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Catastrophic antiphospholipid syndrome and pregnancy

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ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) is a rare but life-threatening condition that may be precipitated by pregnancy. The condition can be hard to diagnose since it mimics other thrombotic microangiopathies that are associated with pregnancy. Accurate and timely diagnosis is critical for effective treatment. In this review, we highlight pertinent clinical features of CAPS so that obstetricians will be able to recognize and treat the condition.

Antiphospholipid antibodies and antiphospholipid syndrome

Antiphospholipid antibodies (aPL) are a heterogeneous group of autoantibodies recognizing epitopes expressed by negatively charged phospholipids, proteins, or a protein-phospholipid complex.[1] The true *in vivo* epitope in humans is uncertain. These antibodies are associated with several clinical problems including arterial and venous thrombosis.[1] Approximately 2% of individuals with thrombosis will have aPL[2] as will 4–5% of individuals <50 years of age with stroke.[3,4] The locations of the thromboses may be atypical although deep venous thrombosis and pulmonary embolism are the most common types of thrombosis in people with aPL. Manifestations of arterial thrombosis may include transient ischemic attacks and amaurosis fugax. Other medical complications associated with aPL include thrombocytopenia, livedo reticularis, autoimmune hemolytic anemia, chorea gravidarum, transverse myelitis, pyoderma-like leg ulcers, and cardiac valve disease.[1]

aPl are also associated with obstetric complications including recurrent pregnancy loss, fetal death, fetal growth restriction (FGR), pre-eclampsia, and medically indicated preterm birth.[5,6] A unifying feature of these conditions is placental insufficiency and aPL are thought to damage the placenta via thrombosis and inflammation.[7] Accordingly, most losses associated with aPL occur after 10 weeks gestation.[8]

Antiphospholipid syndrome (APS) is considered present in individuals with specified levels of aPL as well as characteristic clinical features. Clinical and laboratory criteria are shown in Table 1.[9] APS often coexists with other autoimmune conditions, especially systemic lupus erythematosus (SLE). This occurs about 50% of the time and such people are considered to have secondary APS. APS without other autoimmune disease is termed primary APS.

Numerous aPL have been described but three are best characterized, most strongly associated with clinical features of APS and are considered criteria for APS. These include lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-beta-2-glycoprotein-I antibodies (β_2-GP-I). LA is detected by phospholipid-dependent clotting tests. These include the activated partial thromboplastin time, dilute Russel viper venom time, Kaolin clotting time, and plasma clotting time. The LA antibody interferes with these assays, leading to a prolongation in clotting times. Since there are other reasons for prolongation of clotting times such as clotting factor deficiencies and specific inhibitors, confirmatory testing is performed if the assay is prolonged. LA is reported as “present” or “absent.”

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Table 1 – Revised classification criteria for diagnosis of the antiphospholipid antibody syndrome (APS)[a]

Clinical criteria

1. Vascular thrombosis[b]: One or more clinical episodes of arterial, venous, or small-vessel thrombosis, any tissue or organ confirmed by objective, validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology).
2. Pregnancy morbidity:
   a. One or more unexplained deaths of a morphologically normal fetus at or beyond 10 wk of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b. One or more premature births of a morphologically normal neonate before the 34th wk of gestation because of (i) eclampsia or severe pre-eclampsia or (ii) recognized uteroplacental insufficiency, or
   c. Three or more unexplained consecutive euploid spontaneous abortions before 10 wk of gestation, with maternal anatomic or hormonal abnormalities and paternal and parental chromosomal causes excluded.

Laboratory criteria[c]

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 wks apart, detected according to the guidelines of the ISTH Scientific Subcommittee on lupus anticoagulants/phospholipid-dependent antibodies.
2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high tier (i.e., >40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 wk apart, measured by a standardized ELISA.
3. Anti-β_2-glycoprotein-1 antibody or IgG or IgM isotype in serum or plasma (in titer >99th percentile), present on two or more occasions, at least 12 wk apart, measured by a standardized ELISA, according to recommended procedures.

aPL, antiphospholipid antibody; BMI, body mass index; ELISA enzyme-linked immunosorbent assay; GFR, glomerular filtration rate; GPL; IgG phospholipid units; HDL, high-density lipoprotein, IgG, immunoglobulin G; IgM, immunoglobulin M; ISTH, International Society on Thrombosis and Hemostasis; LDL, low-density lipoprotein; MPL, IgM phospholipid units.
(Modified with permission from Miyakis S. et al.[9]).
[a]APS is present is at least one clinical criterion and one laboratory criterion are met.
[b]Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to (1) the presence or (2) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) of such factors are age (>55 y in men, >65 in women); presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL, or low HDS cholesterol, cigarette smoking, family history of premature cardiovascular disease, BMI ≥30 kg/m^2, microalbuminuria, estimated GFR < 60 mL/min), inherited thrombophilias, oral contraceptive use, nephrotic syndrome, malignancy, immobilization, and surgery. Patients who fulfill criteria should be stratified according to contributing causes of thrombosis.
[c]Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa LA present alone; IIb, aCL antibody present alone; IIc, anti-β_2-glycoprotein-1 antibody present alone.

In contrast, aCL is a standard immunoassay using purified cardiolipin as the antigen and beta-2-glycoprotein-I as a cofactor. Standard sera are available and results are reported in a semi-quantitative fashion using GPL (IgG) and MPL (IgM) units. Anti- β_2-GP-I also is detected using a standard immunoassay with beta-2-glycoprotein-I as the antigen. The use of standard sera also allows semi-quantitative results reported as SGU (IgG) and SMU (IgM). Since low titers are often present in normal individuals, positive results are typically defined as greater than the 99% for a normal population.

Of the three antibodies, LA is most strongly associated with adverse obstetric outcomes. The multi-center PROMISSE cohort found LA, but not aCL or anti-β_2-GP-I to be associated with subsequent adverse pregnancy outcomes.[10] Nonetheless, testing for all three antibodies is advised if APS is suspected. Because positive results for aPL may be transient, often due to infection, confirmatory testing should be repeated in 12 weeks.[9] A positive test for all three antibodies also is associated with a higher risk of obstetric complications.

Catastrophic antiphospholipid syndrome

Background

Catastrophic antiphospholipid syndrome (CAPS) is defined as multiple thromboses, usually involving small vessels, resulting in multi-organ failure.[11] The condition is rare accounting for less than 1% of APS cases.[12] However, it can be life threatening and pregnancy may be a trigger. CAPS was first described by Dr. Ronald Asherson 25 years ago.[11] Diagnostic criteria were proposed in 2002,[13] and subsequently validated and reaffirmed with diagnostic and treatment algorithms.[14]

Criteria for CAPS include multi-organ thrombosis over a one-week period of time that affects at least three organs or tissues. However, these are meant to be guidelines used for classification purposes rather than definitive clinical care. Accordingly, some authorities use the term definite CAPS for individuals meeting all criteria and probable CAPS for those likely to have CAPS and meeting some but not all criteria.[15] Individuals with probable CAPS also may benefit from treatment. Criteria for CAPS are shown in Table 2.

Since CAPS is uncommon an international registry was created. The CAPS registry recently reported data on 500 patients enrolled from all over the world.[16] Over 70% of individuals with CAPS are female with a mean age of 38 years. More than half have primary APS and about a third have SLE or SLE-like disease. Fifty percent have CAPS as the first manifestation of APS. Precipitating factors are present in most cases and include infections, surgery, malignancy, contraceptives, pregnancy, and drugs. Pregnancy is the precipitating factor in about 8% of cases.[16]