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

Outline

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

Definition

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)

clinical + laboratory

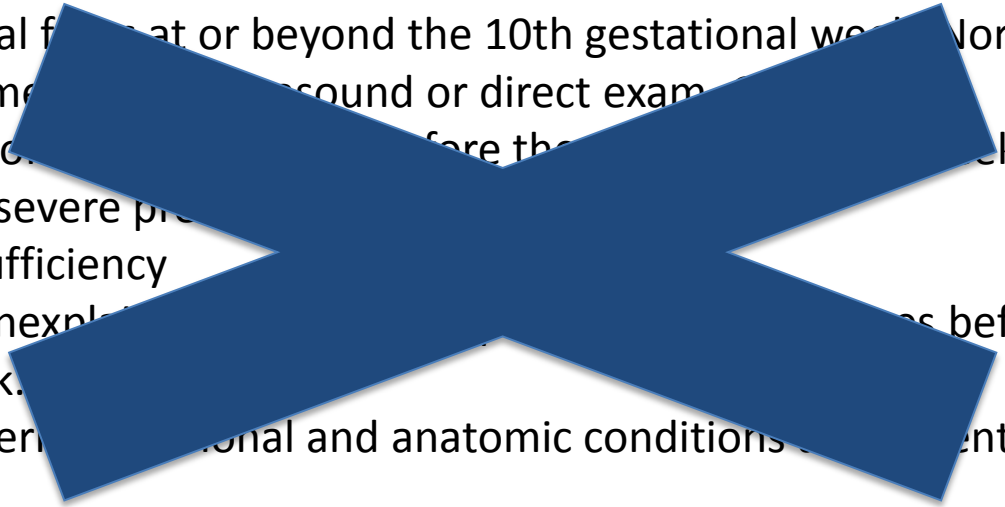
Clinical criteria (2006)

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 f at or beyond the 10th gestational we Normal morphology should be docume ound or direct exam
- Premature birth o ore th ek
  - Eclampsia or severe pr
  - Placental insufficiency
- Three or more unexpl s before the 10th gestational week.
- Exclusion of mater onal and anatomic conditions ental chromosomal causes



J Thromb Haemost. 2006;4(2):295–306.

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**).

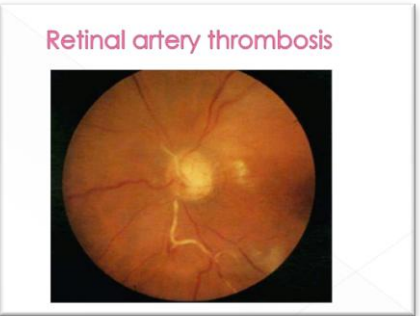
- For histopathologic confirmation, thrombosis should be present **without significant evidence of inflammation in the vessel wall**.

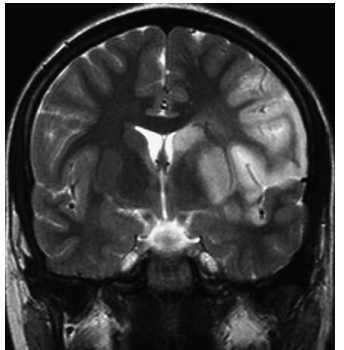
Venous thrombosis

Limbs	Deep vein thrombosis
Lungs	Pulmonary thromboembolism Pulmonary hypertension
Brain	Cerebral venous sinus thrombosis
Liver	Budd-Chiari syndrome
Eyes	Retinal vein thrombosis
Adrenal glands	Addison's disease
Large veins	Superior or inferior vena cava thrombosis
Other	Renal, mesenteric, hepatic, retinal veins

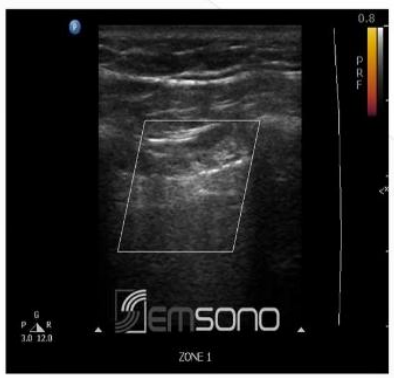
Arterial thrombosis/small vessels

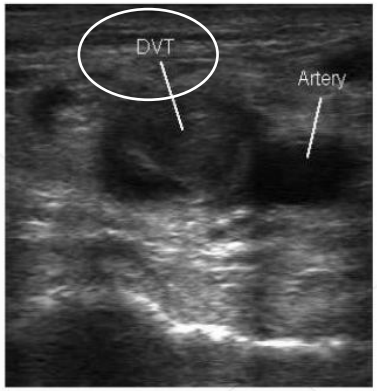
Brain	Stroke, transient ischemic attacks
Limbs	Ischemia, gangrene
Kidney	
Large vessels	Renal artery thrombosis
Small vessels	Thrombotic microangiopathy
Heart	Myocardial infarction
Liver	Hepatic infarction
Gut	Mesenteric artery thrombosis
Other	Skin, retinal, hepatic,...





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 orplasma (> 99th percentile) measured by standardized ELISA on two or more occasions, at least 12 weeks apart.

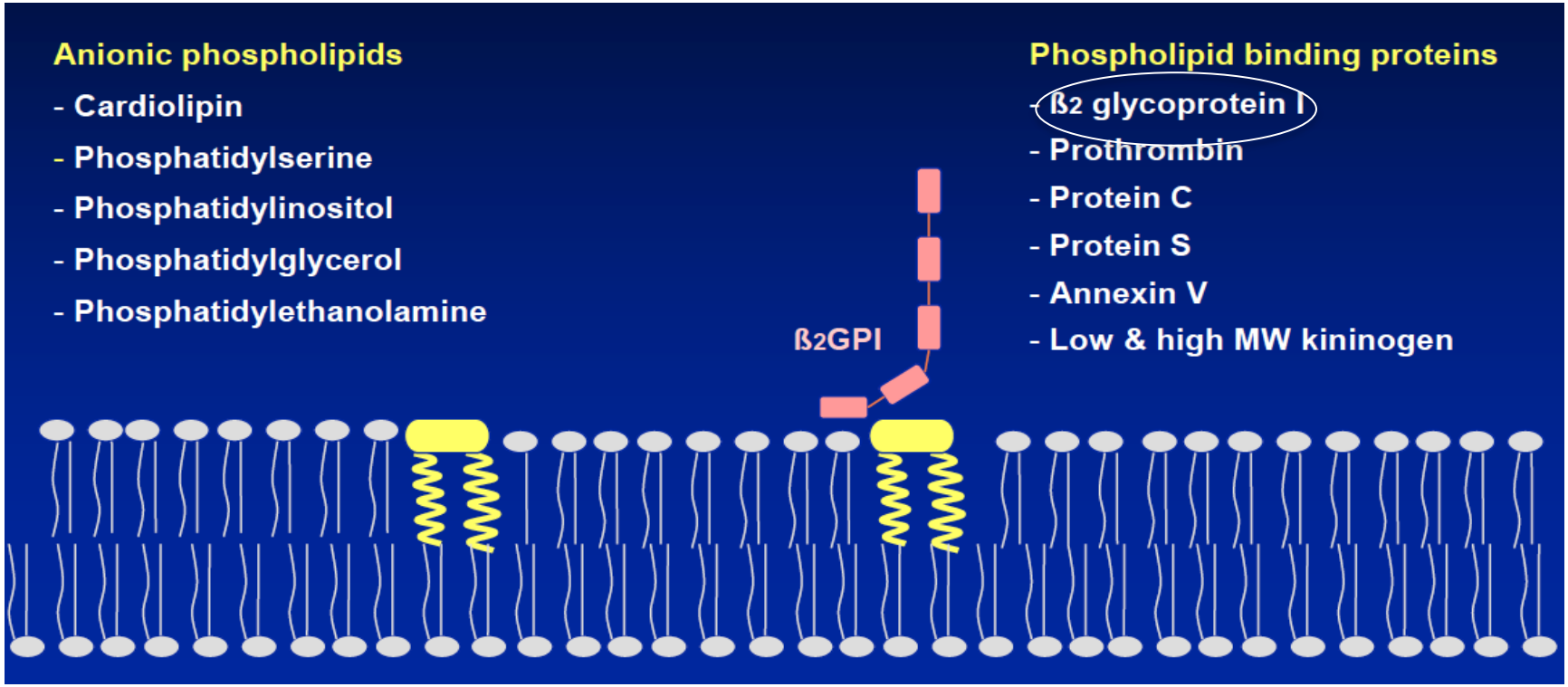
- **Lupus anticoagulant (LA)** demonstrated in plasma on two or more occasions, at least 12 weeks apart detected according to international standards.

Positive + persistent + titer

J Thromb Haemost. 2006;4(2):295–306.

Antiphospholipid Antibodies (aPL)

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



Laboratory criteria (aPL)

Anticardiolipina aCL	anti-β2GP1 aβ2GP1	Lupus anticoagulante
IgG (GPL) IgM (MPL)	IgG IgM	LA
ELISA	**ELISA**	**Clottin test**
➢ 40 GPL or MPL ➢ >99th percentile)	>99% percentile	• 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

522 Blood donors	baseline	After 9 months
GPL	6,5%	1,4%
MPL	9,4%	1,3%

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

Vila P. Thromb Haemost 1994; 72:209

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

Rapizzi, E et al. Journal of Clinical Laboratory Analysis. 14(3):87-90, 2000
Avcin T et al. Rheumatology 40:565. 2001
Male C. J Pediatr 1999, 134(2):199-205

aPL Abs in Childhood JSLE and JIA

JSLE

- aCL 44 %
- aβ2GP1 40 %
- LA 22 %

JIA

- aCL 7-53 %
- aβ2GP1 < 5%
- LA < 5%

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

“ Criteria and Non-criteria" clinical manifestations

- Hematologic
- Cutaneous
- Pulmonary
- Renal
- Cardiovasvular
- Neurological

Non-criteria clinical manifestations can suggest the diagnosis and precede later vascular thrombosis.

“ Criteria and Non-criteria" manifestations of APS

Hematologic manifestations

- Thrombocytopenia
  - 50.000 to 140.000
  - < 50.00 – bleeding
  - Severe: C-APS?

Thrombocytopenia does not Preclude the occurrence of thrombotic complications of APS

- Microangiopathic hemolytic anemia

- Bleeding episodes due to antibodies to prothrombin

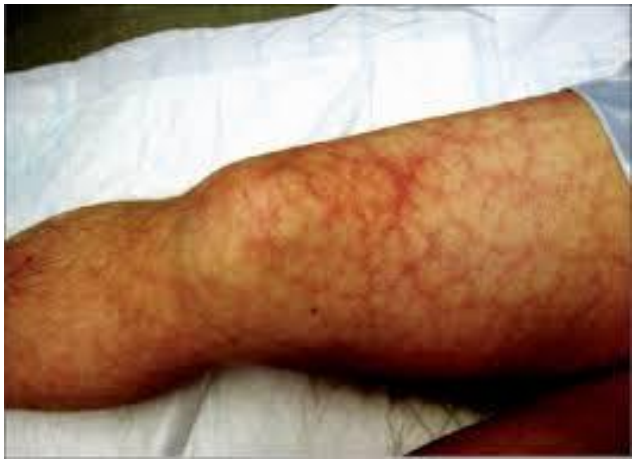
“ Criteria and Non-criteria" manifestations of APS

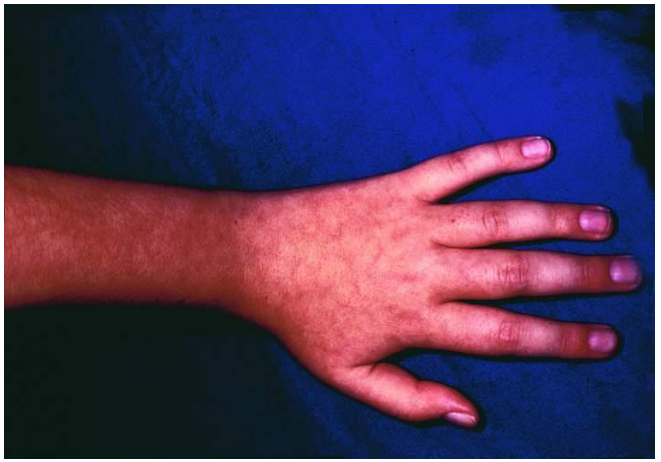
Cutaneous manifestations

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

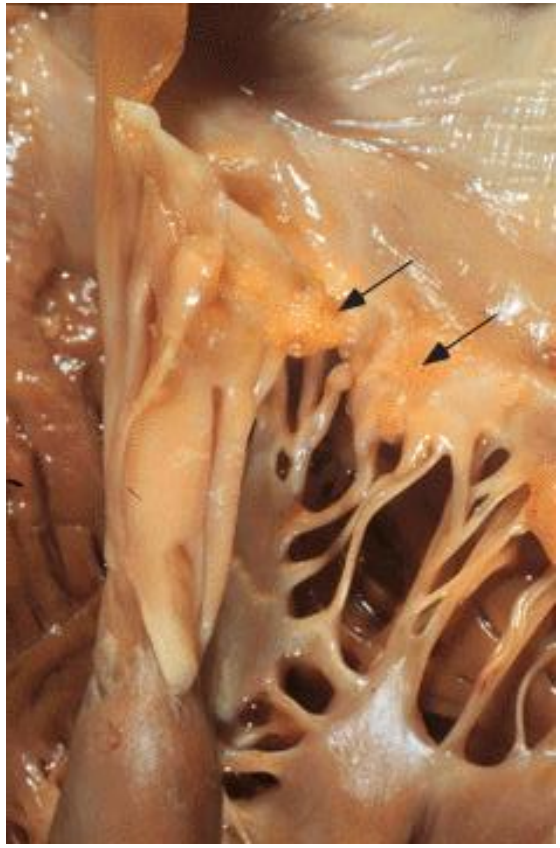
Renal manifestations of APS

- 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

Additional risk factor for thrombosis

Inherited thrombophilia

- Factor V Leiden – mutation G1691A
- Prothrombin – mutation G20210A
- Methylenetetrahydrofolate redutase – 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

Outline

2. **Registries of Pediatric APS**
   - Primary and Secondary APS
   - Catastrophic APS (CAPS)
   - Neonatal APS

European Registry of Pediatric 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

Avcin T. Pediatrics 2008, 122 (5)

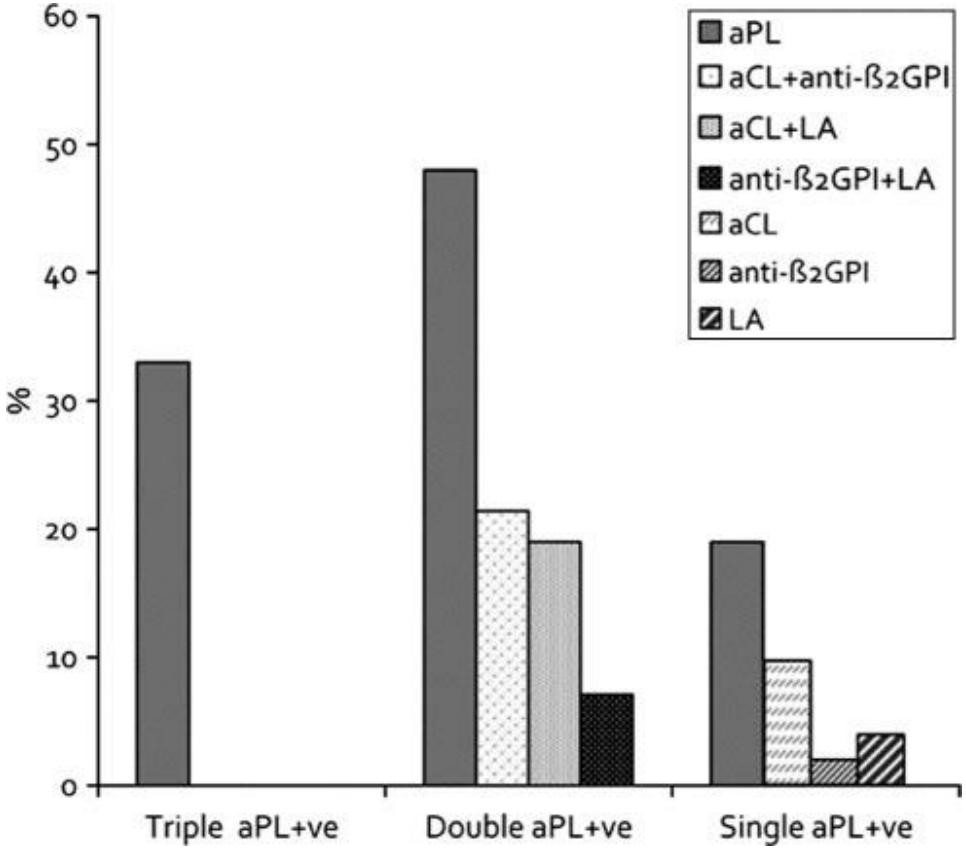
Pediatric APS Registry

- **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)

Ped - APS Registry

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

Ped - APS Registry

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)

Pediatrics 2008 Nov;122(5):e1100-7

Ped-APS Registry

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

	Primary APS 49,5%	Secondary APS 50,5%
Onset age	8,7 ± 5,3 yr	12,8 ± 3,3 yr
Venous thrombosis	31	41
Arterial thrombosis	27	10
Stroke	23	5
Hematologic disorders	10	36
Skin disorders	9	19
Neurological disorders	6	13

Avcin T. Pediatrics 2008, 122

Ped-APS Registry

Follow-up: 6,1years

- 19% developed recurrent thrombosis
- 5% had suggestive catasthrophic APS
- 7% died mainly due to thrombotic complication

APS (children vs adults)

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

Avcin T. pPdiatrics 2008, 122(5)
Berkun Y. Arthritis Rheum 2006,55(6):850-5
Garcia-Carrascoo M. Lupus 2007, 16(5):366-73
Cervera R. Arthritis Rheum. 2002,46(4):1019-27

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%).

Berman H. Autoimmun Rev 2014, 13(2):157

Thromboembolic events in newborns?

Newborn represent the largest childhood group to develop thromboembolic events.

- They have some hemostatic differences
  - Decrease thrombin-plasminogen
  - Decrease coagulation factors
  - Decrease platelet agregation
  - 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

Neonatal-APS Registry
Babies born to mothers with APS

SPECIAL ARTICLE

Follow-up of babies born to mothers with antiphospholipid syndrome: Preliminary data from the European neonatal registry

M Motta[1], MC Boffa[2], A Tincani[3], T Avcin[4], S De Carolis[5] and E Lachassinne[6]

[1]Neonatology and Neonatal Intensive Care Unit, Children's Hospital of Brescia, Italy; [2]Laboratoire d'Hematologie, Hôpital Jean-Verdier, Bondy, France; [3]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy; [4]Allergology, Rheumatology and Clinical Immunology, University Children's Hospital Ljubljana, University Medical Center, Ljubljana, Slovenia; [5]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

Motta M. Lupus 2012 Jun;21(7):761-3

Neuropsychological outcome
Children born to mothers with APS

- **Learning disabilities** → 15 to 20%

- **Behavior abnormalities** → 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 → No comparison to healthy controls

Ross G. Arch Pediatr Adolesc Med. 2003, 157(4): 397
Brewater 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 nenonatal APS
  - Most with additional acquired thrombotic risk factor (**infection**, central vein catheter, dehydration, gestational diabetes, congenital thrombophilias)

Gordon O. Semin Arthritis Rheum, 2014,44(2):241-5

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

Outline

3. Treatment

How to treat

- *There are no recommendations specific for children.*

- *Medications*
  - *Heparin*
  - *Warfarin*
  - *Aspirin*

Primary Thrombosis Prophylaxis

Asymptomatic positive aPL (adults)

- Prophylatic 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

Primary Thrombosis Prophylaxis

SLE and positive aPL

- Consider SLE as a prothrombotic condition
  - Retrospective sudies 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.

Jung H. Arthritis Rheum. 2010, 62(3): 863-8
Erkan D. Autoimmun Rev 2014, 13 (6): 685

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

Recurrences: treatment

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)

Ruiz-Irastorza G . Lupus 2011; 20:206

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

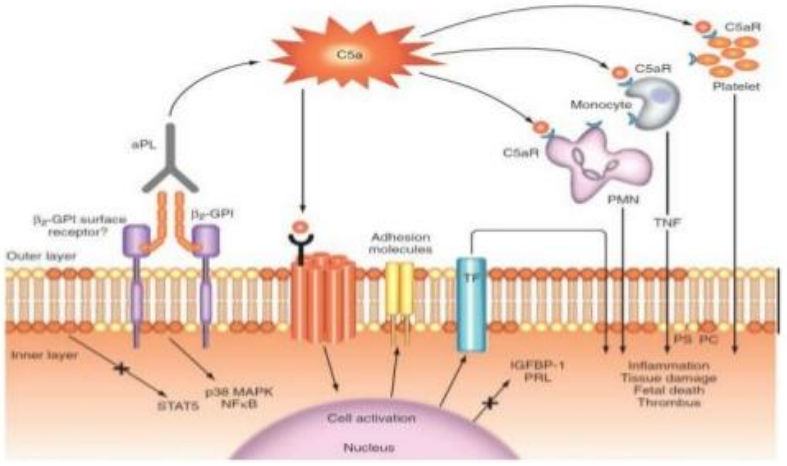
Arthritis Rheum 2006; 54:2568.

Resistant CAPS

- **Rituximab**
  - B-cell depleting anti-CD20
  - 1.000 mg IV for 2 doses in 2 weeks

- **Eculizumab**
  - Monoclonal antibody against C5

Pathogenesis



Thank you!