

Antiphospholipid syndrome (Hughes syndrome)

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Case 1

- 25 year old
- 3 previous normal deliveries
- 20 weeks pregnant
- History of substance abuse
- 3 week history of loss of speech, balance and diplopia
- Transferred to QE neurosciences

Case 1

- MRI brain
 - Multiple small infarcts
- Laboratory investigations – numerous
 - APTT ratio 1.2
 - DRVVT ratio 2.1
 - % correction phospholipid 30%
 - IgM anticardiolipin antibody 38 MPLU/ml
 - ‘Borderline’ B2GP1b
 - Plt count 86

Case 1

- Clinical review:
 - Severe dysarthria
 - Gross stabismus
 - 2 to transfer
 - Hallucinations and paranoid ideation
 - Fetal u/s scan – growth OK but uterine artery notching
- Discussed management with obstetrician, rheumatologist and family
 - Aspirin 75mg
 - Therapeutic LMWH (Enoxaparin 60mg bd)

Case 1

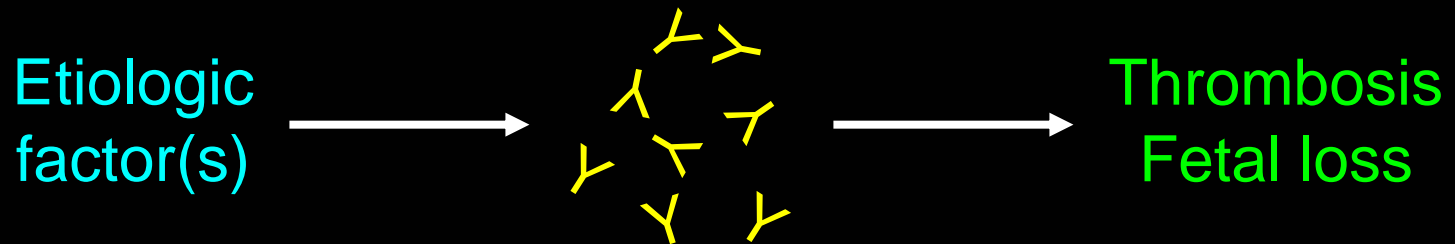
- 1 week later
 - Definite improvement
- 3 weeks later
 - Able to walk unaided and speech intelligible
- 28 weeks pregnant
 - Pre-eclampsia
 - Baby delivered
- 1 year later
 - Baby OK. Mother on warfarin INR target 3.5

Laboratory diagnosis of APS

- 1952 Conley and Hartmann
 - 2 patients SLE
 - Inhibitors of coagulation
 - False positive test for syphilis
- 1963 Bowie et al
 - Circulating anticoagulant associated with thrombosis
- 1972 Feinstein and Rappaport
 - 'Lupus anticoagulant'
- 1980's
 - Solid phase ELISA with cardiolipin substrate
- 1990's
 - β 2-glycoprotein I antibodies

Autoantibodies in the Antiphospholipid Syndrome

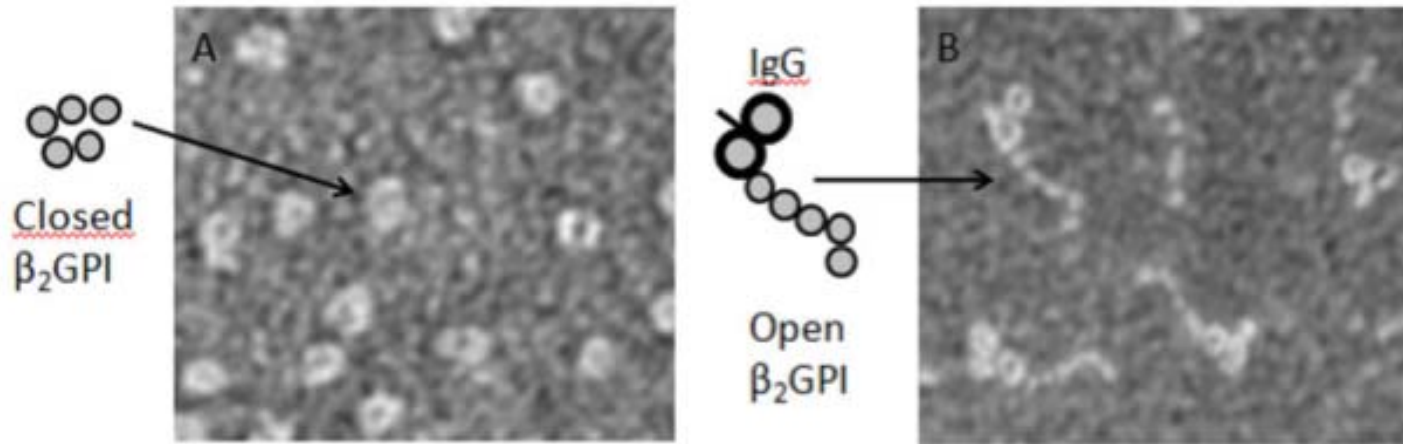
Pathologic agents:



Or epiphenomena:

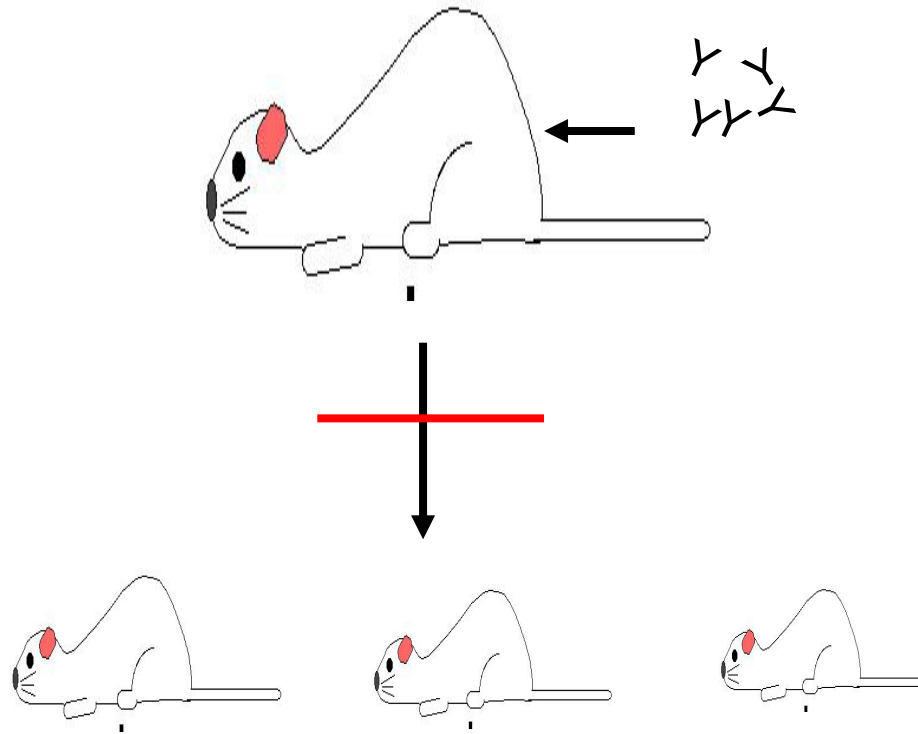


B2GP1



Heparin prevents antiphospholipid antibody–induced fetal loss by inhibiting complement activation

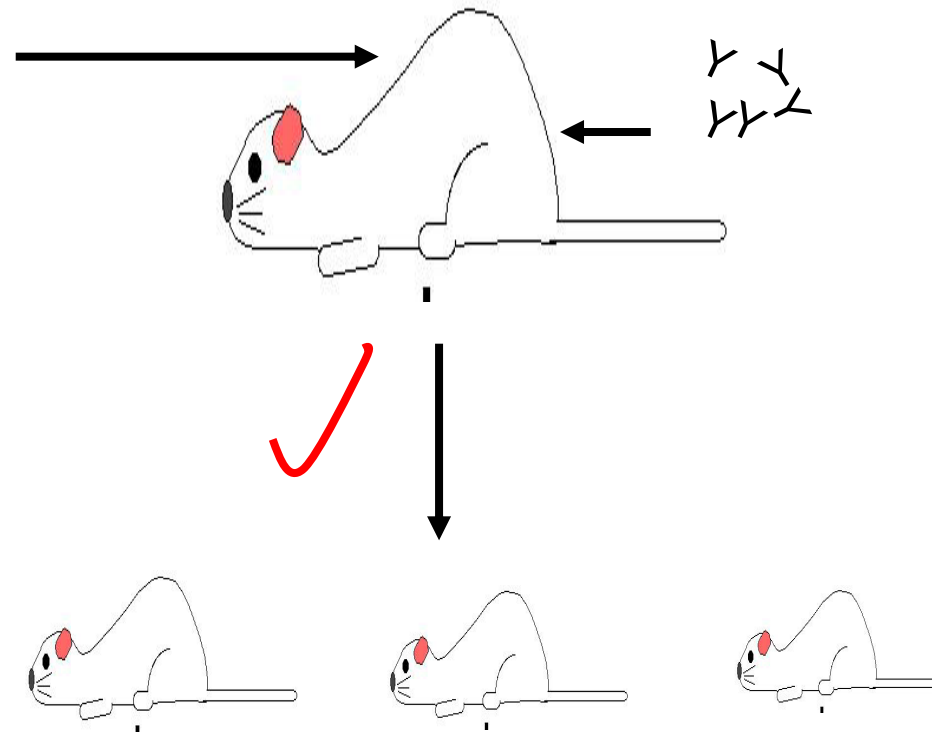
Guillermina Girardi, Patricia Redecha & Jane E Salmon
Nature Medicine **10**, 1222-1226 (2004)



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Low molecular weight heparin



CONCLUSION:

heparin may prevent obstetric complications in women with APS by blocking activation of complement induced by aPL antibodies targeted to decidual tissues, rather than by their anticoagulant effects

Clinical Classification Criteria for Definite Antiphospholipid Syndrome

(Wilson, 1998; Miyakis, 2006; Pengo 2009)

1.VASCULAR THROMBOSIS

Unprovoked venous or arterial thrombosis age <50, thrombosis at unusual sites, thrombosis in patients with autoimmune disease

1.PREGNANCY MORBIDITY

- a) One or more unexplained fetal loss >10 weeks
- b) One or more premature births < 34th week of gestation because of severe preeclampsia, or severe placental insufficiency
- c) Three or more unexplained miscarriage before the 10th week of gestation

Preliminary Classification Criteria for Definite Antiphospholipid Syndrome

Laboratory Criteria (at least 1 must be present)

1. Lupus Anticoagulant

Present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis Scientific Standardization Subcommittee on Lupus Anticoagulants/ Phospholipid-Dependent Antibodies (Brandt 1995, Pengo 2009)

2. Anticardiolipin Antibody

IgG and/or IgM isotype in blood, >40 units/l or >99th centile, on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA

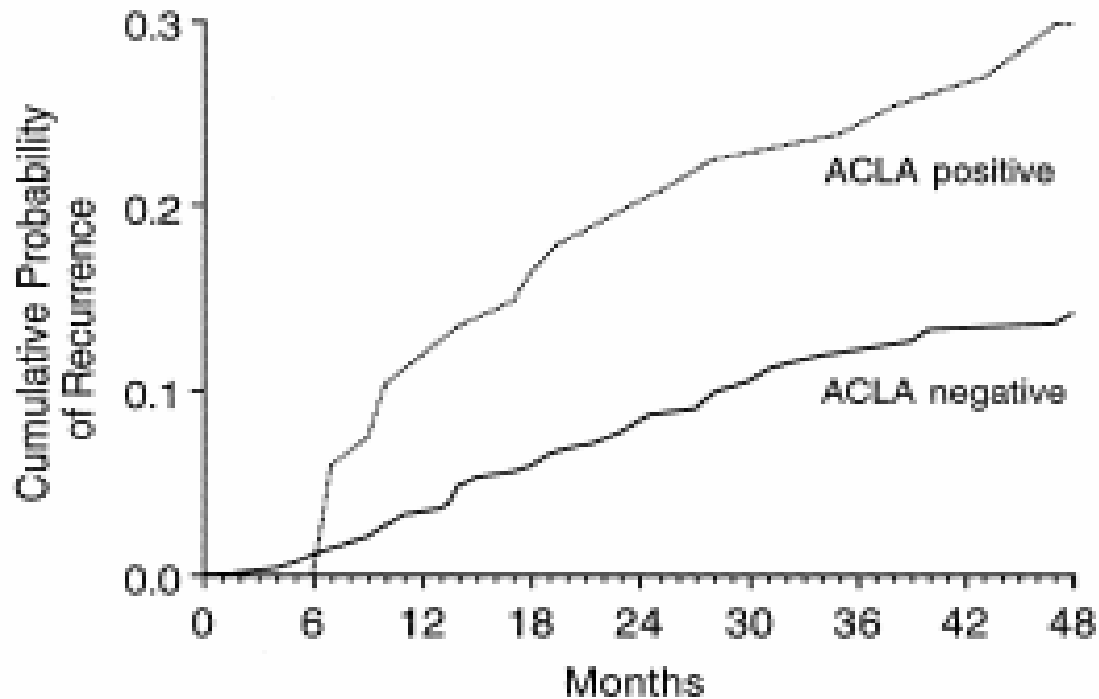
3. B2GP1b Antibody

IgG and/or IgM isotype in blood, >99th centile, on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA

Predicting thrombotic risk from laboratory results

- LA more significant than ACA (Galli et al, Blood 2003)
 - DRVVT the most sensitive and reliable test
- High titre IgG ACA ?more significant than low titre or IgM
- β 2GP-1 antibodies against domain 1 more significant
- Triple positivity (LA, ACA, B2GP1b) has the strongest association with thrombosis (Pengo, JTH 2011)
- Up to 5% normal population have detectable aPL's

Probability of recurrent thrombosis after completion of anticoagulation by anticardiolipin antibody status



Schulman et al, Am J Med. 1998;104:332–338.

Case 2

- 58 year old lady
 - Episode of short lived right sided weakness aged 38 and 50
 - ?Multiple sclerosis
- 1 year ago
 - early retirement
 - Short term memory problems
 - Occasional limb weakness
 - Neurologist recommended relaxation exercises, counselling and anxiolytic

Case 2

- Private MRI brain scan
 - Widespread high signal change, particularly periventricular, with slight cerebral atrophy
 - Differential diagnosis multi-infarct dementia or demyelination
- IgM ACA 68 MPLU/ml and 71 MPLU/ml 12 weeks later
- Referred to Haematology ?Antiphospholipid syndrome

Case 2

- Tired, slow, clumsy, poor short term memory. No headaches
- One miscarriage after 2 normal pregnancies
- LA screen
 - DRVVT ratio 1.32.
 - Mix with normal plasma 43.2-41.8 seconds
 - 26% correction with addition of phospholipid

Case 2

- Possible/probable antiphospholipid syndrome
- Offered anticoagulation with warfarin INR target 3.5
- Annual risk of serious bleeding 3-4%

Case 2

- 6 weeks later
 - Much improved (confirmed by patient and husband)
 - Stable INR
 - 6 month review planned

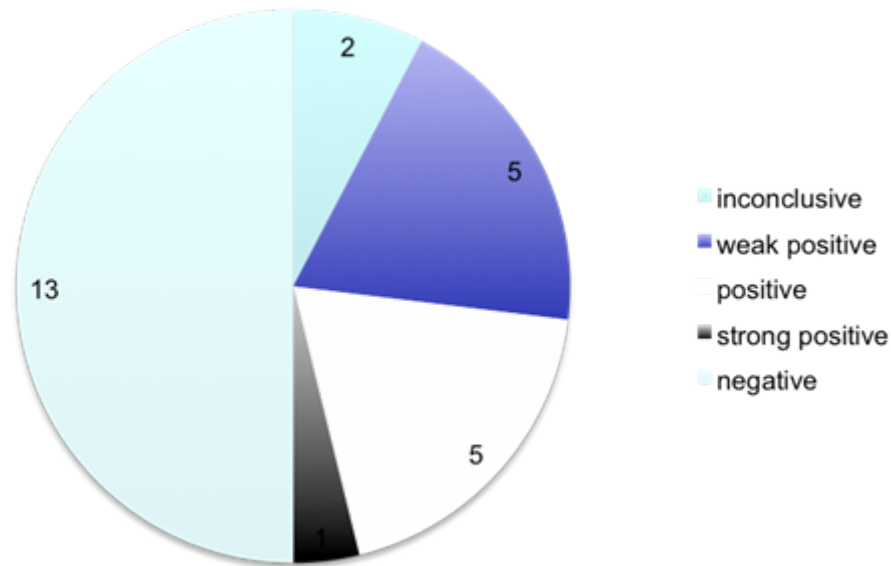
Laboratory diagnosis of APS

Can we diagnose antiphospholipid syndrome in the laboratory?

- Pengo et al, JTH 2007
 - 25% of LA positive patients from referring hospitals had negative test on same sample in central reference laboratory
- Reber et al, T&H 1995
 - 9 commercial kits and in house methods testing 90 control and patient samples
 - IgG positive 31-60%
 - IgM positive 6-50%
 - 50% concordance between labs

CQAS lupus anticoagulant exercise April 2011

- Sample from NBS donor plasma
- DRVVT ratio range 0.83-1.57



- Only test individuals with suspicious clinical presentation
- Consider developing internal normal range using 40 'normal' people less than 50 years old and calculating 99th centile?
- Equivocal results, especially if only LA or ACA or B2GP1 in isolation are highly unlikely to be clinically relevant to thrombosis
- Lower results 'might' be relevant in pregnancy
- There's a lot of 'smoke and mirrors' in this very enigmatic disorder