4/49 (8%)) (p = 0.044).

The mean (SD) duration of the disease was 65.1 (51) months (range 1–190). The antibody profile was as follows: 31 (72%) patients were LA positive; medium or high aCL titres were found in 23 (58%) patients for IgG aCL and in 11 (26%) patients for IgM aCL; in 22 (51%) both antibodies (aCL and LA) were positive in the same patient.

Abnormal ABIs were found to be significantly more common in the patients than in the healthy group (8 (19%) patients vs 2 (4%) controls; p = 0.026). The median ABIs for patients and controls were very similar (1.16 and 1.18 for the right and left sides in patients and 1.16 and 1.12 for controls).

Figure 1 shows the distribution of the ABI values in cases and controls. There were more ABI values below 1.0 in cases than in controls. We analysed all the cardiovascular risk factors and the aPL (LA and aCL separately and together at the same time). However, none of the variables correlated with the presence of abnormal ABIs.

**DISCUSSION**

Many non-invasive tests have been evaluated to determine their ability to predict cardiac risk, including B mode ultrasound, transcranial Doppler ultrasonography, intravascular ultrasound, helical and electron beam computed tomography, exercise tolerance testing, magnetic resonance imaging, and the ankle-brachial blood pressure index. The electrocardiogram may be useful but is relatively insensitive. However, echocardiography may be used to assess left ventricular hypertrophy as a marker of cardiac risk.

The ABI is a good predictor of peripheral artery disease, stroke, and cardiovascular events in middle aged and older populations. We used the ABI test in our patients with primary APS to assess the degree of atherosclerosis affecting these patients. To date there have been no previous studies of the ABI in this patient population.

Our preliminary study showed that abnormal ABIs are more common in primary APS than in healthy subjects. aPL correlate with atherosclerosis, and there is some evidence that anti-b2-glycoprotein 1 (anti-b2GPI) antibodies have a pro-atherogenic effect. Matsuura and Koike showed that b2GPI antibodies are present this effect is blocked. Thus macrophage uptake of oxidised LDL is increased, leading to accelerated atherosclerosis. Petri found that the presence of aPL was a risk factor for atherosclerosis in SLE. Nevertheless, Roman et al recently showed that although accelerated atherosclerosis undoubtedly occurs in SLE, this may be not related to any autoantibody, including aPL. They found that carotid plaques in SLE were not related to aPL after the multivariate analysis. On the other hand, several studies have shown that aCL can cross react with oxidised LDL antibodies; these antibodies may therefore have the same pro-atherogenic effect as oxidised LDL antibodies. We found no association between aPL and abnormal ABI, but this might be explained by the small number of patients and the fact that by definition all were positive for aPL. Disease duration did not seem to be associated with the presence of an abnormal ABI. If aPL is indeed responsible for the atherothrombotic process, it may be unrelated to prolonged exposure to the antibody.

Interestingly, when we analysed the relationship between the traditional cardiovascular risk factors and the presence of an abnormal ABI, we found no associations. Hypertension...
was present in almost 35% of the patients with APS. However, it was not related to an abnormal ABI statistically. The explanation for this remains uncertain, although this supports the notion that APS itself may lead to an atherosclerotic process without the contribution of other cardiovascular risk factors. Another explanation may be the fact that none of our patients had severe hypertension.

The results of this study should be considered preliminary, owing to the relatively small number of patients who were analysed and its cross sectional design. Nevertheless, the finding of an abnormal ABI in these asymptomatic patients deserves further study.

In conclusion, this study shows that an abnormal ABI test is more common in patients with primary APS than in a healthy control group. As the ABI is a recognised test for detecting atherosclerosis, these findings suggest that patients with primary APS are at increased risk of accelerated atherosclerosis. Furthermore, the simplicity of this test makes it applicable to routine clinic testing.

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