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Antiphospholipid syndrome: Autoimmunity and thrombosis

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Abstract

The rare systemic autoimmune disease known as antiphospholipid syndrome (APS) is typified by persistent antiphospholipid antibodies (aPL) along with obstetric morbidity, recurrent thrombosis in the veins and/or arteries, and other non-thrombotic related complications. Obesity, diabetes, hypertension, and cardiovascular diseases are among the long-term health problems that children from difficult pregnancies may be more susceptible to, which could impact their wellbeing both during childhood and into adulthood. Antiphospholipid antibodies' precise etiology is unknown. Being an autoimmune disease, APS causes antibodies to target healthy molecules such as phospholipids, which interferes with coagulation and makes the patient more prone to thrombophilia. The cornerstones of the current preventative treatment standard for APS are anticoagulation and antiplatelet therapy. One significant preventable cause of early pregnancy loss is APS. Preventing obstetric complications requires early risk assessment and individualized treatment, which may include vitamin D, folic acid, and aspirin.

Keywords: Autoimmune disease; Thrombophilia; Antiphospholipid antibodies (aPL); Coagulation; Obstetric complications

1. Introduction

Antibodies/aPLs (anticardiolipin antibodies/ACLA, lupus anticoagulant/LA, and anti-ß2-glycoprotein/anti-ß2-GPI) that identify and target phospholipid-binding proteins rather than phospholipid itself are found in blood of people with Antiphospholipid Syndrome (APS), an autoimmune thrombophilic disorder. [1,2] These antibodies are linked to venous and/or arterial thromboses as well as a number of early and late pregnancy complications.[3]

Lupus anticoagulant (LA), anticardiolipin antibodies (aCL) IgG and IgM, and anti-â2-glycoprotein 1 IgG and IgM antibodies are the three primary antiphospholipid antibodies. Pregnancy complications like preeclampsia (PE), fetal growth restriction (FGR), recurrent early fetal loss, and fetal death are linked to antiphospholipid syndrome.[4]

Generally, children born into such difficult pregnancies may be more susceptible to a number of diseases throughout their childhood and adulthood, including obesity, diabetes, hypertension, and cardiovascular conditions.[5]

The so-called antiphospholipid syndrome, a novel autoantibody-mediated pathology, was initially identified in 1983 as an acquired form of thrombophilia. APS can appear as a secondary disorder in combination with other autoimmune diseases, particularly systemic lupus erythematosus (SLE), or as a primary, isolated condition. In addition to the immune system's malfunction, which is one of its primary causes, the dysregulation of complement also seems to play a role by

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generating harmful antibodies.[6] There is currently agreement that APS patients with thrombosis should be treated with long-term oral anticoagulation and that heparin and aspirin should be used to avoid obstetric symptoms.[7]

2. Etiology

The cause of these antibodies is unknown. Because antiphospholipid syndrome is an autoimmune condition, the body may create antibodies that identify different molecules in the body that it would not normally recognize. In addition to their other roles, these molecules (phospholipids, for example) play a part in the coagulation cascade. It is unknown exactly how antiphospholipid antibodies cause a thrombophilic state.[8]

There are several hypotheses to explain the probable cause.

Autoimmune diseases in the fetus and newborn are mediated by the passive transfer of maternal antibodies. It is unclear how immune complex formation and excessive autoantibody production occur.

There have been reports of aPL occurring in families, and HLA-DR4, DR7, DRw53, and the C4 null allele have been proposed as genetic associations (11).

Microorganisms and the inner surface of cells both contain PL molecules, which are found throughout nature. Thus, cellular membranes may be disrupted during infectious disease processes, such as bacterial (e.g., bacterial endocarditis, tuberculosis, Mycoplasma pneumonia), viral (e.g., HIV, Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenoviruses), spirochetal (e.g., syphilis, leptospirosis, Lyme disease), and parasitic (e.g., malaria infection). APL antibodies are stimulated and released by PLs.[9]

Antiphospholipid antibodies can be broadly classified as either anticardiolipin antibodies (aCL), which target a molecular congener of cardiolipin (a bovine cardiac protein), or lupus anticoagulants (LA), which prolong phospholipid-dependent coagulation assays. In coagulation tests based on the activated partial thromboplastin time, lupus anticoagulants (LA) lengthen the clotting time and decrease the plasma's coagulant potential.[10]

3. Pathophysiology

Immune cells, endothelial cells, and the coagulation cascade interact intricately in the pathophysiology of APS. B-cells produce antibodies against antiphospholipids (aPLs). APLs were thought to be able to bind anionic phospholipids like cardiolipin and phosphatidylserine at first, but it was later found that they target specific phospholipid-binding proteins like prothrombin, annexin, β2 glycoprotein I (β2-GPI), and others. By interacting with these proteins, these antibodies can stimulate inflammatory processes, activate endothelial cells, and upregulate procoagulant factors, all of which greatly contribute to the pathophysiology of thrombosis observed in antiphospholipid syndrome.[11]

4. Tests used for diagnosis of the antiphospholipid syndrome

A combination of coagulation tests and immunoassays is used to diagnose antiphospholipid syndrome (APS). Certain antiphospholipid antibodies, such as anti-β2 glycoprotein I (β2-GPI), anticardiolipin, antiprothrombin, and antiphosphatidylserine antibodies, can be found using immunoassays. APS may also be indicated by a biologic false-positive serologic test for syphilis, such as the VDRL or RPR. The goal of coagulation tests is to detect anticoagulant activity in lupus. These include activated partial thromboplastin time (aPTT) using a panel of aPL-sensitive and aPL-insensitive reagents, the dilute Russell viper venom time (DRVVT) and confirmatory tests, and mixing studies to find inhibitors. The diagnosis is further supported by other techniques like the platelet neutralization procedure (PNP), kaolin clotting time (KCT), and plasma clotting time. [12]

5. Management

Anticoagulation and antiplatelet therapy are the cornerstones of the current preventative treatment standard for APS. A live birth rate of 70–80% has been achieved when heparin (unfractionated heparin, or LMWH) and low-dose aspirin (LDA) are combined; however, some trials have not demonstrated any increases in live birth rates with LMWH.

Prospective randomized controlled trials are therefore required to validate the role of novel medications, such as the antimalarial hydroxychloroquine and pravastatin, which are suggested by more recent data. In a retrospective single center case control study, Lefkou et al. emphasized the possible positive effects of pravastatin on women with aPL-

related PET and/or IUGR undergoing standard of care treatment, such as LDA and LMWH. Furthermore, the European Medicines Agency (EMA) has licensed the antimalarial hydroxychloroquine (HCQ) for the treatment of APS, and HCQ is currently the focus of attention in both obstetric and thrombotic APS. According to retrospective data, HCQ lowers the risk of thrombosis in APS.

Two flawed retrospective studies have linked the use of HCQ in obstetric APS to better pregnancy outcomes for women with pregnancy complications related to aPL. Due to its favorable safety profile, HCQ is currently advised globally for expectant mothers who need immune-modulation for systemic lupus erythematosus. Randomized controlled trials evaluating the role of HCQ in women with aPL are still desperately needed, though, and the outcomes of HYPATIA, a current randomized controlled trial in pregnancy, are eagerly anticipated. [13]

6. Conclusion

APS is the most prevalent acquired risk factor for a treatable cause of recurrent first-trimester pregnancy loss. Understanding the risk factors linked to a poor pregnancy outcome at preconception or the start of pregnancy could be a critical step in managing and treating APS in order to prevent obstetrical complications and determine the best combination therapy. A treatment plan must be developed (conventional vs. additional therapy), and a regimen involving low-dose aspirin, folic acid, and vitamin D supplements should be recommended during the preconception evaluation. In actuality, extra care must be customized for every patient.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare no conflict of interest regarding this review article.

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