Primary Antiphospholipid Antibody Syndrome—Current Concepts

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Introduction

- Acquired autoimmune disorder characterized by recurrent venous or arterial thrombosis and/or recurrent fetal loss associated with persistence of antiphospholipid antibodies.

Epidemiology

- 1-5% healthy individuals have aPL antibodies
- Incidence is 5 cases per 100000 persons/year
- 50% of APS is **Primary** APS
- Mean age of onset: 31 years
- Risk of thrombosis: 0.5-30%
- Women: Men – 5:1

Criteria

- 1999, Sapporo, South Korea
- 2006, Sydney, Australia

Clinical Criteria

Vascular Thrombosis

- One or more clinical episodes of arterial/venous/small vessel thrombosis
- Thrombosis must be confirmed by objective validated criteria.

Pregnancy-related morbidity

- One or more unexplained deaths of a morphologically normal fetus at or beyond 10^{th} week of gestation.
- Three or more unexplained consecutive spontaneous abortions before 10^{th} week of gestation with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

- One or more premature births of a morphologically normal neonate before 34th week of gestation because of
  - eclampsia or severe pre-eclampsia
  - placental insufficiency

Laboratory Criteria

- Lupus anticoagulant
- Anti-cardiolipin antibody IgG or IgM subtype in serum or plasma
- Anti-beta 2-Glycoprotein 1 antibody IgG or IgM subtype in serum or plasma

- **All should be present on two or more occasions at least 12 weeks apart**

Diagnostic Criteria

- At least
  - one of the clinical criterion
  - one of the laboratory criterion

Noncriteria Manifestations

- **Clinical**

  - livedo reticularis

  - thrombocytopenia

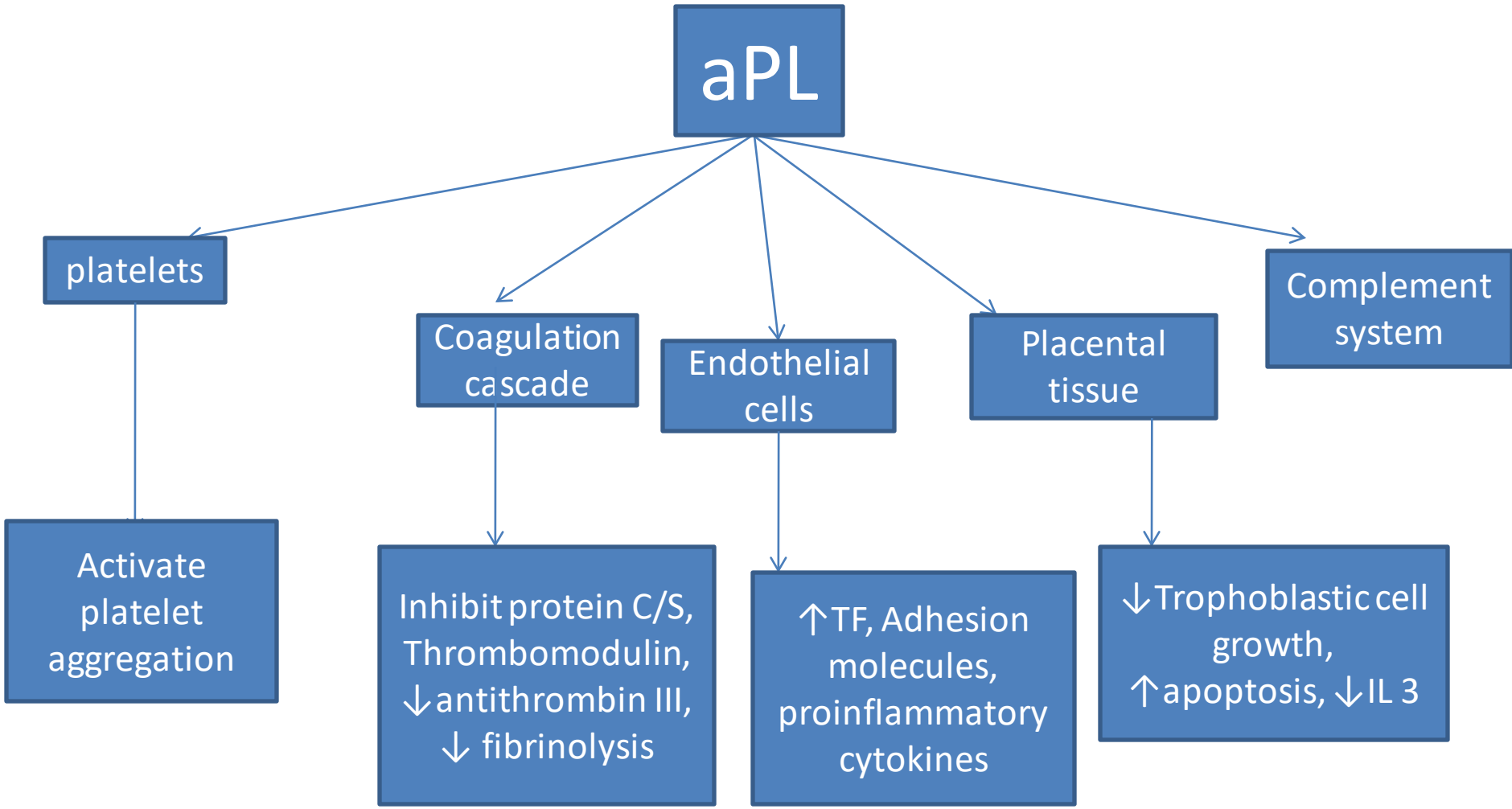
  - autoimmune hemolytic anemia

  - cardiac valvular disease

  - multiple sclerosis-like syndrome, chorea or other myelopathy

- **Laboratory**
  - IgA anti-cardiolipin antibody
  - IgA anti-B2 GP1

Pathophysiology of APS



- T cell hyperactivity and B cell overstimulation
- Role of TLR4
- Genetic factors

Treatment

- Asymptomatic individuals do not require specific treatment.
- Primary prevention of thrombosis in individuals who are persistently aPL positive lacks an evidence-based approach.

- For secondary thrombosis prevention, current recommendation is life-long warfarin, although the necessity, duration and intensity of warfarin treatment are still under debate.
- Prospective studies of patients with APS receiving antithrombotic therapy report an incidence of recurrent thrombosis of 3% to 24% per year.

- Retrospective studies report higher recurrence rates, ranging from 53% to 69%.
- General consensus is to treat patients with indefinite duration of anticoagulation.

- An observational cohort in 26 APS patients using **dabigatran** or **rivaroxaban** described a recurrent thrombotic event in only 1 patient after 8 months of treatment.
- The event-free survival rate was 87.9% at 12 months.
- Three controlled clinical trials are underway to evaluate the thrombotic risk of NOACs (RAPS, TRAPS, and ASTRO-APS).

- Recent RAPS trial revealed that APS patients treated with rivaroxaban had a significant twofold-increased thrombin potential, suggesting a higher thrombotic risk, in comparison with warfarin users.

- **Rituximab** can be considered for recurrent thrombosis despite adequate anticoagulation.
- A non-randomized prospective study (**RITAPS trial**) showed rituximab to be effective for noncriteria aPL manifestations (ie, thrombocytopenia and skin ulcers).

- Prophylaxis during pregnancy is provided with subcutaneous heparin and low-dose aspirin.
- Therapy is withheld at the time of delivery and is restarted after delivery, continuing for 6-12 weeks or long-term in patients with a history of thrombosis.

- Corticosteroids have not been proven effective rather increase maternal morbidity and fetal prematurity rates.

Potential Future Therapy

- Statins
- Eculizumab
- Autologous hematopoietic stem cell transplantation
- Combination anti-aggregant therapy

Challenges for Future

- Physiological function of B2GP1
- Pathophysiology of thrombosis and pregnancy loss in PAPS patients
- Treatment is still poorly defined
- Evidence-based guidelines for management of neurologic manifestations remain unavailable

Conclusion

- There should be high index of suspicion for diagnosis of PAPS.
- Early recognition, appropriate treatment and lifestyle modifications can help the patients to lead a healthy life.

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