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# Prevalence of deep venous thrombosis in the lower limbs and the pelvis and pulmonary embolism in patients with positive antiphospholipid antibodies

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***Background:*** Antiphospholipid antibodies (AA) are immunoglobulins that cross-react with phospholipid on cell membrane, and are therefore associated with a hypercoagulable state manifested by arterial/venous thromboses. We aimed to determine the prevalence of deep venous thrombosis in the lower limbs and the pelvic region (DVT) and pulmonary embolism (PE) in patients with positive AA. ***Methods:*** Sixty-six patients (48 female, 18 male) with positive lupus anticoagulant (LA) and/or positive anticardiolipin antibody (aCL) underwent radionuclide (RN) venography with 370 MBq of $^{99m}$Tc-MAA. Pulmonary perfusion scintigraphy was performed in 58 patients. Fifteen patients had positive LA and positive aCL (LA+/aCL+), 33 patients had positive LA only (LA+/aCL−) and 18 patients had positive aCL only (LA−/aCL+). 43 patients were diagnosed with primary antiphospholipid syndrome (APS) and 19 were diagnosed with APS associated with SLE. ***Results:*** DVT was detected in 21 of 66 patients (32%). Patients with LA+/aCL+ showed higher prevalence of DVT (53%) as compared to LA+/aCL− (27%) and LA−/aCL+ (22%). PE was found in 13 of 58 patients (22%). The prevalence of PE was higher in patients with positive aCL (33% in LA+/aCL+; 36% in LA−/aCL+) than in patients with negative aCL (10%). ***Conclusion:*** Because of the high prevalence of DVT and PE in patients with AA, RN scintigraphy must be recommended in screening for these clinical troubles. These results indicate that the prevalence of DVT and PE may vary in subgroups of AA.

**Key words:** antiphospholipid antibody, deep venous thrombosis, pulmonary embolism, RN venography, $^{99m}$Tc-MAA

## INTRODUCTION

ANTIPHOSPHOLIPID ANTIBODIES (AA) such as lupus anticoagulant (LA) and anticardiolipin antibody (aCL) are associated with a hypercoagulable state manifested by arterial/venous thromboses, which may cause cerebral infarction, central retinal arterial/venous occlusion, myocardial infarction, pulmonary infarction, mesenteric arterial/venous occlusion, habitual abortion, and arterial/venous occlusion and ulceration in four limbs.

The LA is a unique inhibitor that acts at the junction of the intrinsic and extrinsic coagulation pathways by interfering with the activation of prothrombin by the prothrombin activator complex (factor Xa, V, calcium and phospholipid). It is manifested biochemically by prolongation of the partial thromboplastin time, but the specific site on the complex at which the inhibition occurs has not

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been fully clarified. Although originally described in patients with SLE,[1] the LA has been reported in subjects with no identified underlying disease, and in patients with a wide spectrum of illnesses, particularly malignancies and immunologic disorders.[2]

aCL reacts with a complex of negatively charged phospholipids and cofactor(s) derived from normal human sera and has been reported to be associated with clinical events such as recurrent arterial/venous thrombosis, spontaneous abortion, and thrombocytopenia.[3] An aCL level above the 95th percentile is an important risk factor for deep venous thrombosis or pulmonary embolus in healthy adult men.[4]

Harris et al. proposed that the combination of both venous and arterial occlusive events, often accompanied by thrombocytopenia, in the presence of the AA be termed the antiphospholipid syndrome (APS).[5] APS unrelated to any of the major clinical or serologic features of systemic lupus erythematosus (SLE) was defined as primary APS.[6]

Recurrent thrombosis is a potentially serious problem for patients with positive AA. Intermediate- to high-intensity warfarin therapy may confer better antithrombotic protection than low- to intermediate-intensity warfarin therapy or aspirin therapy[7] and the probability of being free of recurrent venous thromboembolic episodes was significantly influenced by the use of anticoagulant drugs.[8]

An anatomic distribution of venous thrombosis in patients with positive AA detected by the radiological methods was reported by Provenzale et al. and they found that deep veins of the leg were the most common site of venous thrombosis.[9] We investigated the prevalence of deep venous thrombosis in lower limbs and pelvic region (DVT) and pulmonary embolism (PE) in patients with positive AA by radionuclide (RN) venography and pulmonary perfusion scintigraphy.

## SUBJECTS AND METHODS

*Subjects*

Sixty-six patients with positive LA and/or positive aCL (48 female, 18 male, age 7–79 years old, mean 46.8 years old) were enrolled in this study. Fifteen patients had positive LA and positive aCL (LA+/aCL+), and 33 patients had positive LA only (LA+/aCL–), and 18 patients had positive aCL only (LA–/aCL+). Patients suffering from acute infectious disease were excluded from this study. Nineteen patients were diagnosed with SLE according to the criteria developed by the American Rheumatism Association. Forty-three patients were diagnosed with primary APS and 19 were diagnosed with APS associated with SLE.

*Protocol*

Sixty-six patients underwent RN venography with 370 MBq of $^{99m}$Tc-MAA. After intravenous injection of 60–90 MBq of Technetium-99m macroaggregated albumin ($^{99m}$Tc-MAA) in the bilateral pedal region with added pressure around the proximal sites of the bilateral ankle joints, the dynamic study was performed with a single/dual head gamma camera (GCA-90B or GCA-901A/W2, Toshiba, Tokyo, Japan) with a low-energy high-resolution collimator from anterior projection in a 64 × 64 matrix. Examination of the lower limbs and pelvis was performed with a few repeated trials. Pulmonary perfusion scintigraphy was consecutively performed from six to eight directions in 58 patients.

To determine the presence of LA, the following tests were performed: a mixing test based on the kaolin clotting time (KCT), with Kolin (Sigma Diagnostics, MO, USA),[10] the tissue thromboplastin inhibition test (TTI) with Thromboplastin (Sigma Diagnostics, MO, USA)[11] and a rabbit brain neutralization procedure (RBNP) with Platelin (Organon Teknika, NC, USA).[12] Patients were considered to be positive for LA if the mixing tests based on KCT and/or TTI were abnormal, and the RBNP test was abnormal.[13]

aCL was measured by an enzyme-linked immunosorbent assay (ELISA) with Asserachrom APA-IgG (Diagnostica Stago, Asnieres- Sur- Seine, France). In this assay, we measured anti-$\beta$2 glycoprotein I/cardiolipin antibodies.[14]

## RESULTS

DVT was revealed in 21 of 66 patients (32%). Patients with LA+/aCL+ showed a higher prevalence of DVT (8/15, 53%) than patients with LA+/aCL– (9/33, 27%) and patients with LA–/aCL+ (4/18, 22%). PE was revealed in 13 of 58 patients (22%). Prevalence of PE was higher in patients with positive aCL (5/15, 33% in LA+/aCL+; 5/14, 36% in LA–/aCL+) than in patients with negative aCL (3/29, 10%).

In patients with primary APS, DVT was recognized in 12 of 43 patients (28%) and PE in 8 of 37 patients (22%). In patients with SLE, DVT was recognized in 6 of 19 patients (32%) and PE in 4 of 18 patients (22%) and those are comparable to the prevalence in patients without SLE (28%, n = 47 and 23%, n = 40, respectively).

## DISCUSSION

In our retrospective study of patients with positive AA, overall prevalences of DVT and PE were comparable with those reported by Provenzale et al. They detected nine venous thrombosis lesions in the legs (29%), and five PE (16%) out of 31 patients with positive AA in radiological studies including contrast angiography/venography, MR angiography/venography, and Doppler sonography.[9]

In the clinical study by Derksen, there were 19 patients (20%) in February 1992 with a history of venous thromboembolic episodes in the total group of 96 patients with

positive AA.[8] Bacharach reviewed 102 patients with positive aCL and systemic venous occlusive disease or PE was recognized in 17% over a nine-months period.[15] Peck reported that thrombophlebitis occurred in 14 (12%) of 114 patients with active SLE, and PE was verified in seven (6%).[16] Gladman reported that venous syndrome with or without PE occurred in about 9% of patients with SLE.[17]

Relatively high prevalence in our study and in the report by Provenzale et al. compared to those studies based on clinical findings suggest that scintigraphy and radiological studies may be able to detect DVT and PE in subclinical patients without symptoms.

In our study according to AA subgroups, patients with LA+/aCL+ and patients with /aCL+ had higher prevalence of DVT and PE, respectively, in each comparison with other groups. Despite the comparisons between small groups, these results indicate that the prevalence of DVT and PE may vary in subgroups of AA, and further study is required.

In 1990, Love noted that in patients with SLE or SLE-related disorders, thromboembolic episodes were revealed in 42% in contrast to 22% in patients with non-SLE disorders.[18] In our study, prevalence in patients with SLE was comparable to those in patients without SLE and this suggests that AA are independent risk factors regardless of the coexistence of SLE.

RN venography and pulmonary perfusion scintigraphy may have a great potential in the non-invasive detection of DVT and PE even in asymptomatic patients with positive AA. They must be recommended as a first screening examination for the judgement of needs of antithrombotic drugs. They must also be recommended as a follow-up examination.

## CONCLUSION

RN venography and pulmonary perfusion scintigraphy may have a great potential in the non-invasive detection of DVT and PE even in asymptomatic patients with positive AA. Because of the relatively high prevalence of DVT or PE in patients with positive AA, scintigraphy must be recommended as a screening examination for the judgement of needs of antithrombotic drugs. Our results indicate that the prevalence of DVT and PE may vary in subgroups of AA, and further study is required.

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