Correlations between thrombotic and non-thrombotic APS manifestations
Lesions from the Serbian National Registry

Ljudmila Stojanovich

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ANTIPHOSPHOLIPID SYNDROME

Very frequent Sy:

- 1 / 5 YOUNG WITH CVI
- 1 / 5 DVT
- 1 / 5 PREGNANCY LOSS

Stojanovich L, MD, PhD
Factors Predicting Autoimmune Diseases

Changeable factors

- Psychological stress
- Infection
- Vaccination
- Smoking
- Obesity
- Ultraviolet light exposure
- Drugs...

Unchangeable factors

- Genetic
- Hormonal
- Immune deficiency state
- Gender
Sapporo Criteria on Antiphospholipid Syndrome (1998)

**Clinical criteria**
- ✓ Vascular thrombosis
- ✓ Pregnancy morbidity

**Laboratory criteria**
- ✓ Lupus anticoagulant
- ✓ Anticardiolipin antibody
  
  *dependent of $\beta_2$-GPI*

Stojanovich L, MD, PhD
Issued by the Ministry of Science of the Republic of Serbia:

• **Grant number 145020 for 2006-2010:**

  *Multi-disciplinary Study of Risk Factors for the Development of Thromboses in APS*

• **Grant number 175041 for 2011-2014:**

  *Multidisciplinary study of genetic and acquired abnormalities of the immune response for the occurrence of systemic antiphospholipid syndrome manifestations.*

Stojanovich L, MD, PhD
Research Goal

1. To determine prevalence and types of aPL titer (LA, ACL, β2GPI) in patients with thrombotic and non-thrombotic manifestations of the disease.
2. Analysis of gene polymorphisms that are important for the T (H) 17 and regulatory T cells differentiation in APS patients, and their correlation with the disease.
3. Determination of aPL association with the innate Thrombophilia (deficiency of AT, PC, PS, FXII, polymorphisms FV Leiden, prothrombin 20210 and MTHFR) and clinical expression.
4. Determination of aPL role in the development of induced atherosclerosis, including subclinical forms of the disease using the latest technology methods such as multi sliced computed tomography (64 MSCT), which would present the extent and location of changes in blood vessels.
5. To determine the importance of oxidative stress, markers of inflammation, endothelial adhesion receptor molecules induction and activation, as additional factors in the complicated pathophysiology and multifactorial etiology of APS thrombosis.
6. To continue in obtaining the national APS patients registry with the possibilities of its participating in international studies.
7. To overview the patient outcomes with various APS therapeutic protocols.

Stojanovich L, MD, PhD
• Aim of this study was to observe and investigate association between thrombotic and non-criteria manifestations, in prospective study of APS patients.
• Differences between patients with primary and secondary APS were also analyzed.
• This study presents the first results from our national cohort.
Patient Group Description

501/383 patients:

358/ 260 PAPS patients:
- 201 female and 59 male
- mean age 45.2 + 13.7 years

143/ 114 SLE patients with secondary APS
- 106 female and 9 male
- mean age 46.9 + 15.9 y

14 (4.5%) patients with CAPS: 7 SLE+ 7 PAPS

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# Distribution of aPL in PAPS and SAPS

## Table 2. Distribution of aPL in the PAPS and SAPS groups

<table>
<thead>
<tr>
<th>aPL type/ aPL category</th>
<th>PAPS (N=260)</th>
<th>SAPS (N=114)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL IgG</td>
<td>95 (36.5)</td>
<td>68 (59.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>aCL IgM</td>
<td>141 (54.2)</td>
<td>73 (64.0)</td>
<td>0.049</td>
</tr>
<tr>
<td>β₂GPI IgG</td>
<td>83 (31.9)</td>
<td>49 (43.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>β₂GPI IgM</td>
<td>98 (37.7)</td>
<td>51 (44.7)</td>
<td>0.122</td>
</tr>
<tr>
<td>LA</td>
<td>133 (51.2)</td>
<td>56 (49.1)</td>
<td>0.402</td>
</tr>
<tr>
<td>I</td>
<td>160 (61.5)</td>
<td>81 (71.1)</td>
<td>p=0.020</td>
</tr>
<tr>
<td>Ila</td>
<td>41 (15.8)</td>
<td>5 (4.4)</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>46 (17.7)</td>
<td>23 (20.2)</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>13 (5.0)</td>
<td>5 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

Legend: PAPS= primary antiphospholipid syndrome, SAPS= secondary antiphospholipid syndrome, aCL= anticardiolipin antibodies, β₂ GPI= anti- β₂ glycoprotein I antibodies, LA= lupus anticoagulant, aPL= antiphospholipid antibodies
Categories: I-more than one aPL present, Ila LA present alone, IIb-aCL present alone, IIc- anti-β2GPI present alone
Distribution of patients according to antibody category

- More than one type of antibodies (category I) was present in 64.5%
- Lupus anticoagulant was present alone in 12.1% patients (category IIa)
- aCL antibodies were present alone in 16% patients (category IIb)
- anti-β2GPI antibodies were present alone in 7.4% patients (category IIc)

PengoV et al.  
Antibody profiles for the diagnosis of APS.  
Thromb Haemost 2005
Results
APS Manifestations

✓ Pregnancy loss:  41% pts
✓ Venous thrombosis:  28% pts
✓ Arterial thrombosis:  51% pts
Diagnostic of vascular APS manifestations

- Physical examination
- X-ray diagnosis of chest
- Vascular ultrasonography (Doppler)
- Peripheral angiography
- Vascular magnetic resonance imaging/ MRA angiography
- Computed tomographic angiography (CTA)

64-multi slice CT - whole body angiography can allow us excellent visualization of all major and minor blood vessels
Thrombosis was diagnosed:

✓ 83 (51.2%) PAPS patients
✓ 36 (38.3%) SLE patients

p = 0.045
Results

✓ Arterial Thrombosis: 51% pts

✓ Venous thrombosis: 28% pts

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Arterial Thrombosis

✓ 35% PAPS patients

✓ 34% SLE patients

$p = 0.932$

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Venous thrombosis

☑ 25.9% PAPS patients

☑ 8.5% SLE patients

p = 0.001
Incidence of thrombosis in APS pts in Serbia

- SLE
- PAPS

Bar chart showing incidence of various types of thrombosis:
- V. JUGULARIS
- V. SUBCLAVIA
- Arms Venous Thrombosis
- Legs Venous Thrombosis
- Superficial Thrombophlebitis
- Arms Arterial Thrombosis
- Legs Arterial Thrombosis
CVI in PAPS

There was a correlation between:

**CVI** and:

- pts with $\beta_2$GPI-IgM $p=0.008$
- pts with LA $p=0.009$

Stojanovich L, MD, PhD
CVI in SLE

There was a correlation between:

CVI and:

✓ pts with $\beta_2$GPI  $p=0.008$
✓ pts with LA  $p=0.009$

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Analysis of aPL and localization of thrombosis

There was no correlation between:

other localization of arterial thrombosis and the type of aPL

\[ p > 0.05 \]

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Thrombosis in PAPS was significantly more frequent than in SLE:

✓ superior extremity  \( p=0.004 \)

✓ inferior extremity deep vein  \( p=0.027 \)

✓ inferior extremity superficial thrombophlebitis  \( p=0.004 \)

Stojanovich L, MD, PhD
Analysis of aPL and localization of thrombosis

✓ aCL-IgM and cerebral venous sinus thrombosis

✓ aCL-IgM and jugular venous thrombosis

\[ p = 0.040 \]

Stojanovich L, MD, PhD
Analysis of aPL and localization of thrombosis

There was no correlation between:

other localization of venous thrombosis and the type of aPL

p > 0.05

Stojanovich L, MD, PhD
Distribution of arterial and venous thrombosis in PAPS and SAPS patients under and over 45 years of age

<table>
<thead>
<tr>
<th>Age</th>
<th>PAPS</th>
<th>Secondary APS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT</td>
<td>VT</td>
</tr>
<tr>
<td>≤45 years</td>
<td>17 (28.5%)</td>
<td>20 (24.15%)</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>39 (49.2%)</td>
<td>22 (27.8%)</td>
</tr>
<tr>
<td></td>
<td>p=0.028</td>
<td>p=0.238</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
Analysis of localization of thrombosis and age

Age was a significant risk factor for:

- **CVI:** 51.92 and 41.97 years, respectively  
  \( p=0.001 \)

- **MI:** 56.6 and 43.6 years, respectively  
  \( p=0.0001 \)

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Analysis of activity of SLE (SLEDAI) and thrombosis

The median SLEDAI score was 9 in patients without thrombosis.

The median SLEDAI score was 13.5 in patients with thrombosis.  

\[ p = 0.03 \]

The activity of SLE was in significant correlation with the prevalence of thrombosis.

Stojanovich L, MD, PhD
Distribution of aCL IgG/IgM levels in PAPS patients with arterial and venous thrombosis

<table>
<thead>
<tr>
<th>PAPS</th>
<th>Level of aCL IgG</th>
<th>Level of aCL IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>medium</td>
</tr>
<tr>
<td>Thrombosis %</td>
<td>50.0</td>
<td>65.2</td>
</tr>
<tr>
<td>AT</td>
<td>33.3</td>
<td>52.2</td>
</tr>
<tr>
<td>VT</td>
<td>25.9</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
Distribution of aCL IgG/IgM levels in SAPS patients with arterial and venous thrombosis

<table>
<thead>
<tr>
<th>Secondary APS</th>
<th>Level of aCL IgG</th>
<th>Level of aCL IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low</td>
<td>medium</td>
</tr>
<tr>
<td>Thrombosis %</td>
<td>29.8</td>
<td>37.5</td>
</tr>
<tr>
<td>AT</td>
<td>25.5</td>
<td>37.5</td>
</tr>
<tr>
<td>VT</td>
<td>4.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
**Distribution of β2GP1 IgG/IgM levels in patients with PAPS**

<table>
<thead>
<tr>
<th>PAPS</th>
<th>β2GPI-IgG</th>
<th>2GPI-IgGM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low</td>
<td>medium</td>
</tr>
<tr>
<td>Thrombosis %</td>
<td>50.0</td>
<td>65.2</td>
</tr>
<tr>
<td>AT</td>
<td>33.3</td>
<td>52.2</td>
</tr>
<tr>
<td>VT</td>
<td>25.9</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
### Distribution of β2GP1 IgG/IgM levels in patients with SAPS

<table>
<thead>
<tr>
<th>Secondary APS</th>
<th>β2GPI-IgG</th>
<th>β2GPI-IgGM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low</td>
<td>medium</td>
</tr>
<tr>
<td>Thrombosis %</td>
<td>32.7</td>
<td>33.3</td>
</tr>
<tr>
<td>AT</td>
<td>28.8</td>
<td>25.0</td>
</tr>
<tr>
<td>VT</td>
<td>9.6</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
### Comparisons between Pulmonary Manifestations and Gender in PAFS

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=54</td>
<td>18.5%</td>
<td>13.2%</td>
<td>0.464</td>
</tr>
<tr>
<td>N=159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism and infarction</td>
<td>1.9%</td>
<td>1.3%</td>
<td>0.999</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>13%</td>
<td>3.2%</td>
<td>0.019*</td>
</tr>
<tr>
<td>Secondary pulmonary hypertension</td>
<td>24.1%</td>
<td>13.3%</td>
<td>0.099</td>
</tr>
<tr>
<td>Major pulmonary arterial thrombosis</td>
<td>5.6%</td>
<td>1.3%</td>
<td>0.203</td>
</tr>
<tr>
<td>Pulmonary microthrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>3.7%</td>
<td>1.9%</td>
<td>0.814</td>
</tr>
</tbody>
</table>

*Significant difference
Comparisons between Pulmonary Manifestations and Gender in SAFS

<table>
<thead>
<tr>
<th></th>
<th>Male N=13</th>
<th>Female N=99</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism and infarction</td>
<td>15.4%</td>
<td>7.1%</td>
<td>0.621</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>0</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>Secondary pulmonary hypertension</td>
<td>0%</td>
<td>2%</td>
<td>0.999</td>
</tr>
<tr>
<td>Major pulmonary arterial thrombosis</td>
<td>0%</td>
<td>2%</td>
<td>0.999</td>
</tr>
<tr>
<td>Pulmonary microthrombosis</td>
<td>23.1%</td>
<td>6.1%</td>
<td>0.114</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>0%</td>
<td>3%</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Pulmonary events in antiphospholipid syndrome: influence of antiphospholipid antibody type and levels

L Stojanovich¹, M Kontic², A Djokovic¹, N Ilijevski³, N Stanisavljevic¹, D Marisavljevic¹

¹Internal Medicine, ‘Bezanijska Kosa’, University Medical Centre, Belgrade, ²Pulmonology Clinic, Clinical Centre of Serbia, University in Belgrade, and ³Institute of Cardiovascular Disease ‘Đedinje’, Belgrade, Serbia
Amputation of Digits or Limbs in Patients with Antiphospholipid Syndrome

Ronald A. Asherson, MD, FACP, FRCP,*
Ricard Cervera, MD, PhD, FRCP,† Evandro Klumb, MD,‡
Ljudmila Stojanovic, MD,§ Piercarlo Sarzi-Puttini, MD,‖ Janet Yinh, MD,‖
Silvia Bucciarelli, MD, PhD,‖ Gerard Espinosa, MD, PhD,‖
Roger Levy, MD,** and Yehuda Shoenfeld, MD, FRCP††

Digital gangrene/with amputations

Stojanovich L, MD, PhD
Wrapping up

✓ Thrombosis was diagnosed with higher prevalence in PAPS compared to SLE patients.

✓ Patients over 45 years of age were at a higher risk for arterial thrombosis, particularly for cerebral ischemic attack and myocardial infarction.

Stojanovich L, MD, PhD
Wrapping up

LA positivity was a risk factor for deep venous thrombosis and CVI in PAPS patients, and for CVI and pulmonary embolism in SLE patients.

The activity of SLE (SLEDAI) was in significant correlation with the prevalence of thrombosis.

Stojanovich L, MD, PhD
Wrapping up

✓ The prevalence of thrombosis was similar in all antibody category groups. Any aPL level and type is risk factor for thrombotic event in ours APS patients.

✓ After 10 years follow-up, we observed no thrombotic manifestations in any patients with high aPL levels. All patients were treated according to international protocols.
LUPUS AROUND THE WORLD

Influence of antiphospholipid antibody levels and type on thrombotic manifestations: results from the Serbian National Cohort Study

L Stojanovich¹, O Markovic¹, D Marisavljevic¹,², I Elezovic³,², N Ilijevski⁴,² and N Stanisavljevic¹

¹Internal medicine, “Bezanijska Kosa”, University Medical Center, Belgrade, Serbia; ²University of Belgrade, Faculty of Medicine, Belgrade, Serbia; ³Hematology Clinics, Clinical Center of Serbia, Belgrade, Serbia; ⁴Institute of Cardiovascular Disease “Dedinje”, Belgrade, Serbia
Systemic APS by Shoenfeld Y

Lupus. 2003

1) Skin (livedo reticularis)
2) Heart (non-verrucal endocarditis)
3) Kidneys (renal artery stenosis)
4) Circulation (hypertension, atherosclerosis)
5) Lung (pulmonary hypertension)
6) Brain (cognitive impairment)
7) Brain Vasculature (migraine)
8) Blood elements (AIHA, thrombocytopenia)
9) Bones (osteonecrosis)
10) Adrenals (apoplexy)
11) Placenta (insufficiency, fetal death)
12) Pregnancy (eclampsia, pregnancy loss)
13) Coagulation (hypercoagulable state)
14) Blood vessels (accelerated atherosclerosis)
15) Eyes (amaurosis fugax, optic neuritis)
16) Ears (acute hearing loss)
17) GI involvement (spleen, Budd Chiari)

Stojanovich L, MD, PhD
Methods

✓ Cardiac non-thrombotic manifestations

✓ Neurological non-thrombotic manifestations

✓ Skin non-thrombotic manifestations

✓ Hematological

Stojanovich L, MD, PhD
## Results

### Table 1. Prevalence of non-thrombotic manifestations in patients with primary and secondary APS

<table>
<thead>
<tr>
<th>Non-criteria manifestations</th>
<th>PAPS (N=260)</th>
<th>SAPS (N=114)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>5 (8.4)</td>
<td>21 (18.4)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Chorea</td>
<td>0 (0)</td>
<td>9 (7.9)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>34 (13.1)</td>
<td>76 (66.7)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Pseudovasculitis</td>
<td>33 (12.7)</td>
<td>68 (59.6)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Skin ulcerations</td>
<td>25 (9.6)</td>
<td>40 (35.1)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 (16.5)</td>
<td>44 (38.6)</td>
<td><strong>p=0.0001</strong></td>
</tr>
<tr>
<td>Valve thickening and dysfunction</td>
<td>9 (3.5)</td>
<td>7 (6.1)</td>
<td>0.182</td>
</tr>
</tbody>
</table>

*Stojanovich L, MD, PhD*
Incidence of non-criteria manifestations in pts with/without LA

<table>
<thead>
<tr>
<th>Non-criteria manifestation</th>
<th>PAPS</th>
<th>SAPS</th>
<th>p value</th>
<th>PAPS</th>
<th>SAPS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative %</td>
<td>Positive %</td>
<td></td>
<td>Negative %</td>
<td>Positive %</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8.0</td>
<td>5.7</td>
<td>0.397</td>
<td>17.0</td>
<td>17.0</td>
<td>0.608</td>
</tr>
<tr>
<td>Migraine</td>
<td>33.3</td>
<td>24.1</td>
<td>0.132</td>
<td>42.6</td>
<td>27.7</td>
<td>0.097</td>
</tr>
<tr>
<td>Chorea</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>6.4</td>
<td>12.8</td>
<td>0.243</td>
</tr>
<tr>
<td>Dementia</td>
<td>11.5</td>
<td>3.4</td>
<td>0.038*</td>
<td>17.0</td>
<td>12.7</td>
<td>0.773</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>16.0</td>
<td>10</td>
<td>0.272</td>
<td>34</td>
<td>28</td>
<td>0.138</td>
</tr>
<tr>
<td>Pseudovasculitis</td>
<td>11</td>
<td>14</td>
<td>0.383</td>
<td>33</td>
<td>23</td>
<td>0.058</td>
</tr>
<tr>
<td>Skin ulcerations</td>
<td>6</td>
<td>8</td>
<td>0.506</td>
<td>13</td>
<td>17</td>
<td>0.254</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>18</td>
<td>0.036*</td>
<td>16</td>
<td>21</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
## Distribution of non-criteria manifestation according to different aPL levels in APS pts

<table>
<thead>
<tr>
<th></th>
<th>Level of aCL IgG</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (%)</td>
<td>Medium (%)</td>
<td>High (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td>7.4</td>
<td>24.8</td>
<td>7.4</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>29.0</td>
<td>11.3</td>
<td>17.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Level of aCL IgM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td>33.3</td>
<td>22.2</td>
<td>14.8</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Skin ulcerations</strong></td>
<td>34.1</td>
<td>15.9</td>
<td>6.8</td>
<td>0.013</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Level of β_2GPI IgG</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.2</td>
<td>25.9</td>
<td>3.7</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.4</td>
<td>14.5</td>
<td>11.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Level of β_2GPI IgM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pseudovasculitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.5</td>
<td>2.5</td>
<td>8.6</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>Skin ulcerations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.5</td>
<td>4.5</td>
<td>11.4</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
## Distribution of pts with PAPS according to aCL-IgG levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Negative %</th>
<th>Low %</th>
<th>Medium %</th>
<th>High %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetations</td>
<td>60.1</td>
<td>26.6</td>
<td>13.3</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Pseudoinfective endocarditis</td>
<td>40.0</td>
<td>60.0</td>
<td>0</td>
<td>0</td>
<td>0.547</td>
</tr>
<tr>
<td>Non stable angina</td>
<td>61.9</td>
<td>28.6</td>
<td>9.5</td>
<td>0</td>
<td>0.588</td>
</tr>
<tr>
<td>Coronary bypass occlusion</td>
<td>50.0</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
<td>0.312</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>81.8</td>
<td>9.1</td>
<td>9.1</td>
<td>0</td>
<td>0.494</td>
</tr>
<tr>
<td>Migraine</td>
<td>65.2</td>
<td>23.9</td>
<td>10.7</td>
<td>0</td>
<td>0.530</td>
</tr>
<tr>
<td>Dementia</td>
<td>76.9</td>
<td>15.4</td>
<td>7.7</td>
<td>0</td>
<td>0.645</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>60.0</td>
<td>20.0</td>
<td>4.0</td>
<td>4.0</td>
<td>0.013*</td>
</tr>
<tr>
<td>Pseudovasculitis</td>
<td>20.0</td>
<td>38.5</td>
<td>7.7</td>
<td>0</td>
<td>0.680</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td>18.7</td>
<td>14.2</td>
<td>7.1</td>
<td>0</td>
<td>0.645</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>56.0</td>
<td>20.0</td>
<td>8.0</td>
<td>16.0</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
## Distribution of pts with PAPS according to aPL levels

<table>
<thead>
<tr>
<th>Level of aCL IgG</th>
<th>N (present)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livedo reticularis</td>
<td>22</td>
<td>22.7%</td>
<td>4.6%</td>
<td>4.6%</td>
<td>0.013</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25</td>
<td>20.0%</td>
<td>8.0%</td>
<td>16.0%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

| Level of β₂GPI IgG | Thrombocytopenia | 25     | 24.0%  | 12.0% | 20.0% | 0.0003 |

| Level of β₂GPI IgM | Migraine | 45     | 41.3%  | 4.3%  | 2.2%  | 0.003  |

Stojanovich L, MD, PhD
## Distribution of pts with SAPS according to aPL levels

<table>
<thead>
<tr>
<th>aPL</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of aCL IgM</strong></td>
<td>N (present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin ulcerations</td>
<td>30</td>
<td>40.0%</td>
<td>20.0%</td>
<td>16.7%</td>
</tr>
<tr>
<td><strong>Level of β₂GPI IgG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>9</td>
<td>44.4%</td>
<td>44.4%</td>
<td>11.1%</td>
</tr>
<tr>
<td><strong>Level of β₂GPI IgM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>9</td>
<td>22.2%</td>
<td>33.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>62</td>
<td>38.7%</td>
<td>3.2%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Pseudovesiculitis</td>
<td>54</td>
<td>39.3%</td>
<td>3.6%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37</td>
<td>21.6%</td>
<td>8.1%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
Methodology

In all patients, clinical observation was performed to reveal the presence of skin manifestations:

- Livedo reticularis
- Skin ulcerations
- Pseudovasculitis
- Digital Gangrene
Skin non-thrombotic manifestations

Stojanovich L, MD, PhD
31% pts had Livedo reticularis
$\beta_2$GPI IgM levels in APS with and without skin ulcerations

p = 0.044

Stojanovich L, MD, PhD
β₂GPI IgM levels in APS with and without pseudovasculitis

Stojanovich L, MD, PhD
Patients with skin ulcerations

% of SLE patients with skin ulcerations

Level of aCL IgM

Stojanovich L, MD, PhD
β₂GPI IgM levels in SLE with and without livedo reticularis

Patients with livedo reticularis

% of SLE patients with livedo reticularis

Level of β₂GPI IgM

Patients with livedo reticularis

Patients without livedo reticularis

p=0.008

Stojanovich L, MD, PhD
Wrapping up

- Our study results showed correlations between skin lesions and various levels of antiphospholipid antibodies.

- Patients with Hughes Sy and high levels of $\beta_2$GPI IgM are more prone to skin ulcerations and pseudovasculitis.

- Pseudovasculitis is more common in patients with high levels of aCL IgM.

- High levels of $\beta_2$GPI IgM may play a predictive role in livedo reticularis in SLE patients /from our registry/.

Stojanovich L, MD, PhD
Results

There was no correlation between non-criteria APS cardiological manifestations and:

- others clinical manifestations of SLE
- cardiovascular risk factors (including diabetes) (p > 0.05)
- SLE activity (SLEDAI) and other parameters

Stojanovich L, MD, PhD
Results

There was a correlation between:

Patients with aCL – IgM and:

- CABG/PTCA \((p=0.026)\)
  coronary artery bypass grafting/ percutaneous coronary artery angioplasty

- Pseudoinfective endocarditis \((p=0.037)\)

Stojanovich L, MD, PhD
Results

There was a correlation between:

Pseudoinfective endocarditis and:

- Patients with aCL - IgM ($p=0.037$)
- Patients without LA ($p=0.014$)
Results

PAPS and SLE patients did not differ among themselves with regard to the occurrence of MI (p = 0.102) and UAP (p = 0.123) unstable angina pectoris (UAP)

Stojanovich L, MD, PhD
Results

Unstable Angina Pectoris (UAP)

Stojanovich L, MD, PhD
Close Association between valvular heart disease and central nervous system manifestations in the antiphospholipid syndrome

Ilan Krause, Shaul Lev, Abigail Fraser, Miri Blank, Margalit Lorber, Ludmilla Stojanovich, Josef Rovensky, Joab Chapman and Yehuda Shoenfeld

488 Patients

Average age:
45.03±13.61 years

81.5% female
18.5% male

Stojanovich L, MD, PhD
Distribution of aPL

- aCL IgG 38.70%
- aCL IgM 53.10%
- B2GPI IgG 34.10%
- B2GPI IgM 41.80%
- LA 53.20%

Stojanovich L, MD, PhD
Prevalence of Valvular Manifestations in %

PAPS
- overall valvular manifestations: 8.70
- PIE: 3.20
- valvular thickening and dysfunction: 5.00

SAPS
- overall valvular manifestations: 29.60
- PIE: 28.20
- valvular thickening and dysfunction: 4.90

*p = 0.0001

*PIE - pseudoinfective endocarditis

Stojanovich L, MD, PhD
Valvular Vegetations on Mitral Valve in Patient with Antiphospholipid Syndrome

Stojanovich L, MD, PhD
**Valvular Manifestations and aPL Type**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aCL IgG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIE</td>
<td>19.5%</td>
<td>10.1%</td>
<td>0.004</td>
</tr>
<tr>
<td>Valvular dysfunction</td>
<td>6.5%</td>
<td>2.0%</td>
<td>0.013</td>
</tr>
</tbody>
</table>

|                  |          |          |        |
| **aCL IgM**      |          |          |        |
| PIE              | 9.1%     | 2.6%     | 0.002  |

*PIE – pseudoinfective endocarditis*
Valvular Manifestations and aPL Titer

- Valvular manifestations in our cohort were significantly related to titers of aCL antibodies.

- The level of aCL IgG ($p=0.005$, Pearson $+0.138$) were in positive correlation with presence of pseudoinfective endocarditis.
Take-home messages

✓ The Serbian National APS Registry allowed us to ascertain a significantly increased incidence of endocarditis development in APS patients with aCL-IgM.

✓ Presence of LA was significantly connected to lower incidence of pseudoinfective endocarditis.

✓ Patients with APS had higher incidence of CABG: coronary artery bypass grafting.
Does the presence of secondary antiphospholipid syndrome in patients with systemic lupus erythematosides accelerate carotid arteries intima-media thickness changes?

Aleksandra Djokovic, Lj. Stojanovich, N. Stanisavljevic, V. Bisenic, S. Radovanovic, I. Soldatovic &
Neurological Manifestations

- Chorea: 1
- Transient ischemic attack: 38
- Cerebellar ataxia: 8
- Epilepsy: 34
- Migraine: 89
- Stroke: 91
- Cerebral vein thrombosis: 3
- Acute ischemic encephalopathy: 3
- Transverse myelopathie: 3
- Cerebral vein sinus thrombosis: 3
- Multi-infarct dementia: 7
- Transient global amnesia: 5

Stojanovich L, MD, PhD
TIMETABLE

May 5th, 2013
08:00-08:30 - Registration
08:30-9:00 - Entrance test
09:00-10:00 - Prof. Hughes GV
Hughes syndrome (the antiphospholipid syndrome): a disease of our time
10:00-11:00 - Prof. Shoenfeld Y
Infections and vaccines in the etiology of antiphospholipid syndrome
11:00-12:00 - Prof. Khamashta MA
Management of antiphospholipid syndrome
12:00-12:30 - Break
12:30-13:30 - Prof. Cervera R
APS: Lessons from the Euro-Phospholipid Project
13:30-14:30 - Prof. Alekberova Z
The problem of APS in the Russian Federation
14:30-15:30 - Prof. Stevanovic L.
Lessons from the Serbian Antiphospholipid Project

May 6th, 2013
09:00-10:00 - dr N. Stanisavljević, mr sc med
The role of endothelial and haematological factors for the development of thrombosis in antiphospholipid syndrome
10:00-11:00 - dr B. Pazin, mr sc med
The role of antiphospholipid antibodies in pregnancy outcomes
11:00-12:00 - dr A. Djaković, mr sc med
Cardiological manifestations of antiphospholipid syndrome
12:00-12:30 - Break
12:30-13:30 - dr M. Kanić, dr sc med
Pulmonary manifestations in APS
13:30-14:30 - dr B. Trninić
Skin manifestations in APS
14:00-14:30 - Doc. J. Šaponjski, dr sc med
New approaches for early diagnosis of occlusive disease in APS
14:30-15:00 - Doc. S. Jelić, dr sc med
Metabolic syndrome in APS patients
15:00-16:00 - Exit test and Congress evaluation
16:00 - Certificate distribution

Bezanijska Kosa
University Medical Center
Belgrade University, Serbia
presents
INTERNATIONAL CONGRESS
ANTIPHOSPHOLIPID SYNDROME
(HUGHES SYNDROME)
IMPORTANCE OF MULTIDISCIPLINARY APPROACHES
30 YEARS SINCE DEFINITION

AMPHITHEATER
"BEZANIJSKA KOSA" BELGRADE
May 5-6, 2013
METHODOLOGY

electrophysiological tests

- Electroencephalography (EEG)
- Evoked potentials (EP)
- Electromyoneurography (EMNG)
METHODOLOGY

MRI Findings

Multiple microinfarctions: 41.4%
Brain atrophy: 18.9%
Large infarction: 10.3%
Increased gray matter density: 5.3%
More than one abnormal finding: 20.7%

Stojanovich L, MD, PhD
Frequency of Neurology Manifestations in PAPS patients

Thrombotic neurology manifestations
- TIA (N=31)
- CVI (N=35)

Non-thrombotic neurology manifestations
- epilepsy (N=11)
- dementia (N=13)
- migraine (N=46)

Stojanovich L, MD, PhD
Frequency of Neurology Manifestations in SLE patients

Thrombotic neurology manifestations
- TIA (N=26)
- CVI (N=28)

Non-thrombotic neurology manifestations
- epilepsy (N=16)
- migraine (N=33)
- chorea (N=9)
- dementia (N=14)

Stojanovich L, MD, PhD
# Comparison of frequency of neurological manifestations between PAPS and SAPS pts

<table>
<thead>
<tr>
<th></th>
<th>PAPS</th>
<th>SAPS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack</td>
<td>21.6%</td>
<td>27%</td>
<td>0.237</td>
</tr>
<tr>
<td>Chorea</td>
<td>0%</td>
<td>7.8%</td>
<td>0.000*</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5%</td>
<td>19.1%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Migraine</td>
<td>28%</td>
<td>34.8%</td>
<td>0.026*</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>1.4%</td>
<td>1.7%</td>
<td>0.769</td>
</tr>
<tr>
<td>Acute ischemic encephalopathy</td>
<td>1.4%</td>
<td>4.3%</td>
<td>0.305</td>
</tr>
<tr>
<td>Anterior spinal artery syndrome</td>
<td>0%</td>
<td>0.9%</td>
<td>0.550</td>
</tr>
<tr>
<td>Cehalea</td>
<td>24%</td>
<td>13.9%</td>
<td>0.031*</td>
</tr>
<tr>
<td>Vertigo</td>
<td>8.3%</td>
<td>3.5%</td>
<td>0.093</td>
</tr>
<tr>
<td>Sy depressivum</td>
<td>3.7%</td>
<td>0%</td>
<td>0.037*</td>
</tr>
</tbody>
</table>

Stojanovich L, MD, PhD
Results

There was statistically significant correlation between

• epilepsy and high levels of aCL IgG (p=0.021) and IgM (p=0.032)
• dementia and medium levels of β2GPI IgG (p=0.047)
• TIA and medium levels of aCL IgG (p=0.007)

Stojanovich L, MD, PhD
There was statistically significant correlation between:

- **TIA** and high levels of $\beta_2GPI$ IgM ($p=0.0137$)

- **migraine** showed negative correlation with high levels of $\beta_2GPI$ IgM ($p=0.003$)

Stojanovich L, MD, PhD
Results
SLE patients

There is statistically significant correlation between chorea and

- medium aCL IgG (p = 0.003)
- β2GPI IgM titers (p = 0.047)

Stojanovich L, MD, PhD
Patients with epilepsy

% of APS patients with epilepsy

p = 0.021

Stojanovich L, MD, PhD
aCL IgM levels in APS with and without epilepsy

Stojanovich L, MD, PhD
$\beta_2$GPI IgM levels in PAPS with and without migraine

Stojanovich L, MD, PhD
Patients with chorea: 30.6% with low level of aCL IgG

Patients without chorea: 11.1% with low level of aCL IgG

% of SLE patients with chorea

% of SLE patients without chorea

p = 0.003

Level of aCL IgG

Patients with chorea
Patients without chorea

Stojanovich L, MD, PhD
Correlation between neurological and cardiac manifestations in PAPS

<table>
<thead>
<tr>
<th>PAPS patients</th>
<th>Transient ischemic attack</th>
<th>Epilepsy</th>
<th>Transient global amnesia</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>p</td>
<td>-</td>
</tr>
<tr>
<td>Non stable angina pectoris</td>
<td>158</td>
<td>36</td>
<td>0.002*</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>11</td>
<td>0.006*</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>p</td>
<td>193</td>
</tr>
<tr>
<td></td>
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<td>22</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>-</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.002*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.285</td>
<td>0.002*</td>
</tr>
<tr>
<td>Valve vegetations</td>
<td>-</td>
<td>160</td>
<td>40</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>0.064</td>
<td>17</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>0.01*</td>
<td>15</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.285</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.002*</td>
<td>5</td>
</tr>
</tbody>
</table>

Association between non-thrombotic neurological and cardiac manifestations in patients with antiphospholipid syndrome

L. Stojanovich¹, M. Kontic², D. Smiljanic³, A. Djokovic⁴, B. Stamenkovic⁴ D. Marisavljevic¹,⁵

¹Internal Medicine, “Bezanijska Kosa”, University Medical Centre, Belgrade, Serbia; ²Clinic for Pulmonology, Clinical Center of Serbia, University in Belgrade, Serbia; ³Department of Neurology, Clinical-Hospital Centre (KBC) Zemun, Belgrade, Serbia; ⁴Rheumatology Clinic, Institute Niska Banja, Medical Faculty, University of Nis; ⁵Faculty of Medicine, University of Belgrade, Belgrade, Serbia.
**Correlation between neurological and cardiac manifestations in SAPS**

<table>
<thead>
<tr>
<th>SAPS patients</th>
<th>Transient ischemic attack</th>
<th>Acute ischemic encephalopathy</th>
<th>Vertigo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not present</td>
<td>present</td>
<td>p</td>
</tr>
<tr>
<td>Non stable angina pectoris</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not present</td>
<td>80</td>
<td>24</td>
<td>0.004*</td>
</tr>
<tr>
<td>present</td>
<td>4</td>
<td>7</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

**International Conference on Cardiology (Cardiology’11) (part of Summer WORLDMED)**
Prague, Czech Republic, September 26-28, 2011

Plenary Lecture 3:

**Non-Thrombotic Neurological and Cardiac Manifestations in Antiphospholipid Syndrome**
by Prof. Ljudmila Stojanovich, Belgrade University, SERBIA.
Take-home messages

✓ APS patients can be presented with a wide variety of nontrombotic manifestations.

✓ The certain aPL type and level correlated with non-criteria APS manifestations, suggesting their predictive or protective role.

✓ Our study confirmed that presence of cardiac manifestations may be a risk factor for several types of CNS involvement in APS.

Stojanovich L, MD, PhD
Take-home messages

✓ The number of aPL do not play a role in non-criteria APS manifestations.

✓ Not only high, but also medium and low levels of aPL, correlate with the onset of non-criteria APS manifestations, including cardiological, neurological, and dermatological.

Stojanovich L, MD, PhD
Association between systemic non-criteria APS manifestations and antibody type and level: results from the Serbian national cohort study

L. Stojanovich¹, M. Kontic², A. Djokovic¹, D. Marisavljevic¹, N. Ilijevski³, N. Stanisavljevic¹, Z. Mikovic⁴, M. Petkovic¹, V. Kovcin¹

¹Internal Medicine, “Bezanijska Kosa” University Medical Centre, Belgrade; ²Clinic for Pulmonology, Clinical Centre of Serbia, University of Belgrade, Belgrade; ³Institute of Cardiovascular Disease “Dedinje”, Belgrade; ⁴High Risk Pregnancy Department, Obstetrics and Gynaecology University Clinic “Narodni Front”, Belgrade, Serbia.