Epidemiology, Evaluation and Management of Anti-phospholipid Syndrome

Abstract: The presence of antiphospholipid antibodies in the context of thrombosis and/or pregnancy loss is known as antiphospholipid syndrome (APLS). Antiphospholipid syndrome (APS) is an autoimmune thromboinflammatory condition that affects individuals and their families in a negative and often fatal way. There are the two types of APS: Primary APS, which develops on its own, and secondary APS, which is linked to another autoimmune disorder, most often systemic lupus erythematosus (SLE). The HLA-DR7, DR4, DRw53, DQw7, and C4 null alleles have all been linked to APLS. APS is frequently misdiagnosed due to clinical diversity and a lack of diagnostic test consistency. The classification criteria were created to categorise APS patients for research reasons, but they can also be used by professionals to establish diagnoses. Long-term warfarin or other vitamin K antagonist medication is the current standard treatment for unprovoked thrombosis. Low-dose aspirin and prophylactic heparin, mainly low-molecular-weight heparin, are used to avoid repeated obstetric problems. In this article we'll be looking at Anti-phospholipid Syndrome, it's etiology, epidemiology, evaluation and management**.**

Introduction:

Antiphospholipid antibodies are autoantibodies that target proteins that bind to phospholipids. The presence of antiphospholipid antibodies in the context of thrombosis and/or pregnancy loss is known as antiphospholipid syndrome (APLS). The lower limbs and cerebral arterial circulation are the most prevalent locations of venous and arterial thrombosis, respectively. Thrombosis, on the other hand, can affect any organ. [1] Antiphospholipid syndrome (APS) is an autoimmune thromboinflammatory condition that affects individuals and their families in a negative and often fatal way. Obstetrical issues, such as eclampsia or severe preeclampsia, which causes premature birth, as well as foetal death beyond the 10th week of pregnancy, are well-known in APS. Other clinical features such as persistent thrombocytopenia, hemolytic anaemia, livedo reticularis, APS nephropathy, and cognitive dysfunction, in addition to thrombosis and pregnancy complications, have been linked to APS and are often referred to as "non-criteria" or "extra-criteria" manifestations. [2,3-6]

In the presence of APLA, a small number of patients develop catastrophic anti-phospholipid syndrome (CAPS), which is defined as small vessel thrombosis in three or more organs in less than one week with histopathologic confirmation of small vessel thrombosis in the absence of inflammation in less than one week. CAPS is associated with a significant (50 percent) death rate, largely owing to cerebral and heart thrombosis, infections, and multi-organ failure, which is typically initiated by a precipitating event such as infection. Premature birth of one or more morphologically normal neonates before the 34th week of gestation due to either eclampsia or severe preeclampsia, and/or three or more unexplained, consecutive spontaneous abortions before the 10th week of gestation are all examples of obstetrical morbidity in APS. Thrombocytopenia, livedo reticularis, skin ulcers, and transient ischemic episodes are among the APLA's 'non-criteria' clinical correlations. [7-14]

Primary APS, which develops on its own, and secondary APS, which is linked to another autoimmune disorder, most often systemic lupus erythematosus (SLE), both are the two types of APS. The prevalence of APS in the general population is estimated to be 50 cases per 100,000, with an annual incidence of 2.1 cases per 100,000. Antiphospholipid antibodies (aPL) have been shown to be positive in as many as 13% of patients with stroke, 11% of patients with myocardial infarction, and 9.5 percent of patients with deep vein thrombosis, according to observational studies. It's still unclear how often consistently positive aPL is in the general population. [2,15-17]

Etiology and Pathophysiology:

Antiphospholipid syndrome can be primary when no signs or symptoms of autoimmune illness are present, or secondary to autoimmune diseases such as systemic lupus erythematosus (SLE) in 40% of cases. Coagulation factor mutations, for example, increase the incidence of antiphospholipid antibody-associated thrombosis. The HLA-DR7, DR4, DRw53, DQw7, and C4 null alleles have all been linked to APLS. Antiphospholipid antibody (APLA) production has been linked to infections such as borrelia burgdorferi, treponema, HIV, and leptospira. APLA production can be induced by a variety of medications, including chlorpromazine, procainamide, quinidine, and phenytoin. Low amounts of APLA are also often seen. [1,18,19]

Most APLA are now known to be directed against phospholipid binding proteins produced on or coupled to an appropriate surface such as a cellular membrane. APLA were previously supposed to react with anionic phospholipids such as cardiolipin. Although additional antigenic targets such as prothrombin have been discovered, anti-2GPI antibodies appear to be crucial to the pathophysiology of APS. In a mouse model, affinity-purified anti-2GPI antibodies from patients with APS potentiate thrombosis, and anti-2GPI antibodies are linked to a greater risk of thrombosis than aCL or anti-prothrombin antibodies. [7]

Several organisations have studied miRNAs in the pathophysiology of APS in recent years. Forced overexpression of particular miRNAs (miR-19b and miR-20a) in tissue factor-expressing cell lines lowered tissue factor messenger RNA levels and cellular procoagulant activity, according to one study. When compared to healthy controls, monocytes from APS patients appear to have considerably lower levels of miR-19b and miR-20a, with low levels of these miRNAs indicating an elevated amount of tissue factor. In vitro treatment of healthy-donor neutrophils, monocytes, and endothelial cells with pure aPL IgG reduced the expression of several miRNAs, according to another research. At the same time, differences in circulating miRNA expression can distinguish APS patients from healthy controls; for example, transcriptomic analysis of plasmacytoid dendritic cells from APS and SLE patients revealed that lower miRNA expression (miR-361-5p, miR-128-3p, miR-181a-2-3p, and others) is linked to a higher type I interferon signature. [2,20-23]

Complement activation appears to have a role in the pathogenesis of pregnancy morbidity in APS patients, according to animal models. In comparison to control placental specimens, the histopathology of placental tissues from individuals with APS reveals indications of complement activation, according to preliminary data from recent publications. Complement deposition, on the other hand, may be identified in both abortive and term placentas, with no obvious link to pregnancy outcome or treatment. Although further research is needed to prove solid results about complement's participation in APS-related pregnant morbidity, the possibility of complement's role in aPL-mediated clinical symptoms should not be overlooked. Complement components can influence the actions of pro-coagulant cells (monocytes, endothelial cells) as well as decidual or trophoblastic cells, in addition to generating acute local inflammation. [24]

In conclusion, the prothrombotic and proinflammatory processes mediated by aPL are expected to include a variety of pathways. The significance of miRNAs in APS pathogenesis is becoming more well-known. Neutrophils and NET formation have just recently been studied, thus further study is needed to determine if neutrophils are feasible treatment targets in APS patients, as well as how neutrophils interact with other well-known participants in APS pathophysiology such endothelial cells and platelets. It's believed that medicines targeting NETs, at least for a subgroup of APS patients, may hold significant potential. [2]

Epidemiology:

According to literature, 30 to 40 percent of patients with aPL had a history of thrombosis, with the arterial bed accounting for 30 percent of the occurrences. The cerebral circulation is the most usually afflicted arterial area, followed by the coronary arteries and other arterial regions. A meta-analysis of research on the relationship between LAC, IgG/IgM aCL, and arterial thrombosis indicated a robust link between LAC and arterial thrombosis, but a considerably weaker link between aCL and arterial thrombosis. Only the aCL IgG isotype and moderate/high antibody titers were shown to be substantially linked to arterial thrombosis in general (first cerebral stroke or myocardial infarction). Arterial events are also the most common recurrences, even in APS patients who have already been identified and treated, according to the 5-year follow-up on the European dataset. [24-27]

Anticardiolipin antibodies of low titer can be found in up to 10% of healthy people, and the likelihood of a positive APLA test rises with age. High titers and long-term positive are uncommon in healthy people (less than 1 percent). Patients with SLE are more likely to have a positive APLA test, as well as a clinical result linked to APLA (thrombosis or pregnancy-related morbidity). Patients with SLE who have a positive APLA test proceed to APLS in 50 to 70% of cases. Up to 20% of individuals with rheumatoid arthritis have been shown to have APLA positive. A study of 197 couples with a history of abortions discovered that 20% of them had APLA. In another research, 14 percent of patients with recurrent venous thromboembolism had APLA (lupus anticoagulant or anticardiolipin antibodies). [1,28-31]

Since the discovery of a link between aPL and syphilis, aPL has been linked to a variety of viral, bacterial, and parasitic illnesses. Hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus, varicella-zoster, Epstein–Barr virus, adenovirus, and parvovirus B19 are the most prevalent infections linked with aPL, with HIV infections having a frequency of up to 49 percent. Antibodies discovered in most infections were 2GPI independent, meaning they didn't interfere with anticoagulation, although there were a few exceptions. In bacterial infections, aCL are often found in leprosy (42.7%), where they frequently demonstrate anti-2GPI activity (44.8%), and in syphilis infections (8 to 67 percent). Antiphospholipid antibodies linked with infections are typically transitory, with just a few occurrences of APS clinical symptoms. [24]

Evaluation:

APS is frequently misdiagnosed due to clinical diversity and a lack of diagnostic test consistency. The classification criteria were created to categorise APS patients for research reasons, but they can also be used by professionals to establish diagnoses. At least one of the clinical requirements (vascular thrombosis and/or pregnancy morbidity) and one of the laboratory criteria (lupus anticoagulant persistence for more than 12 weeks and/or medium–high titers of IgG or IgM autoantibodies against 2GPI or cardiolipin) must be met. Many symptoms are excluded from this categorization since they may reduce the diagnosis' specificity. IgA aCL and anti-2GPI Abs, antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antivimentin/cardiolipin antibodies, antiphosphatidylinositol antibodies, antiphosphatidylglycerol antibodies, antibodies against prothrombin, and antibodies to the phosphatidylserine/prothrombin complex are all antibodies (Abs) that have been linked to APS but are not currently included in the classification criteria of APS. [32]

aPL profile and thrombotic risk: Anticardiolipin antibodies are a better predictor of arterial and venous thrombosis than LA positive. However, the strength of the link varies significantly between studies, which might be due to the diverse methodologies used to identify LA or the variable inclusion of LA that were not persistently positive. There is no consistent link between thrombosis and aCL in retrospective and prospective investigations. The anti-2GPI antibody has been

recommended as the more clinically important and predictive aPL since 2GPI is the main antigen in APS. Although several retrospective studies have shown that anti-2GPI antibodies do correlate with thrombotic risk, these findings have not been universally confirmed, and recent studies suggest that the thrombotic risk conferred by anti-2GPI antibodies is modest, with odds ratios ranging from 1.5 to 2.5. [33]

Antibodies to cardiolipin and 2GPI are identified using standardised enzyme-linked immunosorbent assay techniques. The partial thromboplastin time, the dilute Russell's viper venom time, and the Kaolin clotting time are all phospholipid-dependent laboratory procedures that can identify LA. The LA test should be done according to the International Society on Thrombosis and Haemostasis standards. Because both heparin and warfarin impair the LA test, testing during therapy is typically not recommended. [32]

Management:

Long-term warfarin or other vitamin K antagonist medication is the current standard treatment for unprovoked thrombosis. Low-dose aspirin and prophylactic heparin, mainly low-molecular-weight heparin, are used to avoid repeated obstetric problems. Although nonanticoagulation medicines that address several established causes of illness are being studied, the best treatment for conventional therapy failures or some nonthrombotic symptoms is unknown. [34]

Primary thromboprophylaxis refers to preventing thrombosis in people who have never had a clot before, whereas secondary thromboprophylaxis refers to preventing clot recurrence after a first thrombotic episode. Thromboprophylaxis is still one of the most difficult aspects of APS. In primary thromboprophylaxis, traditional control of cardiovascular risk factors through lifestyle modifications is critical. Antiplatelet medications like low-dose aspirin (LDA) should only be used by people who are at extremely high risk. Anticoagulation is used in secondary thromboprophylaxis, mostly with vitamin K antagonists (such as warfarin or heparin), however direct oral anticoagulants (DOACs; such as rivaroxaban) may also play a role. [35]

Because of food and medication combinations, bleeding issues, and the necessity for regular monitoring, the use of VKAs may be troublesome in certain individuals.

Furthermore, aPL has a distinct effect on thromboplastin reagents, which might influence the international normalised ratio. DOACs have the potential to address some of these concerns because they are fixed-dose, don't require frequent monitoring, and are successful in treating venous thrombosis in those who aren't pre-screened. However, there is little experience with these medications in APS patients. Recurrent thrombosis was recorded in eight of the 18 patients in three recent case series, indicating care when contemplating the use of DOACs in patients with APS. Rivaroxaban is being tested in court. DOACs should be used with caution in these patients in the lack of prospective evidence, and should be confined to those who fail or are intolerant of a VKA or low molecular weight heparin. [33]

Low-dose prednisolone in recurrent first-trimester pregnancy loss improved the rate of live births in refractory antiphospholipid antibody-related pregnancy loss or losses to 61 percent in a retrospective cohort of 18 patients when combined with conventional treatment with LDA and LMWH administered from positive pregnancy test until week 14. Two randomised controlled trials looked at the use of intravenous immunoglobulins. The first trial, which randomised 40 women with antiphospholipid antibody-related recurrent first-trimester pregnancy loss to intravenous immunoglobulins or a combination of LDA and LMWH, found that intravenous immunoglobulins had no effect. In a second experiment, intravenous immunoglobulins were found to have no advantage over LDA and LMWH in terms of obstetrical or newborn outcomes. However, women who were randomly allocated to the intravenous immunoglobulins arm had a decreased likelihood of foetal growth restriction and newborn critical care hospitalisation, prompting some physicians to explore intravenous immunoglobulins as an adjuvant in situations when other treatments have failed. [35-39]

Primary thromboprophylaxis focuses on careful management of any extra vascular risk factor (e.g., hypercholesterolemia, obesity, lack of physical activity, smoking) that should be treated according to current guidelines. Oral contraceptives that contain oestrogen should be avoided, but progestin-only contraception (sometimes known as the mini-pill) is thought to be safe. Thromboprophylaxis is especially recommended in high-risk scenarios (surgery, post-partum, long-term immobilisation). The use of low-dose aspirin (LDA, 75–100 mg per day) in people with persistent positive of numerous and/or high-titer

aPL is still debatable, but it should be considered in persons with persistent positivity of multiple and/or high-titer aPL. [32]

Provoked and unprovoked venous thromboembolic events can be distinguished; provoking variables include recent hospitalisation, the use of oestrogen-containing medications, or pregnancy. Many doctors just provide a brief course of anticoagulation (3–6 months) in provoked incidents, regardless of the existence of antiphospholipid antibodies, and then offer thromboprophylaxis at the time of haemostatic stress, just as they would in anybody who has had a previous thrombotic event. Unprovoked venous and arterial thrombosis are dangerous and should be treated with long-term anticoagulation with a vitamin K antagonist (such as warfarin) or, in rare cases, LMWH. [35]

Conclusion:

There's no doubt that antiphospholipid syndrome is one of serious conditions that can face the healthcare systems. diagnosis of such syndrome is important because early diagnosis plays key role in reducing complications and mortality, however it is also problematic because it's frequently misdiagnosed due to clinical diversity and a lack of diagnostic test consistency. That's why more reliable diagnoses techniques need to be developed. Treatment Long-term warfarin or other vitamin K antagonist medication is the current standard treatment for unprovoked thrombosis. There are multiple trials for new type medications are being researched and hopefully can lead to improvement in the management protocols for the syndrome.

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