Vascular Thrombosis Associated with Antiphospholipide Syndrome

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ABSTRACT

The aim of this study was to present our diagnostic and therapeutic experience with antiphospholipide syndrome (APS) and vascular thrombosis. Ninety-nine patients with positive antiphospholipide antibodies (aPL) and vascular thrombosis were included in the study: forty patients, according to clinical classification criteria, had primary antiphospholipide syndrome (PAPS), and fifty-nine patients had secondary antiphospholipide syndrome (SAPS). In PAPS group, 82.5% of the patients were LA-positive, 37.5% of the patients were IgG aCL-positive, 27.5% of the patients were IgM aCL-positive, and 15% of the patients were IgG anti-β2GPI-positive. In SAPS group, 61% of the patients were LA-positive, 50.8% of the patients were IgG aCL-positive, and 47.5% of the patients were IgM aCL-positive. Administered therapy was low molecular weight heparin (LMWH) throughout 7 days, followed by warfarin with prothrombin time maintained between 2.0 and 3.0 INR.

Key words: antiphospholipid syndrome, vascular thrombosis, antibodies

Introduction

Antiphospholipide syndrome (APS) is characterized by venous and/or arterial thrombosis, recurrent pregnancy loss and presence of antiphospholipide antibodies¹. Two antiphospholipide antibodies related to repeat thrombosis episodes are anticardiolipin antibodies (aCL) and lupus anticoagulant (LA)³. Anti-β2-glycoprotein I (anti-β2GPI) antibodies are found in sera of many, but not all patients with APS. Primary antiphospholipide syndrome (PAPS) occurs in patients without clinical evidence of another autoimmune disease, whereas secondary antiphospholipide syndrome (SAPS) occurs in association with autoimmune or other disease⁵.

The most common clinical manifestation of antiphospholipide syndrome is thrombosis, which can affect vessels of any organ. Venous thrombosis, particularly of the lower limb, occurs in up to 55% of patients with this syndrome, half of which also have pulmonary embolism⁶–⁷. Arterial thrombosis affects the brain, causing transient ischemic attacks (TIA) or strokes. Other anatomical sites for arterial thrombosis are heart, eye, kidney and peripheral arteries³–⁵. Vascular occlusion may occur due to embolism from central sources such as vegetations on a mitral or aortic valve, which are reported in up to 4% of patients with antiphospholipide syndrome⁶.

We present our diagnostic and therapeutic experience involving patients with APS and vascular thrombosis.

Subjects and Methods

Ninety-nine patients who fulfilled Sapporo classification criteria for APS, revised according to Sydney criteria, were included in the study⁸–⁷. Forty of those patients had PAPS, while 59 had SAPS. All patients had aPL anti-
body level determined, and as a clinical manifestation they had vascular thrombosis affecting one of the organs. Lupus anticoagulant was determined with test of Dade Behring Marburg firm using LA 1 screening reagent and LA 2 confirming reagent, which is simplified reagent Dilute Russell’s Viper Venom Test (DRVVT) for lupus anticoagulant verification. Anticardiolipin antibodies were determined with AutostatTMII ACA test of Hycor firm, for every isoclass, based on enzyme-linked immunosorbent assay (ELISA), which is used for detection of specific antibodies against cardiolipin in human serum. Anti-β2-glycoprotein-1 antibodies were identified with ETI-Beta-Glycoprotein I IgG kit for quantitative analysis of IgG antibodies against β2-glycoprotein 1 in human serum. Preliminary tests, prothrombin time, activated partial thromboplastin time, fibrinogen and thrombin time (DADE Behring) were used for coagulogram screening, and platelet number was determined with Cell-Dyn-4000. Protein C (APC resistance) was determined with ProC Global test (DADE Behring). Factor V von Leiden mutation was determined according to Bertin⁸, prothrombin mutation was determined according to Poort⁹, and C667T mutation MTHFR was determined according to Frosst¹⁰. Data input and processing was done in a computer table calculator Microsoft Excel 2003, whereas software packages SPSS 13.0 for Windows and Statistica 6.0 were used for statistical analysis.

Results

Average age in PAPS group was 54.7±14.4, while in SAPS group it was 57.3±13.9. Ninety-nine patients, who fulfilled clinical classification criteria for APS were included in the study. Forty of them had PAPS, and 59 had SAPS. All patients had aPL antibody level determined, and as a clinical manifestation they had vascular thrombosis affecting one of the organs. Table 1 shows distribution of patients according to gender. aPL antibody analysis showed that 82.5% of patients from PAPS group, and 61% of patients from SAPS group were LA-positive. In SAPS group, 50.8% of the patients were aCL-positive, while in PAPS group 37.5% of the patients were aCL-positive. Picture 1 shows share of specific aPL antibodies in patients with APS and vascular thrombosis. Distribution analysis results for patients with PAPS and SAPS, obtained by Kolmogorov-Smirnov test, lead to conclusion that analysed distributions are not normally distributed. Since the study included relatively small number of patients, distribution normality analysis needed to be done with Mann-Whitney test, which is a nonparametric test. On the significance level p<0.05, it is accepted as possible the hypothesis that between patients with primary antiphospholipide syndrome (PAPS) and patients with secondary antiphospholipide syndrome (SAPS) exists significant difference in β2-GPI IgG and IgA aCL values (Table 2). In order to examine connection that exists between analysed variables (LA, β2-GPI IgG, IgG aCL, IgM aCL, IgA aCL, IgA aCL), tables 3 and 4 show Spearman’s correlation rank coefficients and belonging p-values obtained by testing significance of the hypothesis. Based on obtained results, it can be concluded that statistically significant correlation exists only between IgG aCL and IgM aCL variables, in both (PAPS and SAPS) groups of patients.

The most often clinical manifestation of APS was deep vein thrombosis (DVT) of lower leg, with 45% incidence in PAPS group and 32.2% incidence in SAPS group. Cerebral stroke had similar incidence, 27.5% in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Z (Normal approximation)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>-1.801</td>
<td>0.072</td>
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<tr>
<td>β2-GP1 IgG</td>
<td>-3.774</td>
<td>0.000</td>
</tr>
<tr>
<td>IgG aCL</td>
<td>-1.130</td>
<td>0.258</td>
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<tr>
<td>IgM aCL</td>
<td>-1.348</td>
<td>0.178</td>
</tr>
<tr>
<td>IgA aCL</td>
<td>-3.363</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LA – lupus anticoagulant, aCL – anticardiolipin antibody, Ig – immunoglobulin antiβ2-GP1, IgG – antiβ2glycoprotein1
PAPS group, and 30.5% in SAPS group. Myocardial infarction (MI) had greater incidence in SAPS group with 22%, than in PAPS group with 12.4%. Peripheral arteries were affected almost the same in both groups of patients, 10% in PAPS group and 11.7% in SAPS group. Peripheral veins were least affected, with 5% incidence in PAPS group, and 3.4% incidence in SAPS group.

**Discussion**

From clinical point of view, it can be said that APS is a subject of many medical specialities. Given time, the syndrome has become described in detail. At first in case reviews, and then based on randomised controlled clinical trials. Treatment approach for this syndrome, interpretation of laboratory results, which are often contradictory, and connecting them with clinical manifestations present today’s great challenge for clinical doctors.

One clinical and one laboratory criterion is necessary to make a diagnosis of APS. The most often clinical manifestation of APS is vascular thrombosis, arterial or venous. Cerebral stroke and transient ischemic attack (TIA) are the most often presentations of arterial thrombosis, and recurrent cerebral strokes can cause ischemic dementia. Large blood vessels can also be affected in this syndrome, including aorta, causing aortal occlusion. Affection of peripheral blood vessels is variable and any artery can be affected, what causes ischemy of an end organ.

Prospective studies support a theory that antiphospholipid antibodies can be a risk factor for coronary artery disease and myocardial infarction, especially in young
REFERENCES


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ANTIFOSFOLIPIDNI SINDROM KAO UZROK VASKULARNIH TROMBOZA

SAŽETAK

Cilj nam je bio pokazati naša iskustva u dijagnosticiranju i liječenju vaskularnih tromboza u sklopu antifosfolipidnog sindroma (APS). 99 pacijenata s pozitivnim antifosfolipidnim antitijelima (aPL) i vaskularnim trombozama bilo je uključeno u studiju: 40 pacijenata, sukladno klasifikacijskim kliničkim kriterijima imalo je primarni antifosfolipidni sindrom (PAPS), te 59 sekundarni antifosfolipidni sindrom (SAPS). Svim pacijentima je određen profil protutijela. U grupi s PAPS 82,5% pacijenata bilo je LA pozitivno, 37,5% IgG aCL, 27,5% IgM aCL, te 15% na IgG anti-β2GPI. U grupi sa SAPS 61% bilo je pozitivno na LA, 50,8% na IgG aCL, 47,5% bilo je IgM aCL pozitivno. Na IgA aCL klasu antitijela bilo je pozitivno 6,7% pacijenata, dok na anti-β2GPI u grupi sa SAPS 3,4% pacijenata. Nije nađen niti jedan pacijent pozitivan isključivo na IgA aCL, kao ni na anti-β2GPI, te oni nemaju klinički značaj. Kao terapija korišten je niskomolekularni heparin (LMWH) kroz 7 dana, potom nastavljeno s varfarinom uz održavanje protrombinskog vremena između 2,0–3,0 INR.