Antiphospholipid Syndrome

Sheila Knupp Feitosa de Oliveira
Universidade Federal do Rio de Janeiro

PRES-LA
Outline

1. Classification criteria
2. Registries of Pediatric APS
   - Primary and Secondary APS
   - Catastrophic APS
   - Neonatal APS
3. Treatment
1. Classification criteria
Case report

• Girl, 10 years old
• Pain in the right lower limb and calf swelling

• Physical examination revealed swelling, heat, redness of the calf.

• Doppler ultrasonography disclosed thrombosis in her right iliac and femoral veins.

• Family history negative for coagulation disorders.
Case report - Labs

- WBC=9.5, Hgb= 10g/dL, platelet = 120,000
- ESR = 40 mm/h, CRP = 3 mg/dL
- PT=65%, aPTT= 64 sec (normal 32 sec)
- Liver and renal tests normal
- Rheumatoid factor negative
- Complement normal
- ANA positive (1:160), a-DNA negative, a-Sm negative
- aCL (GPL)= 66 (normal=20), LA positive
- Protein C, protein S, antithrombin III, homocysteine levels within normal limits
- Factor V Leiden mutation was absent

DVT + positive aPL → APS
Antiphospholipid syndrome (APS) is a multisystemic autoimmune condition characterized by:

1 - vascular thrombosis and/or pregnancy loss associated with

2- persistently positive antiphospholipid antibodies (aPL)
1- Vascular Thrombosis
• Arterial, venous or small vessel thrombosis in any tissue or organ.
• Thrombosis confirmed by appropriate imaging studies or histopathology.
• Thrombosis without evidence of vessel wall inflammation on pathology.

2- Pregnancy Morbidity
• Death of a normal fetus at or beyond the 10th gestational week. Normal morphology should be documented by ultrasound or direct exam.
• Premature birth of a normal neonate before the 34th gestational week.
• Eclampsia or severe pre-eclampsia.
• Placental insufficiency.
• Three or more unexplained consecutive spontaneous fetal losses before the 10th gestational week.
• Exclusion of maternal hormonal and anatomic conditions and parental chromosomal causes.

Vascular thrombosis

- One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ.

- Thrombosis must be confirmed by objective validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology).

- For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
<table>
<thead>
<tr>
<th>Venous thrombosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pulmonary thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Brain</td>
<td>Cerebral venous sinus thrombosis</td>
</tr>
<tr>
<td>Liver</td>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinal vein thrombosis</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Large veins</td>
<td>Superior or inferior vena cava thrombosis</td>
</tr>
<tr>
<td>Other</td>
<td>Renal, mesenteric, hepatic, retinal veins</td>
</tr>
</tbody>
</table>
## Arterial thrombosis/small vessels

<table>
<thead>
<tr>
<th>Organ</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Stroke, transient ischemic attacks</td>
</tr>
<tr>
<td>Limbs</td>
<td>Ischemia, gangrene</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Large vessels</td>
<td>Renal artery thrombosis</td>
</tr>
<tr>
<td>Small vessels</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>Heart</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatic infarction</td>
</tr>
<tr>
<td>Gut</td>
<td>Mesenteric artery thrombosis</td>
</tr>
<tr>
<td>Other</td>
<td>Skin, retinal, hepatic, ...</td>
</tr>
</tbody>
</table>
Imaging and histology studies

**Imaging**
- USG + Doppler for DVT
- CT or MRI for strokes
- Angio-CT or angio-MRI if clinical findings suggest medium or large vessel disease
- ECHO or cardiac MRI for intracardiac thrombi

**Histology**
- Thrombotic occlusion of any kind of vessel
- No signs of perivascular inflammation
Laboratory criteria

Antiphospholipid antibodies

• **Anticardiolipin (aCL) antibody** (IgG, or IgM isotype) in serum or plasma at medium-high titer (> 40 GPL or MPL) measured by standardized ELISA assay on two or more occasions, at least **12 weeks apart**.

• **Anti-β2-glycoprotein-I (aβ2GP1) antibody** (IgG, or IgM isotype) in serum or plasma (> 99th percentile) measured by standardized ELISA on two or more occasions, at least **12 weeks apart**.

• **Lupus anticoagulant (LA)** demonstrated in plasma on two or more occasions, at least **12 weeks apart** detected according to international standards.

Positive + persistent + titer

Antiphospholipid Antibodies (aPL)

Heterogeneous group of autoantibodies directed against phospholipid-binding proteins (cofactors)

- Anionic phospholipids
  - Cardiolipin
  - Phosphatidylserine
  - Phosphatidylinositol
  - Phosphatidylglycerol
  - Phosphatidylethanolamine

- Phospholipid binding proteins
  - β2 glycoprotein I
  - Prothrombin
  - Protein C
  - Protein S
  - Annexin V
  - Low & high MW kininogen
Laboratory criteria (aPL)

**Anticardiolipina (aCL)**
- IgG (GPL)
- IgM (MPL)
- **ELISA**
  - ➢ 40 GPL or MPL
  - ➢ >99<sup>th</sup> percentile

**anti-β2GP1 (aβ2GP1)**
- IgG
- IgM
- **ELISA**
  - >99% percentile

**Lupus anticoagulante (LA)**
- **Clottin test**
  - • Prolonged aPTT
  - • Dilute Russell viper venom time (dRVVT)
  - • Kaolin clotting time

Prior the development of aPL tests → False positive test for syphilis
Specificity of aPL

- **Type:** LA is the best predictor of aPL-related thrombosis

- **Titer:** The risk for thrombosis increases with the titer of aPL

- **Number:** The number of positive aPL correlates with a high risk for thrombosis:
  - Triple positive > double positive > single positive

Neville C. Thromb Haemost 2003; 90:108
Positive aPL: What to do?

Adults

<table>
<thead>
<tr>
<th>522 Blood donors</th>
<th>baseline</th>
<th>After 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPL</td>
<td>6.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>MPL</td>
<td>9.4%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

The tests should be repeated after at least 12 weeks. Transient elevations are common.

aPL Abs Profile in Healthy Children

- aCL is positive in 3 to 28%
- aβ2GP1 is positive in 3 to 7%
  Low risk of thrombosis

- Bacterial infection
- Viral infection
- Vaccination
  Triggers may induce transitory aPL positivity

**aPL Abs in Childhood JSLE and JIA**

<table>
<thead>
<tr>
<th></th>
<th>JSLE</th>
<th>JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL</td>
<td>44 %</td>
<td>7-53 %</td>
</tr>
<tr>
<td>aβ2GP1</td>
<td>40 %</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>LA</td>
<td>22 %</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

aPL in SLE are more specific and more frequent. aPL in JIA is less frequent and not related to thrombotic events.

Avcin T. Lupus 2007, 16(8):627

Caporali R. ARD 1991, 50(9):599-601
Southwood TR. ARD 1990, 49(12):968-72
Non-criteria clinical manifestations can suggest the diagnosis and precede later vascular thrombosis.
Hematologic manifestations

- Thrombocytopenia
  - 50,000 to 140,000
  - < 50.00 – bleeding
  - Severe: C-APS?

- Microangiopathic hemolytic anemia

- Bleeding episodes due to antibodies to prothrombin
“Criteria and Non-criteria" manifestations of APS

Cutaneous manifestations

Livedo reticularis
Livedo racemosa
Raynaud phenomenon
Pulmonary manifestations of APS

- Pulmonary thromboembolic disease
- Pulmonary arterial thrombosis
- Pulmonary microthrombosis
- Pulmonary hypertension
- Acute respiratory distress syndrome (ARDS)
- Diffuse alveolar hemorrhage
Renal manifestations of APS

- Thrombosis at any site
- Flank pain, proteinuria – check for aPL
- Urine analysis – proteinuria, hematuria
- Ischemic mesangiolysis, vessel hyperplasia
- Acute renal failure
Cardiovascular manifestations of APS

- Valvular thickening
- Mitral valves nodules
- Nonbacterial vegetations
- Mitral and aortic regurgitation
- Pericardial effusion
- Cardiomyopathy
- Ischemic heart disease
- Intracardiac thrombi
“Non-criteria” manifestations of APS

Neurological non-thrombotic

- **Cognitive deficit**
  - Subtle findings
  - Permanent and profound cognitive functioning

- **White matter lesions**
  - MRI suggestive of vasculopathy (high intensity lesions)

- **Other manifestations**
  - Epilepsia
  - Chorea and hemiballismus
  - Transverse myelopathy
  - Sensorioneural hearing loss
  - Migraine

Avcin T. Pediatrics 2008, 122(5)
Non-criteria lab manifestations of APS

Negative aPL and strong suspicion of aCL

• Low titers of aCL (GPL or MPL): 20 - 39 units

• Test for additional IgA aPL
  – IgA aCL
  – IgA anti- β2GP1

• Test for another “non-criteria” aPL (prothrombin, phosphatidylserine, phosphatidylinositol)
  – Not well standardized
  – Sensitivity?
  – Specificity?
  – Clinical significance?

• Test for heritable thrombophilias
  • Differential diagnosis and additional risk factor in patients with APS
Inherited thrombophilia

- Factor V Leiden – mutation G1691A
- Prothrombin – mutation G20210A
- Methylene tetrahydrofolate reductase – mutation C677T
- Antithrombin (AT)
- Protein C
- Protein S

A patient with APS can have another risk for thrombosis.
Additional risk factor for thrombosis

Acquired risk factors for thrombosis

- Central venous catheter
- Surgery, especially orthopedic
- Trauma
- Immobilization
- Malignancy
- Oral contraceptives
- Hormone replacement therapy
- Myeloproliferative disorders
- Nephrotic syndrome

A patient with APS can have another risk for thrombosis.
Clinical Spectrum of aPL +

1. aPL positive without clinical events

2. aPL positive with non-thrombotic manifestation

3. APS diagnosis (vascular thrombosis + positive aPL)
   - Primary APS - isolated clinical entity (primary APS)
   - Secondary APS - associated with an underlying systemic disease
   - Catastrophic APS
   - Neonatal APS
2. Registries of Pediatric APS

- Primary and Secondary APS
- Catastrophic APS (CAPS)
- Neonatal APS
121 patients with APS from 14 countries

– **Age** < 18 years

– **Inclusion criteria:**
  • Meet the preliminary criteria for classification of APS
    – a thrombosis vascular
    – a positive aPL, 2 times in more than 12 wk

– **Exclusion criteria:**
  • infants born to mother with APS
  • Infant with congenital thrombophilia
Pediatric APS Registry

- **Age:** 10.7 yr (range: 1.0 – 17.9yr)

- **Gender:** 1.2: 1 (65 girls and 56 boys)
  
  adults: 5:1

- **Primary APS:** 49.5%
  
  adults: 53 -57%

- **Secondary APS -** 50.5%
  
  83% had SLE or lupus-like disease
  52% had thrombosis before or at the time of SLE diagnosis.

Avcin T. Pediatrics 2008, 122 (5)
Multiple positivity of aPL in pediatric APS patients

- **Triple positive**: 33% (14/42)
- **Double positive**: 48% (20/42)
- **Single positive**: 19% (8/42)

T Avcin. Pediatrics, 2008, 122
Laboratory - aPL

- aCL: 81%
- aβ2GP1: 67%
- LA: 72%

Inherited risk factors

13/29 patients (45%)

- MTHFR C677T polymorphism (6)
- Factor V Leiden (3)
- Protein S deficiency (3)
- Protein C deficiency (2)
- Prothrombin G20210A heterozygosity (1)
- Antithrombin deficiency (1)

Acquired prothrombotic risk factors (7/16)

- Autoimmune disease (4)
- Immobilization (2)
- Infectious disease (2)
Spectrum of trombotic manifestations

- Venous thrombosis ........................................60%
- Arterial thrombosis ........................................32%
- Small vessels thrombosis ...............................6%
- Arterial and venous thrombosis .................2%
Ped-APS Registry

Spectrum of clinical manifestation
Non-trombotic events

- Evans syndrome
- Cytopenia
- Livedo reticularis
- Raynaud phenomenon
- Neurological non-thrombotic — Migraine, headache and chorea.

Hematologic = 38%
Skin = 18%
Neuro non-thrombotic 16%
Ped-APS Registry

<table>
<thead>
<tr>
<th></th>
<th>Primary APS 49,5%</th>
<th>Secondary APS 50,5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age</td>
<td>8,7 ± 5,3 yr</td>
<td>12,8 ± 3,3 yr</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Stroke</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

Avcin T. Pediatrics 2008, 122
Ped-APS Registry

Follow-up: 6.1 years

• 19% developed recurrent thrombosis

• 5% had suggestive catastrophic APS

• 7% died mainly due to thrombotic complication
# APS (children vs adults)

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male</td>
<td>1,2 or 1.5 : 1</td>
<td>5: 1</td>
</tr>
<tr>
<td>Primary APS → Secondary APS</td>
<td>28% (4/14)</td>
<td>13%</td>
</tr>
<tr>
<td>LA frequency</td>
<td>72%</td>
<td>40-54%</td>
</tr>
<tr>
<td>Other prothrombotic risk factors</td>
<td>Inherited</td>
<td>Acquired</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>32%</td>
<td>21%</td>
</tr>
<tr>
<td>Recurrences</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>Association with malignancy</td>
<td>rare</td>
<td></td>
</tr>
</tbody>
</table>

Avcin T. pPdiatrics 2008, 122(5)
Classification criteria for C-APS

1. Evidence of involvement of 3 or more organs, systems or tissues

2. Development of manifestations occurs simultaneously or within a week of each other

3. Confirmation by histopathology of small-vessel occlusion in at least 1 organ or tissue

4. Laboratory confirmation of the presence of aPL

Definite CAPS = 4 criteria +

Probable CAPS = 3 criteria
• 2: > 1 wk but less 1 month

Asherson RA. Lupus 2003
Registry - Pediatric C-APS

45 patients (2014)

- Clinical, laboratory features, treatments and outcome (= adults).

- Infection is a frequent precipitating factor in children (60.9% vs 26.8% in adults).

- Most of patients had primary APS (68.9%) and 28.9% had CAPS with SLE.

- CAPS was the first manifestation of APS in 86% of pediatric patients (adults = 45%).

- Trend of lower mortality in children (26% vs 40%).
Newborn represent the largest childhood group to develop thromboembolic events.

• They have some hemostatic differences
  – Decrease thrombin-plasminogen
  – Decrease coagulation factors
  – Decrease platelet aggregation
  – Decrease protein S, protein C, anti-thrombin III
  – Relative vitamin K deficiency

• In the 2nd year until puberty, coagulation factor concentrations change and favor an anticoagulant milieu

• Acquired risk factors in neonatal period
  – arterial or venous access devices
Babies born to mothers with APS

- **Rare**: 16 cases (pre and post-partum in 20 yr)
- **Thrombosis**: mostly arterial (13/16)
- **Positive aPL**: 11/12 had the same aPL isotype as their mother
- **Additional risk factors in 9/14**: preeclampsia, intrauterine growth restriction, asphyxia, sepsis, catheter, congenital thrombophilia
- **No additional risk factor in 5/14**: mother was not treated with heparin or aspirin

Boffa MC. Lupus 2007, 18(8):634-41
Follow-up of babies born to mothers with antiphospholipid syndrome: Preliminary data from the European neonatal registry

Motta M, Boffa MC, Tincani A, Avvicinato T, De Carolis S, Lachassinne E. Neonatology and Neonatal Intensive Care Unit, Children’s Hospital of Brescia, Italy; Laboratoire d’Hematologie, Hopital Jean-Verdier, Bondy, France; Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy; Allergology, Rheumatology and Clinical Immunology, University Children’s Hospital Ljubljana, University Medical Center, Ljubljana, Slovenia; Obstetrics and Gynecology.

- European Registry (2003 – 2013)
- 141 babies
- Preterm – 16%
- Low birth weight = 17%
- Placenta transfer of aPL: aCL (20%), aB2GP1 (25%), LA (43%)
- No evidence of perinatal thrombosis
- Follow-up – 24 months: behaviour abnormalities in 4

Mekinian A. ARD 2013, 72(2): 217
Neuropsychological outcome
Children born to mothers with APS

• **Learning disabilities** $\rightarrow$ 15 to 20%

• **Behavior abnormalities** $\rightarrow$ 4/27 patients (15% of the Neonatal APS registry)
  – 4 children with behavioral abnormalities, all had negative aPL at birth, mother were treated with heparin.
    - Autism
    - Hyperactivity
    - Language delay
    - Psychomotor delay and axial hypotonia

**Limitation** $\rightarrow$ No comparison to healthy controls

Brewer JÁ. J Perinat med 1999, 27(3):183
Mekinian A. ARD 2013, 72(2): 217
Nalli C. Lupus, 2014, 23(6):507-17
De Novo Neonatal APS
(newborn aPL positive and mother aPL negative)

- Review of literature
- 33 cases of thrombosis
  - 11 with postive aPL
  - 11/33 newborn with aPL positive and mother aPL negative – de novo neonatal APS
  - Most with additional acquired thrombotic risk factor (infection, central vein catheter, dehydration, gestational diabetes, congenital thrombophilias)

Neonatal APS
(newborn aPL positive and mother aPL negative)

• 62 cases of perinatal arterial ischemic stroke or cerebral sinus vein thrombosis
  – 49/62 had aPL checked

  • 12 with persistently elevated aPL
    – 10/12 - aPL decreased to normal range within 2,5 yr
    – None showed recurrent thrombosis

  – Although fulfilling criteria of APS these patients can represent a subgroup which the disease:
    • is transitory
    • does not recur
    • do not require anticoagulation unless other risks factors are present

Berkun Y. Lupus 2014, 23 (10):986
3. Treatment
How to treat

• **There are no recommendations specific for children.**

• **Medications**
  – Heparin
  – Warfarin
  – Aspirin
Asymptomatic positive aPL (adults)

• Prophylactic treatment is controversial.

• Thrombotic events in this population are unlikely in the absence of additional risk factors for thrombosis.

• Heparin (LMWH) in high risk situations:
  – surgery
  – long-lasting immobilization

Ruiz-Irastorza G. Lupus 2011; 20:206
SLE and positive aPL

- Consider SLE as a prothrombotic condition
  - Retrospective studies suggest that children and adults with SLE with aPL(+) have a 50% chance of suffering a thrombotic event within 10 year.

- Consider the type and the titer of aPL: LA vs aCL

- Aspirin is recommended (3-5 mg/kg/day)

- Hydroxychloroquine appears protective against development of thrombosis.

Acute thrombotic event

Heparin

- LMWH – low molecular weight heparin
- Unfractionated heparin
Acute thrombotic event

**Warfarin**
- It is the standard of care for the chronic management of patients with APS.
- INR should be maintained between 2 and 3 to prevent recurrent events.
- It is contraindicated in pregnancy.
- Lifelong anticoagulation therapy is recommended in definite APS.

**Aspirin (antiplatelet agent)**
- 3 to 5 mg/kg/d
- Questionable benefit for the prevention of thrombotic event in patients with a previous thrombotic event
If thrombotic events recur during treatment with warfarin (and INR= 2 to 3), the treatment alternatives include:

– Add: low-dose aspirin, heparin (LMWH), or hydroxichloroquine

– Increasing the target INR (3.1 to 4.0)
Catastrophic Antiphospholipid (C-APS)

1. **Treat infection**

2. **Treat the thrombotic event - Anticoagulants**
   - Heparin in the acute phase
   - Warfarin when hemodinamically stable and without evidence of recurrent thrombi or active bleeding

3. **Supress cytokine cascade**
   - **Systemic glucocorticoids**
     - Methylprednisolone – 30 mg/kg/dia – 3 days
     - Prednisone – 1mg/Kg/dia
   - **Plasma exchange** (with or thout IVIG)
     - 5 consecutive days
   - **Intravenous immune globulin (IVIG)**
     - 400 mg/kg/d – 5 days - started in the last day of plasma exchange

Resistant CAPS

- **Rituximab**
  - B-cell depleting anti-CD20
  - 1,000 mg IV for 2 doses in 2 weeks

- **Eculizumab**
  - Monoclonal antibody against C5
Thank you!