Hypercoagulability resulting from opposite effects of lupus anticoagulants is associated strongly with thrombotic risk

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Hypercoagulability resulting from opposite effects of lupus anticoagulants is associated strongly with thrombotic risk

Interference of antiphospholipid antibodies (aPL) with coagulation was investigated in 40 aPL-patients (24 with thrombosis) using thrombography. Impairment of the activated protein C anticoagulant pathway was partially offset by the genuine anticoagulant effect. The net result, a procoagulant phenotype, was associated with a 7-fold increased risk of thrombosis in aPL-patients.

Letters to the Editor

Antiphospholipid antibodies (aPL) are associated with thrombosis and/or pregnancy morbidity in the setting of the antiphospholipid syndrome (APS). Some aPL-positive patients remain asymptomatic suggesting that improved assessment of the thrombotic risk is still required. While aPL-induced inhibition of thrombin formation has been reported, acquired activated protein C (APC) resistance and is thought to be the main cause of aPL-associated thrombosis. However, this remains the subject of debate. Previously, we demonstrated that thrombography could confirm both the extent of the lupus anticoagulant (LA) effect and APC resistance of thrombin generation. Given the range of laboratory aPL characteristics and the complexity of thrombin formation and inhibition, composite interference of immune complexes on pro- and anti-coagulant complexes may determine the overall result. We studied 40 persistently aPL-positive patients and 19 aPL-negative healthy controls. The study aimed to investigate if the net in vitro phenotype is hypercoagulability, and to determine whether total generated thrombin activity, given the two opposite effects of aPL, is associated with an increased risk of thrombosis, to determine whether total generated thrombin activity is associated with an increased risk of thrombosis given the two opposite effects of aPL.

Twenty-four of the aPL-positive patients had experienced thrombosis but were not treated with anticoagulants for medical reasons independent of this study. Two patients were undergoing bridging therapy with low-molecular-weight heparin. In these 2 cases, plasmas were collected from asymptomatic aPL-positive patients (37.2±4.6 vs 24.1±4.6 nM, p<0.05). However, odds ratio (OR) of thrombosis associated with IC50-APC did not reach significance (Figure 1C). The extent to which a phenotype integrates the two opposite effects of LA is associated with thrombosis was assessed by using two combined thrombographic parameters, APC sensitivity ratio (APCsr) and ETP IC50-APC. In fact, APCsr based on ETP ratios was reported to be associated with thrombosis elsewhere previously. We observed a negative correlation between APCsr and ETP and a positive one between APCsr and ETP in the presence of 13.9 nM added APC.

Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>APS- (n=16)</th>
<th>APS+ (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women</td>
<td>3/13</td>
<td>8/16</td>
</tr>
<tr>
<td>Age, years</td>
<td>43±4</td>
<td>41±3</td>
</tr>
<tr>
<td></td>
<td>(23-69)</td>
<td>(21-76)</td>
</tr>
<tr>
<td>aPL-associated thrombocytopenia (platelet count &lt;100 G/L)</td>
<td>0</td>
<td>1 severe</td>
</tr>
<tr>
<td></td>
<td>(blood platelet count, G/L)</td>
<td>(30)</td>
</tr>
<tr>
<td>SLE or lupus-like</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Primary APS</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular thrombosis</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>Pregnancy morbidity</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Catastrophic APS</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Laboratory criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I (more than one laboratory criteria present)</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Category IIa (lupus anticoagulants present alone)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Category IIb (anti-cardiolipin present alone)</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Continuous variables denoted as means ± SEM (range), categorical variables as number. SLE indicates systemic lupus erythematosus; APS, antiphospholipid syndrome; APS- asymptomatic aPL-positive patients; APS+, patients with APS; not applicable. Categories I, IIa and IIb refer to classification according to Sydney criteria. Lupus anticoagulant testing was in agreement with the International Society on Thrombosis and Haemostasis recommendations, taking into account the Sydney revision. Anti-cardiolipin and anti-β2-glycoprotein I Antibodies were detected by home-based ELISA with cut-off levels locally defined by the method of percentiles with more than 50 healthy volunteers. Antibody values were distributed up to 35-fold, 70-fold, 5-fold and 22-fold the cut-off value for IgG anticardiolipin, IgG anti-β2-glycoprotein I, IgM anti-cardiolipin and IgM anti-β2-glycoprotein I respectively.
In conclusion, changes in sensitivity of thrombin activity to APC, taking into account its modulation by the genuine anticoagulant effect of aPL, is associated with an increased risk of thrombosis in aPL-positive patients.

**References**


