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Antiphospholipid syndrome: A diagnostic challenge

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ABSTRACT

The antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilic disorder that is characterized by thrombosis (venous, arterial and microvascular) and obstetric morbidity due to a diverse family of antibodies against phospholipid-binding proteins present in plasma. The term antiphospholipid antibody is actually a misnomer as the antibodies are not against the phospholipid per se, but target the plasma protein co-factors, which bind to anionic PLs. The exact etiology has not been elucidated and is multifactorial.

The initial guidelines for the diagnosis of APS were laid down in Sapporo, 1999, which were subsequently revised as the Sydney Consensus Conference criteria in 2006. Major changes were the inclusion of β2GPI as independent laboratory criteria, addition of ischemic stroke and transient cerebral ischemia as established clinical criteria and the requirement of repeating the test after 12 weeks. The laboratory tests recommended are coagulation assays, which study the effect of lupus anticoagulant on the clotting time and immunological assays, mostly ELISAs to detect IgG and IgM antibodies against cardiolipin and/or β2 glycoprotein I. For the diagnosis of APS, at least one clinical criterion and one laboratory criterion should be present. Limitations pertaining to the standardization, reproducibility and robustness of the currently recommended diagnostic tests still remain.

Despite elaborate guidelines and syndrome defining criteria, the diagnosis of APS still remains a challenge. A greater interaction between the clinicians and the laboratory professionals is necessary for arriving at the correct diagnosis as a misdiagnosis of APS can have grave consequences.

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Introduction

The antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilic disorder characterised by venous/arterial thrombosis and pregnancy morbidity due to a diverse family of antibodies against phospholipid-binding plasma proteins. Although the scientific community has come a long way in understanding APS since its first description in 1983,[1] correct and timely diagnosis of this entity still remains a challenge.

Historical overview

The journey of antiphospholipid antibodies (APLA) began with the discovery of a complement fixation assay for syphilis in 1907 by Wasserman et al.[2] In 1941 Pangborn demonstrated that the reagin used by Wasserman was an anionic phospholipid (PL) and renamed it cardiolipin.[3] However, as serological screening for syphilis became more widespread, it became evident that these tests were positive in many individuals with no symptoms of the disease. In 1952, Moore and Mohr found these transient false-positive tests to be associated with many other contagious diseases besides syphilis, SLE and other autoimmune disorders.[4] Almost concurrently, Conley and Hartmann described an acquired circulating inhibitorin 2 patients of SLE.[5] Bowie et al. in 1963 showed that it led to thrombosis and not bleeding.[6] Finally the term ''lupus anticoagulants'' was introduced in 1972 by Feinstein and Rapaportfor antibodies against PLs which prolonged the in-vitro clotting time. Harris and co-workers introduced the first radioimmunoassay for the detection of anticardiolipin (aCL) antibodies in 1983 by as well as the first quantitative ELISA two years later.[7] Using this ELISA they studied SLE patients and reported an increased incidence of thrombosis and pregnancy morbidity in the subgroup with increased aCL antibodies. Professor Graham RV Hughes, an eminent rheumatologist played a central role in describing this clotting disorder. Thus the entity of anticardiolipin syndrome/antiphospholipid syndrome also known as Hughes Syndrome came into existence in 1983.

In the 1990s various studies showed that the term APLA is actually a misnomer as the antibodies are not against the PL per se, but target the plasma protein co-factors which bind to anionic PLs. Beta2 glycoprotein 1 (β2GPI) is the commonest such autoantigen. Other autoantigens such as prothrombin (PT), annexin V and phosphatidylethanolamine are less commonly found.[8] Further studies showed that β2GPI-dependent antibodies were seen in autoimmune diseases whereas β2GPI-independent APLA were found in patients with infectious diseases.[9]

Etiology

The exact etiology has not been elucidated and is multifactorial. APS can be primary or secondary to an underlying disease. APLAs have been found in autoimmune diseases (most commonly SLE), infections such as hepatitis C, parvovirus B19, human immunodeficiency virus (HIV), adenovirus, human herpes virus, leprosy and syphilis, after treatment with drugs such as quinine, procainamide, oral contraceptives, phenothiazine and anti-tumor necrosis factor, in association with malignancies and even in otherwise healthy individuals. Epitope mimicry has been postulated as a plausible cause in autoimmune diseases. Genetic and environmental factors have also been shown to determine the occurrence and clinical expression of APS.[10] A small amount of antiphospholipid antibody is normal as it helps in removing dying and damaged cells. However people with APLA manifesting as APS have too much of APLA/abnormal variant of APLA and/or abnormal β2-glycoproteinI.

Pathophysiology

The APLAs have both a procoagulant as well as an anticoagulant effect (Table 1). Eventually, it is still not clear why the procoagulant effect predominates over the anticoagulant effect.

APS represents about 15% of the cases of recurrent pregnancy losses. The obstetric complications due to APLA cannot, however, be explained only by thrombotic or ischemic mechanisms. It is proposed that APLAs bind to phosphatidylserine which is exposed during trophoblast syncytium formation causing inhibition of its proliferation and induction of apoptosis. Annexin V has been observed on the surface of syncytiotrophoblasts and is crucial for placental development and integrity. Anti-annexin antibodies found in APS patients could affect embryo implantation and cause pregnancy morbidity by causing apoptosis of syncytiotrophoblasts and loss of trophoblastic gonadotropin secretion. In addition up-regulated coagulation and placental inflammation has been suggested to explain both recurrent miscarriage and fetal losses.[11]

Clinical manifestations

The core clinical manifestations of APS are thrombotic (arterial, venous or microvascular thrombosis) and obstetric complications. Contrary to the other conditions predisposing to hypercoagulability, in APS there is no predilection for any territory and thrombosis can affect both the veins and arteries including capillaries. The commonest venous and arterial sites of thrombosis are the deep veins of lower limbs and the cerebral arteries, respectively. Diagnostic clinical criteria do not include superficial venous thrombosis. The other major clinical manifestations of the APS are obstetrical. As per Sydney criteria they include:

i. Unexplained fetal loss at or after the 10th week of gestation (normal fetal morphology on ultrasonography or direct examination) or
ii. Eclampsia or severe preeclampsia causing premature birth (<34th week of pregnancy) of one or more morphologically normal fetus or
iii. Three or more unexplained, consecutive early pregnancy loss (<10th week of pregnancy) with normal maternal and paternal factors.[12]