

## Antiphospholipid Syndrome (APS)

### Antiphospholipid antibodies (APLA)

-phospholipids (PL) are the anchoring substance for coagulation proteins found in all arms of the coagulation cascade

-APLA are a family of autoantibodies directed against PL's or the plasma proteins that are *bound* to PL's

-3 most common subgroups (each antibody has its specific affinities so none of them are identical)

1. **Anticardiolipin Antibodies(ACL):** more SENSITIVE for APS
  - a. first detected in syphilis pt's b/c its a complement fixing ab. that reacts w/ bovine heart extracts, which therefore led to false positives with VDRL
  - b. the antigen is the mitochondrial PL: Cardiolipin
  - c. identified by immunoassays that measure reactivity to a PL, so see increased Ig G (higher specificity for APS) and Ig M titers
2. **Lupus Anticoagulant Antibodies(LAC):** more SPECIFIC for APS
  - a. identified when a reagent with a few PL's are added, and then PTT "corrects" (though not quite to normal, but *PTT decreases towards normal by a difference of at least 7 to 13*)
  - b. even if initial PTT is normal, still do the above screen which increases the sensitivity when reagent is mixed in w/ pt's plasma
3. **Anti- $\beta$ 2-glycoprotein I Antibodies**
  - a. found that +ACL ab. in either APS or SLE: require the plasma PL-binding protein  $\beta$ 2-glycoprotein I in order to bind to cardiolipin
  - b. whereas +ACL ab. in syphilis: these ab. do NOT require this binding protein since reacts *directly* with cardiolipin
  - c. has led to a focus more on the PL-binding proteins rather than just the PL's themselves
  - d. identified also by immunoassay that measures reactivity to a PL-binding protein (we don't have this assay routinely at UNC yet)
  - e. criteria for classifying APS does NOT yet include the presence of this ab, but "it may replace other assays" per Dr. Moll
  - f.  $\beta$ 2-glycoprotein I acts as a natural anticoagulant, and modulating it is strongly associated w/ many features of APS, like thrombosis

-there are no certain associations btw. specific APLA and particular clinical consequences...therefore should perform multiple tests (pt may be positive for one yet negative for another)

-they interfere with BOTH procoagulant AND anticoagulant pathways via many different mechanisms (FIG 1), and they "bleed in the test tube but clot in the body!"

- a. in VITRO see prolongation of clotting (ie, bleeding) 2° to a greater inhibition of *procoagulant* pathways
- b. in VIVO see thrombosis 2° to greater inhibition of *anticoagulant* pathways

### Pathogenesis (of promoting thrombosis:)

1. activation of endothelial cells
2. injury to vascular endothelium via oxidant mediated mechanisms
3. interfering with the function of PL-binding proteins in all arms of coag cascade (modulating the regulatory functions of Protein C, Tissue Factor, Prothrombin, etc.)
4. inducing thrombosis in both arterial AND venous vessels, similar to HIT
  - a. HIT: site affected determined by prior CV disease (type not specified)
  - b. APS: high recurrence at previous site of thrombosis, ie, if initial site was arterial than recurrence also at arterial, and same for venous sites

### Criteria for Diagnosis of APS

-need 1 of 2 clinical AND 1 of 2 lab criteria

1. **Clinical criteria**
  - a. vascular thrombosis—arterial, venous, or small vessel bed
  - b. pregnancy complication
    - i. 10<sup>th</sup> wk: unexplained death of morphologically normal fetus
    - ii. before 34<sup>th</sup> wk: premature birth of morphologically normal fetus

- iii. before 10<sup>th</sup> wk: 3 or more unexplained consecutive spont. Abortions
  - 2. **Lab** criteria: both detected again *at least six weeks apart*
    - a. Anticardiolipin antibodies: Ig G or Ig M at moderate or high titers
    - b. Lupus anticoagulant antibodies: detected by decrease of PTT after PL added ("hex")
- quick review on approaching the lab diagnosis per Dr. Moll:
- 1. after noting prolonged PT/PTT (since PL's are everywhere in the coagulation cascade) do a mixing study
    - a. corrects=> a factor deficiency
    - b. does not correct=> an inhibitor present (either a specific one eg. Bethesda, or a PL inhibitor)
  - 2. when PTT does not correct
    - a. if pt is bleeding, think Factor 8 Inhibitor (most common)...can repeat mixing with each factor to overcome and saturate the inhibitor present
    - b. if pt is bleeding and already has known APLA, suspect presence of prothrombin antibodies
    - c. if pt is clotting, order Lupus Inhibitor = a coagulation screen that adds (mixes) hexagonal phase PL's...positive if PTT decreases (ie corrects towards normal) by more than 8 seconds ("hexagonal difference")
      - i. remember to *order this even if initial PTT is normal*, as the mixing with PL's increases sensitivity of the test
      - ii. to confirm, may also order DRVVT(Dilute Russel Viper Venom Time), and other venoms: Taipan, Textarin, Ecarin...these venoms modulate various steps in coagulation and are PL-dependent reactions that are all thought to be targeted by LAC in vitro
    - d. also order immunology: Anticardiolipin Antibody titers Ig G and Ig M
- some feel its technically not called a "syndrome" until labs documented at 6 weeks apart
- a. **Primary** APS: no clinical evidence of other autoimmune disease (true vasculitis is rarely, if ever present), and evolution into SLE seems rare
    - i. zero out of 70 pt's developed SLE over 5 yrs
    - ii. 3 out of 80 pt's did develop SLE after mean of 6.5 yrs
  - b. **Secondary** APS: association w/ other autoimmune disease to which vasculitis is attributed (rather than to APS itself)
    - i. most common association is with SLE: those with APS *and* SLE more likely to have Neutropenia, low C4 levels, & autoimmune hemolytic anemia (as opposed to Primary APS)
    - ii. more tenuous link to other rheumatologic diseases
    - iii. many cases of Sneddon's Syndrome may actually represent APS undiagnosed (triad of HTN, Livedo Reticularis, CVA)
- no major differences regarding clinical consequences btw primary and secondary APS  
-APLA do occur in other conditions (drugs, hemodialysis, malignancies, infections)...but tend to see ACL Ig M and are NOT associated with thrombotic events

### Epidemiology

- young
- prevalence of APLA in 1 to 5% in healthy controls; increases with age (espec. Elderly with other chronic diseases); can NOT determine who will have a preg. or thrombotic complication
- in SLE, prevalence of APLA is 12-30% for ACL and 15 to 34% for LAC
  - e. APS may develop in 50-70% of SLE w/ APLA (shown in a 20 yr f/u)
  - f. yet 30% of these kinds of pt's may lack any clinical evidence of APS (shown in a 7 yr f/u)
- APLA have been shown in association with first episodes of: MI, venous thrombosis, recurrent CVA...therefore need to determine who has increased risk factors, namely: LAC, ACL Ig G, h/o clot, *persistence* of APLA
- should screen those presenting with their first thrombotic event
- should modify secondary risk factors (atherosclerosis, OCP use, stasis, nephrotic syndrome)

### Clinical Features: (FIG 2)

- 1. Venous thrombosis: most commonly DVT (up to 55%), half of which have PE
- 2. Arterial thrombosis: 50% are CVA or TIA's > 23% coronary > subclavians/renal/retinal/pedal

3. Arterial emboli, especially in cardiac valvular abnormalities (63% of APS have at least one by ECHO)...uncertain clinical consequence but vegetations seen in 4% of APS
4. Microvasculature (arterioles, caps, venules)—usually acute & similar to HUS/TTP, or thrombomicroangiopathy (TMA) may be indolent
5. Thrombocytopenia (50%), Hemolytic Anemia (up to 23%), Livedo Reticularis (up to 22%), more recently noted renal involvement (often with HTN too)
6. Obstetrics: see those listed in clinical criteria, also premature delivery 2° uteroplacental insufficiency and assoc'd HTN

Catastrophic APS: acute presentation and involvement of smaller vessels

- rare: 8 out of 1000 (0.8%) developed it over 7 yr f/u
- multiple concurrent vascular occlusions throughout body, often leading to death (UNLIKE single events with recurrence from months to years in APS)
- TMA of multiple organs: kidney (in 78%), lung (in 66%), CNS (in 56%), heart (in 50%), skin (in 50%)
- respective manifestations: TMA and HTN with 25% requiring dialysis, ARDS, microthrombi and microinfarctions, DIC in 25% (latter is NOT seen in primary or secondary APS)
- half die (even with anticoagulation) mostly because of multiorgan failure
- precipitating factors: surgery, withdrawal of anticoagulation therapy, infection, OCP's
- in those with hypercoagulable states, may see a "thrombotic storm"

Treatment

1. Prophylaxis
  - a. ASA for women with APS and previous loss pf pregnancy
  - b. Hydroxychloroquine (Plaquenil) protective for thrombosis in SLE and secondary APS
  - c. Possibly modifying anything in FIG. 3 (atherosclerosis, DM, tobacco, etc.)
2. Therapy after a thrombotic event (*various studies have shown: zero recurrence in 19 pt's after 8 years; after stopping it recurrence in 50% at 2 yrs & 78% at 8 yrs*)
  - a. Warfarin for goal INR either 2 to 2.9 OR high intensity goal of greater than 3)
  - b. unclear who requires which INR goal
  - c. clear that discontinuation is associated with increased risk of thrombosis
  - d. likely need long term, if not life long anticoagulation
3. Obstetrics and APS (mostly prospective trials)
  - a. h/o early preg loss: Heparin and low dose ASA to achieve live birth, though may be unnecessary if there is no h/o SLE or thrombosis
  - b. h/o early preg loss and no h/o thromboembolism: Hep 5000u BID
  - c. h/o early preg loss and yes h/o thromboembolism: Hep increased for full anticoagulation
4. Catastrophic APS (all from case reports)
  - a. anticoagulation and steroids + either PLEX (rationale: it works in HUS/TTP) or IVIg
  - b. varying success with fibrinolytics: urokinase, streptokinase

References:

- Levine JS et al., Antiphospholipid Syndrome, NEJM 346(10) March 7, 2002
- Espinosa G et al., The lung in the antiphospholipid syndrome, Ann Rheum Dis 61, 2002
- Winslow TM et al., Five year follow up study of the prevalence and progression of PHTN in SLE, Amer Heart J 129(3) March 1995
- Asherson RA et al., Review: antiphospholipid antibodies and the lung, J Rheum 22,1995
- Cecil's Textbook of Medicine
- Up to Date topics: Antiphospholipid Syndrome, Pulm Manifestations of SLE, Pulmonary Venous Occlusive Disease

