



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

A Review on Hughes Syndrome

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ARTICLE INFO

Published: 04 July 2025

Keywords:

Antiphospholipid syndrome,
anticoagulants, thrombosis

DOI:

10.5281/zenodo.15804664

ABSTRACT

Hughes Syndrome is also known as Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by hypercoagulability, leading to venous and /or arterial thrombosis and pregnancy-related complications. Obstetric manifestations include recurrent miscarriages, fetal death beyond the 10th week of gestation, and/or premature births. The clinical criteria for APS encompasses several specific events : three or more consecutive, unexplained miscarriages occurring before the 10th week of gestation; one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week; and one or more premature births of a morphologically normal neonate before the 34th week of gestation, typically due to eclampsia, severe preeclampsia, or placental insufficiency. From a serological perspective, the standard laboratory tests for APS involve the detection of a lupus anticoagulant(LAC) or IgG and/or IgM anti- β 2 - glycoprotein antibodies (anti- β 2-GpI). For diagnosis, these antibodies must be present on two or more occasions at least 12 weeks apart. According to the international Consensus Criteria (Revised Sapporo Criteria) , a diagnosis of APS requires the presence of at least one clinical and one laboratory criterion. Treatment of APS primarily involves anticoagulant and antiplatelet therapy, typically requiring lifelong anticoagulation. In cases of pregnancy morbidity, low-dose aspirin combined with low molecular weight heparin (LMWH) Is considered the standard treatment. In rare and severe cases such as catastrophic antiphospholipid syndrome, aggressive management with anticoagulation, plasma exchange, and corticosteroids is warranted. The average age of patients with primary APS is reported to be around 35 to 40 years and the conditions is significantly more common in women than in men..

INTRODUCTION

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



APLA were first described by Conely in the 1950's when it was noted that patients with lupus often had prolonged activated partial thromboplastin times (APTT). The original description of the syndrome was made by Graham Hughes in 1983[1], with SLE and LAC date back to late 1950s[2-3]. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations in the APS. Any combinations of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. Prevalence of the APL in the general population ranges between 1 and 5%. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of APS is around 5 new cases for 100,000 persons for year and the prevalence around 40-50 cases for 100,000[4]. In a subset of patients, thrombosis can involve simultaneously multiple organs, configuring the so-called "catastrophic antiphospholipid syndrome" (CAPS)

Epidemiology:

Antiphospholipid antibodies are not specific of APS and can be found in healthy individuals. Nevertheless, the prevalence of APL positivity and APS in the general population has not been extensively analyzed and only two epidemiological population-based studies have been performed so far. In the first one, the authors studied the epidemiology of APS between 2000 and 2015 in an inception cohort of Olmsted County, Minnesota, through a recorded linkage system. The annual incidence of APS in adults aged >18 years was 2.1 (95% confidence interval 1.4-2.80) per 100,000 population. Incidence rates were similar in both sexes. The estimated prevalence of APS was 50 (95% CI 42-58) per 100,000 population, and was similar in both sexes[5]. In the second study, performed in Korea between 2007 and 2018,

with data extracted from Health Insurance and Review Agency, an incidence of 0.75 per 100,000 person – year (95% confidence interval 0.73-0.78) was found, while the prevalence was 6.19 per 100,000 people.[6]

Thrombosis: The presence of antiphospholipid antibodies is a risk factor for thrombosis. The APS Action Group reported a literature review focused on the prevalence of antiphospholipid antibodies in the general population with pre-pregnancy morbidity, strokes, myocardial infarction and deep vein thrombosis. The authors estimated that 13% of individuals with stroke, 11% of individuals with myocardial infarction and 9.5% of individuals with deep vein thrombosis are positive for antiphospholipid antibodies[7]. Another study in women <50 years of age who had a stroke showed that 17% were positive for lupus anticoagulant compared with 0.7% in the control group[8]. Positivity for lupus anticoagulant combined with estrogen-containing oral contraceptive use or smoking increased the risk further[9].

Pregnancy Complication: The APS ACTION group showed that 6% of patients with recurrent pregnancy morbidity were positive for antiphospholipid antibodies[10]. Recurrent miscarriage is the most frequent complication and is observed in the majority (54%) of women with obstetrical APS included in the European Registry of Obstetrical Antiphospholipid Syndrome[11]. Fetal death is considered to be a consequence of placental dysfunction and is strongly associated with antiphospholipid antibodies[12-13]. In an analysis of 512 stillbirths from the Collaborative Research Network from 2006 to 2008, 11% (95% CI 8.4-14.4) of the women were positive for antiphospholipid antibodies[14].

Autoimmune Disease: Antiphospholipid antibodies can be detected in association with



other systemic autoimmune diseases, most frequently SLE the prevalence of antiphospholipid antibodies among patients with SLE ranges from 15% to 34% for lupus anticoagulant, from 12% to 44% for anticardiolipin and from 10% to 19% for anti- β 2- glycoprotein 1 antibodies. Of individual with SLE who are positive for antiphospholipid antibodies, 20-50% develops thrombotic events[15]

Etiology:

APL antibodies are present in a significant proportion of people with certain autoimmune or rheumatic disorders. The following are common autoimmune or rheumatic disorders and the proportion of patients having aPL antibodies (note that this is a percentage of patients, not the clinical state of APS)

- SLE: 25–50%
- 42% have Sjögren syndrome.
- 33% have rheumatoid arthritis.
- 30% have immune thrombocytopenia.
- 28% have psoriatic arthritis.
- 25% have systemic sclerosis.
- Diseases of the mixed connective tissue: 22%
- Rheumatic polymyalgia or giant cell
- 20% have Behçet syndrome.
- Unknown autoimmune hemolytic anemia

The following infections are linked to APS [16]

- HIV infection, hepatitis C, and syphilis
- Type 1 infection of human T-cell lymphotropic virus
Malaria
- Gram-negative septicemia

APS-related drugs include the following:

- Procainamide, quinidine, propranolol, and hydralazine are cardiac drugs.

- Psychiatric or neuroleptic: phenytoin, chlorpromazine
Other: Amoxicillin, quinine, and interferon alfa, quinine, amoxicillin

- Furthermore, there has been a link between APS and certain vaccinations. For instance, because the two molecules share molecular similarities, immunization with tetanus toxoid may cause the development of antibodies that cross-react with beta-2 glycoprotein I.

The following genetic predispositions might be at play:

- There is a higher likelihood of aPL antibodies among relatives of those with confirmed APS. A research revealed a frequency of 33%.
- Certain HLA genes, including as DRw53, DR7 (primarily in individuals of Hispanic descent), and DR4 (mainly in Whites), have been linked to the presence of aCL antibodies.

Pathophysiology:

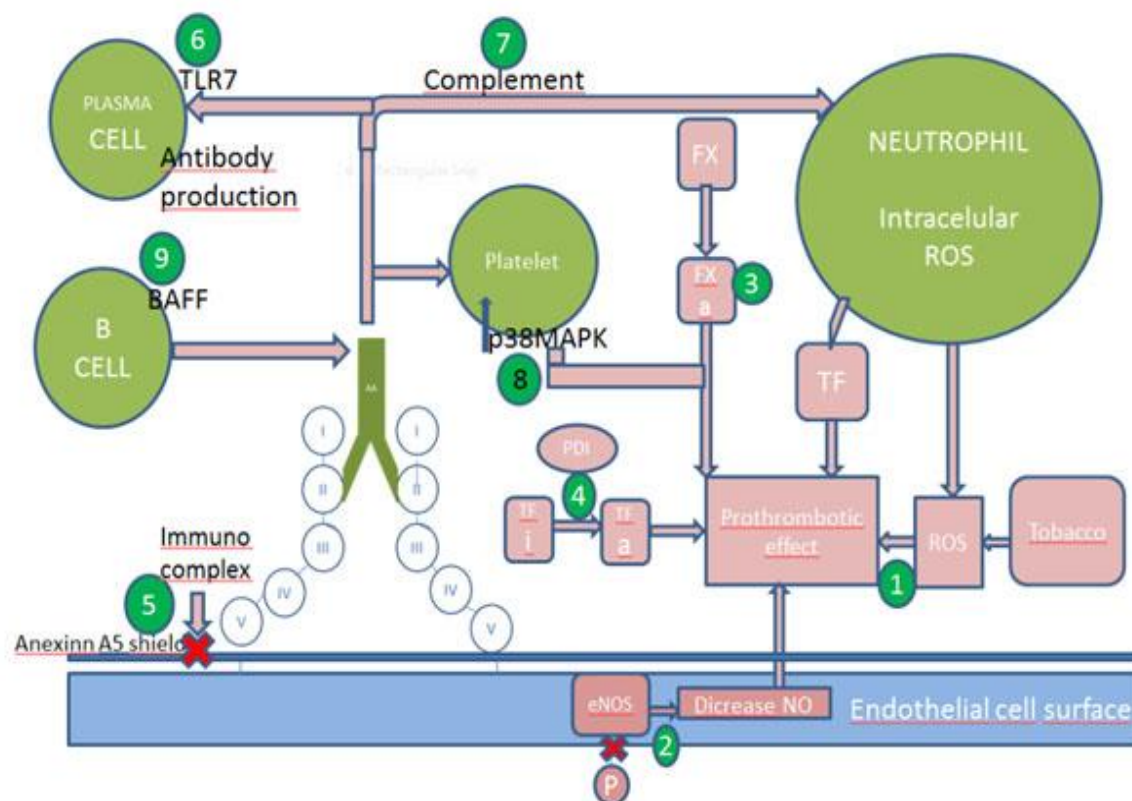
It is recognized APL positivity is the most frequent acquired risk factor and is more related to thrombotic events and gestational morbidity. Antiphospholipid antibodies (lipus anticoagulant, anticardiolipin and anti- β 2-glycoprotein-I) are classificatory antibodies of the diseases, used for diagnosis, but also important elements in the pathogenesis of APS. Although the presence of these antibodies is predisposing factor for thrombotic events, a second triggers, such as infection, prolonged rest or an inflammatory state, is usually necessary for the progression of the syndrome. Antiphospholipid antibodies bind to phospholipids and plasma or membrane proteins expressed in various cells (platelets, endothelial cells, monocytes, fibroblasts and trophoblasts), producing a prothrombotic state.



Despite the known thrombophilic action of antiphospholipid antibodies, the exact pathogenesis of the diseases is not yet fully elucidated. β 2-glycoprotein-I (β 2GPI) and prothrombin appear to be the major binding proteins in these antibodies involved in the

pathogenesis of the disease. There is also a genetic component related to the HLA class II system that needs to be better studied, and which may predispose the individual to the disease.[17-18]

The pathophysiology of Antiphospholipid syndrome



Mechanisms of thrombosis and possible targets. Numbers indicate the sites of action of the following drugs: 1 N-acetylcysteine, 2 statins, 3 hydroxychloroquine, fluvastatin and FXa inhibitors (anticoagulants e.g. low molecular weight heparin, fondaparinux, rivaroxaban and edoxaban), 4 PDI inhibitors and hydroxychloroquine, 5 hydroxychloroquine, 6 TLR7 inhibitors, 7 heparin, eculizumab, 8 belimumab

Diagnosis:

There is no single test that can screen a patient for APL. One must perform the entire panel on patients

suspected of having APLA. The panel would include

- Anticardiolipin antibodies
- Anti-beta2-glycoprotein Plus at least two coagulation based tests such as:
- dRVVT
- "Lupus inhibitor screen" (different aPTT reagents)

There are many confounding factors when testing for APLA. One is that there is a high rate of false positives with acute thrombosis—especially lupus inhibitors. Most patients who have only an isolated positive lupus inhibitor at the time of diagnosis will on repeat testing will have

negative testing. Second, many patients will have low titers tests, especially anticardiolipin assays so only titers >99th percentile or anticardiolipin antibody titers >40 units are significant. Also the direct oral anticoagulants (DOACs) interfere with all coagulation based testing. Currently the Sydney criteria are used to diagnose APLA syndrome-this requires both clinic and laboratory findings

Laboratory:

One or more positive tests repeatedly positive when tested at least 12 weeks apart:

*lupus inhibitor

*Anticardiolipin antibody- greater than either 99th percentile or greater than MPL or GPL units

*Antibeta2glycoprotein –greater than 99th percentile

Triple Positive-Patients are those with all three tests positive. These patients appear to be at high risk for thrombosis and at higher risk of “breaking through warfarin”. Occasional patients are seen who consistently have negative laboratory testing for APLA but have many of the clinical features of APLA such as thrombocytopenia, thrombosis and miscarriages. It is probable that these patients do have “APLA- negative APLA syndrome” and they should be treated as such.[19]

Clinical Manifestation: The main clinical manifestations of APS are the occurrence of thrombosis(arterial and /or venous) and / or pregnancy morbidity, including recurrent miscarriages, fetal deaths and late pregnancy, stroke are frequent complications such as pre-eclampsia and intrauterine growth restriction . in addition, APS can be associated with a wide variety of other clinical symptoms

- Some of clinical manifestations:
- Neurological manifestations
- Cardiac manifestations
- Thrombocytopenia
- Dermatological manifestations
- Renal manifestations

Management:

Although there are few prospective trials of therapy in APL, several lessons may be learned from retrospective. While APLA does appear to be an autoimmune disease, immunosuppression does not prevent recurrent thrombosis, fetal loss, or neurological syndromes. Therefore, immunosuppressants should not play a role in the therapy of thrombotic APLA. The only exception to this is “catastrophic APLA” where plasmapheresis and immunosuppressants play a crucial role. It used to be thought that anticoagulation with warfarin to an INR of 3.0-3.5 was effective in patients with APLA. However, randomized trials demonstrated that an INR range of 2.0-3.0 is just as effective as the higher INR range- at least for venous diseases. As mentioned above, some patients will fail warfarin and will require more aggressive anticoagulation. [20]. Controversial remains about treatment for arterial diseases-some recommend INR 3.0-3.5 while there is data showing INR 2-3 plus aspirin may be effective. The role of DOAC is unclear. A clinical trial showed DOAC were inferior to warfarin in “triple positive” patients and are contraindicated. For select patients with single positive APLA DOAC may be a consideration if there are challenges with warfarin.[21]

Thrombocytopenia:

Thrombocytopenia in patients with APLA occurs in those patients prone to thrombosis due to activated platelets expressing the epitopes for APLA. The low platelet counts makes



anticoagulation hazardous. In addition, patients with APLA are often high surgical risks. Thrombocytopenia may respond to steroids, immunoglobulin and IV-anti-D. Danazol 200mg po QID is effective in many patients with APLA related thrombocytopenia as well as rituximab

Primary Prophylaxis:

There is no evidence to support primary prophylaxis of persistently positive APL patients should without thrombotic or gestational events. However, these patients should receive prophylactic heparin in situations of high thrombotic risk such as immobilization, hospitalization or postoperative. These patients should also avoid situations that increase the risk of thrombosis such as smoking or the use of estrogen[22]. LA is the test with the highest predictive value for thrombotic events and unfavorable gestational outcomes, and its positivity should be considered when introducing prophylaxis.[23]

Secondary Prophylaxis:

After the acute episode, long-term treatment with oral anticoagulant is therapy of choice. The recommended 2.0 and 3.0 and for arterial phenomena, between 2.5 and 3.5. Recent studies have found that higher INRs, between 3 and 4, added an increased risk of bleeding[24]. In addition to anticoagulant therapy, hydroxychloroquine seems to reduce APL titers and has beneficial antithrombotic role for patients with APS. Therefore, it should be added in all patients with APS associated with SLE.[25] In the specific case of a first episode of atherosclerotic ischemic CVA in low-risk patients, treatment with aspirin 300mg or double antiplatelet therapy may be attempted before anticoagulation is indicated. In case of thromboembolic ischemic CVA the treatment of choice is anticoagulants. It is not yet

known whether non-vitamin K antagonist oral anticoagulant (Xa-factor inhibitors and direct thrombin inhibitors) are effective in the treatment of APS. Clinical trials are being conducted to assess the actual benefit in this subpopulation of patients.[26-27]. Nevertheless, several cases reports of thrombotic events in APS patients taking this new oral anticoagulants were recently published[28]

Treatment of catastrophic APS: Patients with CAPS, in addition to anticoagulation with heparin, should receive immunosuppressions with corticoid heparin, should (prednisone, 1mg/kg/day) or pulses of methylprednisolone associated with plasmapheresis or intravenous immunoglobulin. Rituximab can be used in refractory cases[29]. Recent studies have demonstrated benefits from the use of anti-C5 monoclonal antibody (eculizumab) in patients with CAPS, providing the importance of complement activation in cases of thrombotic microangiopathy.[30]

CONCLUSION:

In conclusion, it is evident that a variety of mechanisms may act independently, or in conjunction, to lead to the clinical features associated with APS. The challenge is to determine with venous and/or arterial thrombosis, and pregnancy loss, as well as the key mechanisms in the non-criteria manifestations of APS.

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HOW TO CITE: Dr. Manchineni Prasada Rao*, Dr. V Rajini, Dr. Y Narasimha Rao, Kattimanda Jaya Prakash, A Review on Hughes Syndrome, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 7, 581-588. <https://doi.org/10.5281/zenodo.15804664>

