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

Citation for published version (APA):

Document status and date:
Published: 01/01/2007

DOI:
10.3324/haematol.10577

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:
- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:
repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 23 Sep. 2020
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.

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. The study aimed to investigate 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 examine whether APC resistance alone may favor thrombosis, we studied 40 persistently aPL-positive patients and 19 aPL-negative healthy controls.

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 patients who were undergoing bridging therapy with low-molecular-weight heparin.

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 (30)</td>
</tr>
<tr>
<td>(blood platelet count, G/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE or lupus-like</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Primary APS</td>
<td></td>
<td>16</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 mean±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 accorded to Sydney criteria. Lupus anticoagulant testing was in agreement with the International Society on Thrombosis and Haemostasis recommendations, taking into account the Sydney revision. Anticardiolipin and anti-β2-glycoprotein I antibodies were detected by home-based ELSA 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.

On average, there was no statistical difference in ETP without APC (ETP0) between patients and controls whereas ETP in the presence of any APC concentration was significantly higher (p<0.005) for patients than for controls (mean increase of 1.7-fold; see Figure 1A). Overall response to APC was evaluated using APC concentration at half the ETP0 value (IC50 APC). Analysis showed significantly higher values for patients compared with controls (32.0±3.4 vs 9.1±0.9 nM, p<0.0001). In contrast, ETP0 was lower for LA-positive patients (n=23) than for LA-negative patients (1227±65 vs 1680±131 nM.min, p<0.005) and the respective IC50-APC was higher (42.2±4.6 vs 18.2±2.7 nM, p<0.001) (see Figure 1B). Overall, APC inhibition was greater (evaluated in presence of APC) than prothrombin activation (low ETP0), resulting in a net procoagulant phenotype. This may be due to differences in membrane requirements and binding kinetics between pro- and anti-coagulant factors. Patients with and without thrombosis were compared to examine whether APC resistance alone may favor thrombosis. IC50-APC was higher in APS-patients than in 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. Seventeen of the 24 APS-patients displayed APCsr >99th percentile compared to 5 of the 16 asymptomatic aPL-positive patients (p=0.02). A significantly elevated thrombotic risk was therefore found for APCsr values exceeding the 99th percentile, OR was 5.34; 95% CI=1.35-21.1 (Figure 1C). The use of ETP ratios is limited by the fact that the response to APC is investigated with only one arbitrary concentration of AFC. Considering that ETP0-APC globally assessed the response to APC and had to be combined with ETP0, we...
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.

Thomas Lecompte,† Denis Wahl,‡ Christine Perret-Guillaume,‡ H. Coenraad Hemberg,§ Patrick Lacolley,¶ Véronique Regnault* †Inserm, U734, U1HPP, Nancy University; ‡Haematology Laboratory; §Vascular Medicine, and ¶Internal Medicine, Nancy University Hospital, Nancy, France; #Synapse B.V., CARIM, University of Maastricht, The Netherlands, Inserm, U684; *UHP* Nancy University, Nancy, France

Key words: antiphospholipid antibody, antiphospholipid syndrome, lupus anticoagulant, APC resistance, thrombin generation.

Correspondence: Denis Wahl, Inserm U734, UHP, Faculté de Médecine, 54500 Vandoeuvre-lès-Nancy, France. Phone: international +33.3.83683476. Fax: international +33.3.83683479. E-mail: d.wahl@chu-nancy.fr

References


Figure 1. Association of the in vitro phenotype of the clotting system with definite antiphospholipid syndrome. A. Values obtained with platelet-rich plasma (PRP) of the 19 controls (open symbols) and PRP of the 40 patients (closed symbols). Each subject, measurements are means of triplicate. *p<0.005 compared with controls. B. Values obtained with PRP of the 23 patients with lupus anticoagulants (dark grey symbols) and PRP of the 17 patients without lupus anticoagulants (light grey symbols). C. Association of the in vivo phenotype or in vivo activation of coagulation and risk of thrombosis when comparing patients with (APS) and without (APS) thrombosis. Results are expressed as odds ratios with accompanying 95%CI for a cut-off level set at the 99th percentile of the control values. The markers of in vivo activation of coagulation were F1+2 fragments (thrombin formation) and D-dimers (degradation products of fibrin formed by thrombin). ETP, ETP value without APC; IC50-APC, APC concentration reducing ETP by 50%; APCsr, APC sensitivity ratio: ETP in presence of 13.9 nM APC/ETP.