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A Review on Antiphospholipid Antibody Syndrome

K. Jaya prakash, Dr, k. Nagalakshmi*, M. Prasad Rao, S. Narendra.
Department Of Pharmacy Practice,
M.A.M College of Pharmacy, Kesanupalli, Narasaraopet (522601), Palnadu District, Andhra Pradesh

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ABSTRACT: Antiphospolipid syndrome (APS) is an autoimmune disease it is a hypercoagualability condition characterized by the development of venous and /or arterial thrombosis and pregnancy morbidity (recurrent early miscarriages, featal deaths after the 10week of gestation and/or premature births) The obstetric manifestations include three or more consecutive unexplained miscarriges, one or more unexplained death of a normal fetus at or beyond the 10^{th} week of gestation, evidence of placental insufficiency or one or more premature birth of a normal neonate before the 34^{th} week of gestation because of eclampsia or preeclampsia, or placental insufficiency serologically, the standads tests for APS are the lupus anticoagulant(acl) or IgG and/or IgManti-ß2 -glycoprotein antibodies (anti-ß2-GpI) which to diagnose the patient must be present on two or more consecutive occasions at least 12 weeks apart the international consensus (revised Sapporo) classification criteria state that APS is present if at least one each of the clinical criteria and one of the laboratory criteria are met.APS treatment is still based on anticoagulation and antiplatelet therapy it is based on indenefinite anticoagulation while low-dose asprin and low moleculer weight heparin are the cornerstone of pregnancy morbidity treatments catastrophic antiphospholipid syndrome is treated with anticoagulation, plasma-exchange, and corticoseteroids . The average age of primary APS patients has been reported to about 35-40 years and the disease is more common in women then in men

Keywords: Antiphospholipid syndrome, anticoagulants, thrombosis

I. INTRODUCTION:

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 involment or multiple vascular occulusions may give rise to a wide variety of presentations in the APS. Any combonitions of vascular occulusive 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 develops the APS. Some estimates indicate that the incidence of APS is around 5 new cases for 100,000 persons for year and the prevealence around 40-50cases for 100,000[4] in subset of patients, thrombosis can involove stimultaneously multiple organs, conifiguring the so-called "catastrophic antiphospholipd syndrome"(CAPS)

EPIDEMOLOGY:

Antiphospholipid antibody are not specific ofAPS and can be found in healthy individuals.Nevertheless, the prevalence of APL postitivity and APS inn 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 and epidemiology of APS between 2000 and 2015an inception cohort of Olmsted country, minesota, 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 100,000n 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 date 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 risk factor for thrombosis The APS action group reported a literatrure review focused on the prevalence of

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antiphospholipid antibodies in the general population with preagnancy morbidity, strocks, myocardial infraction and deep vein thrombosis. The authors estimated that -13% of individual with stock,-11% of individual with myocardial infraction and -9.5% of individual with deep vein thrombosis are positive for antiphospholipid antibodies[7]. Another study in women <50years of age who had a strock showd that 17% were positive for lipus anticoagulant compared with 0.7% in the control group[8]. Positivity for lupus anticoagulant combaind with ostrogen-containing oral contraceptive use or smoking increased the risk further[.

PREGANANCY COMPLICATION: The APS ACTION group showed that 6% of patients with relavent pregnancy morbidity were positive for antiphospholipids antibodies[10]. Recurrent miscarriage is the most frequent complication and is observed in the majiorty(-54%) of women with obstetrical APS included in the European Registry Obstetrical Antiphospholipid syndrome11]. Fetal death is considerd to the consequence of placental dysfunction and is strongly associated with antiphospholipid antibodies[12-13]. In an analyasis of 512 stillbirths 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 prevaleance of antiphospholipid antibodies among patients with SLE ranges from 15% to 34% for lupus anticogulent, from 12% to 44% for anticrdiolipin and from 10% to 19% for anti-ß2-glycoprotein 1 antibodies. Of individual with SLE who are positive for antiphopholipid 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 lymphotrophic 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 realted to thrombotic events and gestational morbididty. Antiphospholipid antibodies(lipus anticoagulant, anticardiolipin and anti-ß2-glycoprotein-I) are classificatory antibodies of the diseases,used for diagnosis, but also important elements in the parthogenesis of APS. Althrough the presence of these antibodies is predisposing factor for thrombotic events, a second triggers, such as infection, prolonged rest or an inflammatory state, s usually necessary for the progression of the syndrome .

Antiphospholipid antibodies bind to phospholipids and plasma or membrane proteins expressed in various cells (platelets, endothelial

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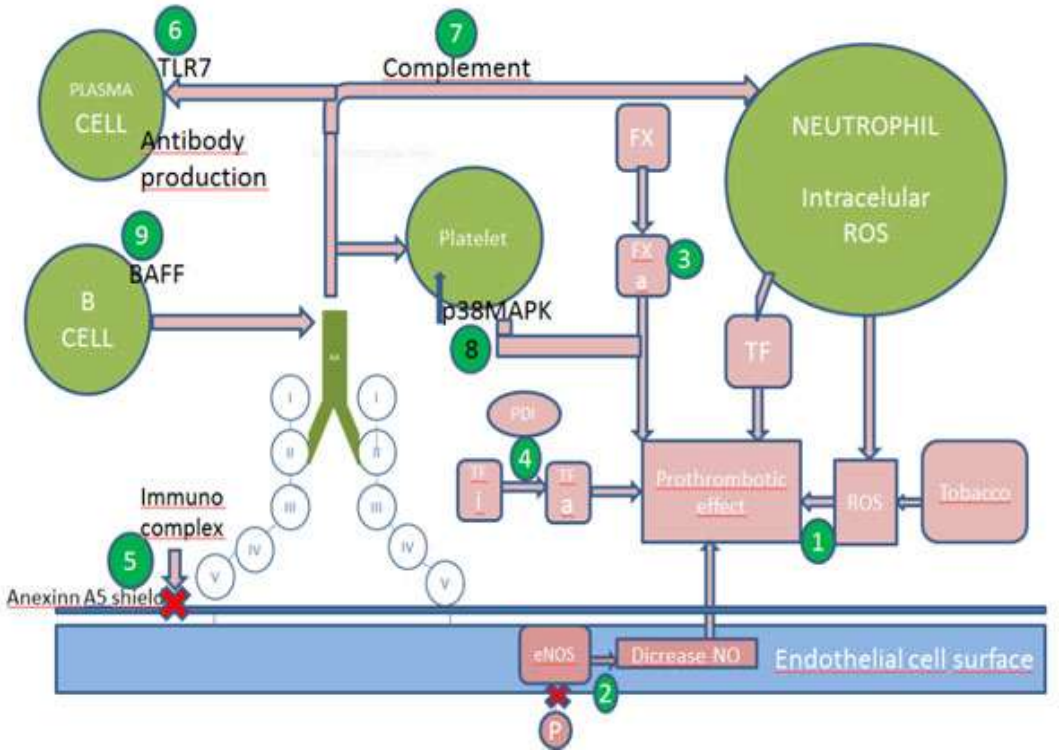
cells, monocytes, fibroblastes and trophoblastes),producing a prothrombotic state. Despite the know thrombophilic action of antiphospholipid antibodies, the exact pathogenises of the diseases is not yet fully elucidated.ß2-glycoprotein-I(ß2GPI) and prothrombin appear to be the major binding proteins in these antibodies involved in the pathogenesis of the disease. There is also a gentic component related to the HLA class2 system that needs to be better studied, and which may predispopose the individual to the disease.[17-18]

The pathophysiology of Antiphospholipid syndrome



Mechanisms of thrombosis and possible targets. Numbers indicates the sites of action of the following drugs: 1N-acetilcystein, 2stains,3 hydroxycholoroquine ,fluvastain and FXa inhibitors(anticogaulents e.g. low molecular weight heparin ,fondaparinux, rivaroxaban and edoxaban),4 PDI inhibitors and hydroxycholorquine, 5hydroxychloroquine, 6 TLR7 inhibitors, 7 heparin, eculizumab, 8 belimumab

DIAGNOSIS:

There is no single test 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 teasting forAPLA. One is the there is ahigh ratye of false postivites with acute thrombosis-especially lupus inhibitors. Most patients who have only an isolsalted positive lupus inhibitor at the time of diagnosis will on repeat testing will have negativite testing. Second, many patients will have low titers tests, especially anticardiolipin assys so only titers >99th percentile or anticardioplipin antibody titers >40units are significant. Also the direct oral anticoagulants (DOACs) interfere with all coagulation based testing.

Currently the Sydney criteria are used to diagnoses APLA syndrome-this requires both clinic and laboratory findings

LABORATORY:

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

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*lupus inhibitor

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

*Antibeta2glycoprotien –greater than 99th percentile

TRIPLE POSTIVE 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 wafarin".

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 preagnancy morbidity, including recurrent miscarriages, featl deths and late preagnancy, strockare frequent complications such as pre-eclamsia and intrauterine growth restrication . in addition, APS can be asspciated with a wide variety of other clinical symptoms

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

MANAGEMENT:

Although there are few prospective trails of therapy in APL, several lessons may be learned from retrosepective. While APLA does apper to be an autoimmune disease, immunosuppression does not prevent recurrent thrombosis, featl loss, or neurological syndromes. Therefore, immunospperssions should not play a role in the therpy of thrombotic APLA. The only exception to this is "catastrophic APLA" were plasmapheresis and immunosuppressions playas a crucial role.

It used to be thought that anticoagulatuion with wafarin to an INRof 3.0-3.5 was effective in patients with APLA. However, randomized trails 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 wafrin and will require more aggressive anticoagulation. [20]

Controversial remains about treatment for arterial diseases-some recommend INR 3.0-3.5 while there is date showing INR 2-3 plus asprin may be effective

The role of DOAC is unclear. A clinical trail show 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 occursin those patients prone to thrombosis due to activated platelets expressing the epitopes for APLA. The low platelet counts makes anticoagulation hazardus. In addition , patients with APLA are often high surgical risks. Thrombocytopenia may responded to steroids, immunoglobulin and IV-anti-D. Danazol 200mg po QID is effective in many patients with APLA realted thrombocytopenia as well as rituximab

PRIMARY PROPHYLAXIX: There is no evidence to support primary prophyloxis 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 somking or the useof 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,longe-term treatment with oral anticoagulant is therapy of choice. The recommened 2.0and 3.0 and for arterial phenomena, between 2.5 and 3.5. recents studies have found that higher INRs, between 3and 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 specifc case of a first epiode of atherpsclerotic ischemic CVAin low-risk patients, treatment with

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asprin 300mg or double antiplatelet therapy may be attempted before anticoagulation is indicated. In case of thromboemoblic ischemiaCVA the treatment of choice is anticoagulants

It is not yet known whether non-vitamin k antagonist oral anticogalent (Xa-factor inhibitors and direct thrombin inhibitors) are effective in the treatment of APS. Clinical trails are being conducted to assess the actual benefit in thise subpopulation of patients.[26-27] . nevertheless, several cases reports of thrombiotic events in APS patients taking this new oral anticogalants were recently published[28]

Treatment of catastrophic APS: Patients with CAPS, in addition to anticoagulation with heparin, should recives 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 monclonal antibody (eculizumb) in patients with CAPS, providing the importance of complement activation in cases of thrombotic microangiopathy.[30]

II. CONCLUSION:

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

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