Recurrent Thrombosis in Patients with Deep Vein Thrombosis and/or Venous Thromboembolism Associated with Anticardiopiolipin Antibodies

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Anticardiopiolipin antibodies represent one of the main hypercoagulation states associated with venous thromboembolism. The aim of this work was to evaluate symptomatic recurrent thrombosis in patients with anticardiopiolipin antibodies and deep vein thrombosis of the lower limbs with or without thromboembolism. Sixty patients who suffered from deep vein thrombosis were observed for a 5-year period, whether they had anticardiopiolipin antibodies or not. The group was made up of 34 females and 26 males with ages ranging from 13 to 73 years. All were diagnosed with deep vein thrombosis by means of phlebography and were tested for anticardiopiolipin antibodies by use of the ELISA method. The symptomatic signs of recurrent thrombosis were evaluated during this period. In total, 56.6% of the group were considered above normal for anticardiopiolipin antibodies, 25% positive, another 31.6% borderline, and 43.4% negative. Patients were tested positive when the anticardiopiolipin antibody count was >15 units/mL, borderline between 10 and 15 units/mL, and normal when <10 units/mL. The method of relative risk was used for statistical analysis of the results. Four positive patients, 1 borderline, and 1 normal patient had recurrent events of thrombosis. In the statistical analysis the relative risk for recurrent thrombosis in the positive patients was 6.0; CI 95%; 1.2 to 29.5. In conclusion patients with deep vein thrombosis who are positive for anticardiopiolipin antibodies present a higher risk of recurrent thrombosis.

Introduction

Antiphospholipid antibodies are a heterogeneous group consisting of circulating autoantibodies against anionic phospholipids. This group includes anticardiopiolipin antibodies, lupus anticoagulant, and the VDRL, which are the most investigated in clinical practice.

Hughes et al, in 1986 described a syndrome of antiphospholipid antibodies associated with arterial and/or venous thrombosis, repetitive miscarriages, thrombocytopenia, and the existence of anticardiopiolipin antibodies.
Numerous reports associate these antibodies with venous thrombosis, myocardial infarction, transitional ischemic attacks, intracardiac thrombus, occlusive arterial disease, retinal artery thrombosis, multiple thrombotic incidents, Buerger’s disease, repetitive miscarriages, mesenteric vein thrombosis, Sneddon syndrome, lower limb ulcers, apoptosis, arteriosclerosis, and other clinical associations. The first associations were made in patients with connective tissue diseases and especially with systemic lupus erythematosus. Thereafter, associations were identified in patients who did not suffer from lupus or other evident disease. These cases are now considered the primary syndrome, and only when associated are they considered secondary.

Increased rates of anticardiolipin antibodies can be present even before venous thromboembolism occurs. The presence of antiphospholipid antibodies is associated with a higher risk of recurrence of venous thromboembolism, for which prolonged anticoagulant treatment is recommended.

In 4 studies where the risk of recurrent thrombosis was evaluated in nonlupus patients with venous thromboembolism, 3 demonstrated a higher risk of recurrent thrombosis when associated with anticardiolipin antibodies and 1 when associated with lupus anticoagulant. The aim of this study was to evaluate the risk of recurrent thrombosis in patients with deep vein thrombosis with or without venous thromboembolism and with a positive anticardiolipin antibody count.

Methods

Sixty patients of a group of 67 consecutive patients who had suffered from deep venous thrombosis of the lower limbs were evaluated for a 5-year period. Thirty-four patients were female and 26 were male with ages ranging from 13 to 73 years with a mean age of 36.1 years.

The diagnosis of deep vein thrombosis (DVT) was confirmed in all the patients by means of phlebography. Pulmonary thromboembolism was confirmed by means of pulmonary scintigraphy and/or angiography when there was doubt. The anticardiolipin antibodies were detected by use of the ELISA method, and the results were considered positive when the anticardiolipin antibody count was >15 units/mL, borderline between 10 and 15 units/mL, and normal when <10 units/mL. The symptomatic status of recurrent thrombosis was evaluated during this period either in the ambulatory or over the telephone. The relative risk method was used for statistical analysis of the results.

Of the patients, 25% were positive, 31.6% borderline, and 43.4% who tested negative became the control group for this experiment for anticardiolipin antibodies (Table I). Seven patients did not complete the 5-year evaluation period.

Results

Fifteen episodes of symptomatic recurrent thrombosis occurred in 6 patients. Four of the patients were tested positive (11 episodes), 1 borderline (3 episodes), and 1 normal (1 episode). In the statistical analysis, the relative risk for recurrent thrombosis in the patients who tested positive was 6.0; CI 95% 1.2 to 29.5.

Discussion

In this study a higher relative risk was detected for recurrent thrombosis in patients who were positive for anticardiolipin antibodies. This conforms to the majority of the findings previously published. One of the studies did not detect an association with the anticardiolipin antibodies but did with lupus anticoagulant. However in this study 9 of 16 patients with anticardiolipin antibodies and DVT presented new episodes during the follow-up period, and therefore there was no statistical significance.

A multicentered study in Sweden evaluated a total of 412 patients with high rates of IgG anticardiolipin antibodies and with venous thrombosis. In this study a higher relative risk was detected for a recurrence during the follow-up period in 29% and 14% for positive and normal individuals, respectively (p = 0.001). The relative risk for death was 15% for positive patients and 6% for normal patients (p = 0.01). Proximal thrombosis was more common in the patients with anticardiolipin antibodies (p = 0.02). In this study the international normalized relation rate (INRR) was maintained at 2.0 to 2.8.
In another multicentered study, in Italy, an annual incidence of 2.5% of thrombotic complications was associated with recurrent thrombosis in patients with high anticardiolipin antibody rates (RR 3.66; 95%; CI; 1.76 to 13.7; p<0.005). In this study, several episodes of recurrent thrombosis in the same patient and the association with arterial involvement were observed. The recurrence of thrombosis was more frequent in the first year, as was reported in the Swedish study.

The levels of these antibodies can change with time, eventually reducing to normal in some cases. In our study, a recurrent thrombotic event was seen, during a phase of normalization of the antibodies, in 1 patient who was positive for 3 years. In this patient, it is necessary to question what is happening with these antibodies.

Some cases of anticoagulation failure were also seen when the INRR was maintained between 2 and 3.

In our work, the INRR was regulated between 2 and 4 and the recurrent thrombosis occurred in 26.6% of the patients with high levels of anticardiolipin antibodies; in the Swedish study, 29% of patients had recurrent thrombosis. These figures are high when they are compared with nonpositive patients.

One question remains unanswered; if the INRR had been maintained between 3 and 4, would this have reduced these percentages, as some scientific works have suggested? An INRR of between 3 and 4 could increase the possibility of bleeding, which justified this approach.

And what is the relation with low levels? An association between low levels and thrombotic events was detected; however, this was insignificant with recurrent thrombosis. Anticoagulation for a period of 6 months for all the thrombosis sufferers seems to be the most consistent therapy. But maintaining anticoagulation for an indefinite period is indicated for those who suffer recurrent thrombosis. Nevertheless, the high levels should serve as a warning.

Also a significant association between chronic lower limb ulcers and repetitive superficial thrombophlebitis was observed during this work. With chronic ulcers, the prevalence was more than 30%. Is it possible that this high prevalence of antibodies with ulcers could be associated with the higher prevalence of the proximal thrombosis?

The prevalence of these antibodies in donors in blood banks was 7%, a total of 1% of which was at high levels. Another important question is about these donors and the repercussion on the receptors of this blood.

**Conclusion**

High levels of anticardiolipin antibodies increase the risk of recurrent venous thrombosis compared with low levels. The different manifestations of these antibodies and the consequence of high levels need further investigation. We also suggest additional studies for a better definition of the ideal period of anticoagulation.

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