Antiphospholipid Syndrome

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Antiphospholipid Syndrome (APS)

- 1983 - Dr. Graham Hughes and his team in London described “sticky blood”
  - Lupus patients had a tendency to blood clots, headaches, strokes and, in pregnancy, clotting of the placenta and miscarriage
  - These patients had “antiphospholipid antibody”
  - Recognized syndrome also occurred without lupus
- Mid 1990s – renamed “Hughes Syndrome”
Entity plagued by Misnomers

- Antiphospholipid antibodies – antigen is a protein that binds phospholipid
- Lupus anticoagulant
  - Frequently found outside the clinical spectrum of SLE
  - Prolong aPTT *in vitro*, but associated with a hypercoagulable state *in vivo*
Antiphospholipid Syndrome

- Primary APS
  - Occurs without underlying disease

- Secondary APS
  - Occurs in the setting of underlying disease
    - SLE
    - Sjögren’s
    - Malignancy
Pathophysiology

“2-hit” hypothesis

- Preexisting or coincident vascular damage
- Antiphospholipid antibody
  - May bind platelet phospholipids and promote coagulation
  - May bind endothelial cell phospholipids and induce cell damage
  - May interfere with protein C, protein S and/or thrombomodulin function
Diagnostic Criteria for APS

- One or more clinical criteria
- One or more laboratory criteria
Clinical Criteria

- ≥ 1 episodes of venous, arterial or small vessel thrombosis
  - Deep vein thrombosis
  - Stroke/TIA
  - Pulmonary embolism
  - Superficial thrombophlebitis

- Pregnancy morbidity
  - Unexplained death at ≥ 10 weeks gestation of morphologically normal fetus
  - ≥ 1 premature births (< 34 weeks gestation) secondary to eclampsia, preeclampsia or placental insufficiency
  - ≥ 3 pregnancy losses (<10 weeks gestation) unexplained by chromosomal, maternal anatomic or hormonal causes
Related clinical & laboratory findings

- Migraine headache
- Raynaud phenomenon
- Thrombocytopenia (50-140K)
- Microangiopathic hemolytic anemia
- Cutaneous ulcers
- Livedo reticularis
- Adrenal insufficiency
- Pulmonary hypertension
- Avascular necrosis
- White matter lesions on MRI
- Valvular heart disease – fibrin and platelet deposits
Thromboses

- Venous > arterial
- DVT & PE
  - More frequent with lupus anticoagulant
  - Antiphospholipid antibody in 5-21% of patients
- Coronary, cerebrovascular and peripheral arterial events
  - More frequent with anticardiolipin antibodies
Catastrophic Antiphospholipid Syndrome

- Rare
- Multiorgan failure
  - Due to widespread thrombotic disease
- + DIC panel
- Frequently fatal (50% mortality)
Antiphospholipid Antibodies

- 1-15% of the general population
- 50-70% of patients with SLE
  - Frequency of APS much lower!
- Transient antibodies
Laboratory Criteria

- Antiphospholipid antibodies
  - Lupus anticoagulant
  - Anticardiolipin antibodies
  - Anti-β2 glycoprotein I antibodies
  - Two or more occasions at least 12 weeks apart
  - No more than five years prior to clinical manifestations
Lupus Anticoagulant (LA)

- Prolongs phospholipid dependent coagulation tests
  - Activated partial thromboplastin time (aPTT)
  - PT rarely affected – reagent contains high concentration of phospholipid
- Undefined epitopes
- 50% of patients with LA meet criteria for SLE
- Can be associated with medications – quinidine, procainamide, chlorpromazine
- With LA ~30% risk of developing APS symptoms
- Clotting assays
  - All testing performed with platelet poor plasma
Evaluation of lupus anticoagulant

- Step 1: Test for prolongation of coagulation in ≥ 1 phospholipid dependent \textit{in vitro} coagulation assay
Laboratory Evaluation of LA

- **PTT-LA**
  - Reduced amount of phospholipid present

- **Dilute Russell Viper Venom Time (dRVVT)**
  - Russell Viper Venom directly activates factor X (common pathway)
    - Phospholipid dependent
  - More sensitive than the aPTT test
    - Not influenced by deficiencies or inhibitors of clotting factors VIII, IX or XI
    - dRVVT reagent is diluted to ensure that it has a low phospholipid concentration, increasing the sensitivity for LA
      - Patient without LA will clot in 36-42 seconds
      - Patient with LA will have prolonged clotting
  - Must use platelet poor plasma
  - Contains heparin inhibitor (Hepzyme)
Dilute Russell Viper Venom Time

Normal plasma dRVVT 36-42 sec

Plasma with lupus anticoagulant dRVVT > 43 sec
Evaluation of lupus anticoagulant

- **Step 2: Mixing studies**
  - Mix equal parts patient and control plasma
  - aPTT will correct if prolongation due to factor deficiencies
  - If LA present will fail to correct aPTT
    - Clotting time > 5 seconds longer than control plasma alone
    - Usually immediate acting
Evaluation of lupus anticoagulant

- Step 3: Neutralization study
  - Addition of phospholipid will neutralize lupus anticoagulant
  - Measured aPTT will become shortened
  - Platelet neutralization
    - Lysates of frozen, thawed and washed platelets
  - Hexagonal phase phospholipid neutralization
LA Confirmatory Tests

Platelet Neutralization

- Prolonged aPTT
- Shortened aPTT

Sta Clot-LA

- Prolonged aPTT
- Shortened aPTT

Clotting time >8 seconds shorter after addition of PL = + for LA
Evaluation of lupus anticoagulant

- Step 4: Rule out other coagulopathies
  - Specific factor assays
    - With LA, factor activity appears to increase with increasing dilutions of plasma
      - Diluting lupus anticoagulant
Lupus Anticoagulant Flow Chart
Lupus Anticoagulant-Sensitive Partial Thromboplastin Time (PTT-LA®) and StaClot LA®

1. If the dRVVT is normal, proceed to the Hepzyme® step. If the dRVVT is prolonged, Hepzyme is unnecessary.
2. If the StaClot LA is positive and the dRVVT is negative, assay FVIII to determine if the positive StaClot LA is due to a FVIII inhibitor.
Anticardiolipin antibodies

- May occur with infections or medications
  - These are rarely of clinical significance
- May be B2-glycoprotein I dependent
  - Usually those found in autoimmune disease
  - Not those antibodies formed secondary to infection
- May behave like a lupus anticoagulant in *in vitro* testing
- Alone, may not be a risk factor for thrombosis
- Presence is a risk factor for recurrence of thromboembolic events
- Measure via ELISA
  - IgG, IgM or IgA
  - + if medium/high titer
    - >40 GPL or MPL or >99<sup>th</sup> percentile
B2-Glycoprotein I Antibodies

- Most common target of APA
- Found in patients with APS and positive anticardiolipin antibodies
  - Without anti-β2-GP-I may not have increased clotting risk
  - Not present with antibodies formed secondary to infection
Other Antibodies

- Anti-prothrombin
- Anti-annexin V
- Anti-phosphatidylserine
- Anti-phosphatidylinositol

Associated with APS

□ Clinical role poorly understood
Thrombotic Risk

- In patients with APS:
  - Thrombosis rate ~2.4%/year
  - Thrombosis risk ↑ 6-10X
  - 10-15%/year recurrence rate without anticoagulation therapy
  - In secondary APS, ongoing vasculitis = continual risk for thrombosis
Venereal Disease Research Laboratory (VDRL)

- Serologic test for syphilis
- Measures agglutination of lipid particles containing cholesterol and cardiolipin
  - Antiphospholipid antibodies may bind and cause agglutination → False + VDRL
  - Occurs in ½ of patients with APS
Treatment

- After venous thrombosis:
  - Heparin followed by Coumadin
    - Highest risk of recurrence in first 6-12 months
- After arterial thrombosis:
  - Aspirin +/- coumadin
- Secondary APS:
  - Aspirin, hydroxychloroquine, pentoxifylline, coumadin or LMW Heparin
- Catastrophic APS:
  - Aspirin, coumadin, corticosteroids, plasmapheresis, IVIG
- Pregnancy
  - Aspirin +/- prednisone
References

- Henry’s Clinical Diagnosis and Management by Laboratory Methods
- Uptodate.com