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Clinical consequences of antiphospholipid antibodies

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ABSTRACT

Antiphospholipid antibodies (aPL), notably the lupus anticoagulant and anticardiolipin antibodies, are the serological hallmarks of the antiphospholipid syndrome. Thrombosis and pregnancy complications are the most prominent clinical manifestations of this syndrome. This paper provides the clinician with guidelines for ordering and interpreting tests for aPL and discusses consequences for treatment if persistently positive tests are found.

INTRODUCTION

Twenty years ago it was recognised that in patients with systemic lupus erythematosus (SLE) the presence of circulating antiphospholipid antibodies (aPL), notably lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL), was associated with thrombosis, pregnancy complications and thrombocytopenia. This association was termed antiphospholipid syndrome (APS).[1] It was soon recognised that APS can also occur in patients without an underlying systemic autoimmune disease (primary APS, PAPS). With the current wide availability of aPL tests, clinicians need to know when such tests should be ordered, how results should be interpreted and what the consequences are of a positive test.

HISTORY OF APL

It was in 1906 that aPL were described for the first time as complement-fixing antibodies that react with alcoholic extracts of beef heart in patients with syphilis.[2] Later on, the essential component within the complex antigen was identified as cardiolipin, a negatively charged mitochondrial phospholipid.[3] This observation led to the development of an agglutination test known as the Venereal Disease Research Laboratory (VDRL) test, which is currently still used as a screening test for syphilis. Mass screening of blood during and after the second world war led to the recognition that the VDRL test can be transient or persistently positive without clinical or serological evidence of syphilis. Transient biological false-positive reactions mainly occurred with (nonsyphilitic) infections and persistent positive reactions were found in patients with systemic autoimmune disorders, mainly systemic lupus erythematosus (SLE).[4] Associations between a positive VDRL test and clinical manifestations in SLE patients were never reported. In 1952, Conley and Hartman described in patients with SLE a peculiar inhibitor of *in vitro* coagulation,[5] which has been known as lupus anticoagulant (LAC) since 1972.[6] The phenomenon refers to antibodies that interfere with the assemblage of proteins of the coagulation cascade on a phospholipid template. *In vitro* plasma clotting times normalise when extra phospholipids are added to the test system. For many years the only importance of identification of LAC was that, in contrast to most other inhibitors of coagulation, it was not associated with bleeding.
As many patients with LAC had a biologically false-positive VDRL test and coagulation tests are relatively complicated, requiring among other things adequately processed plasma samples and a relatively long hand-on time, sensitive solid phase immunoassays for the detection of antibodies to cardiolipin were developed in the 1980s.[7] In contrast to

what was originally presumed, tests for aCL and LAC detect overlapping but not identical antibodies.

In 1990, it was reported that autoimmune aCL as detected in an ELISA system are not directed to phospholipids *per se*, but to a phospholipid binding plasma protein termed β_2-glycoprotein 1.[8,9] It was soon recognised that LAC is more heterogeneous than aCL as antibodies causing LAC use β_2-glycoprotein 1, prothrombin or other plasma proteins as cofactors for phospholipid binding.[9-11] Strictly speaking, the widely used term aPL is incorrect as most APS-related aPL are directed against plasma proteins and not phospholipids *per se*.

THE ANTIPHOSPHOLIPID SYNDROME

Currently used criteria to classify a patient as having APS are given in *table 1*.[12]

By definition, a diagnosis of APS requires persistent presence of medium to high levels of aCL (IgG or IgM isotype), presence of LAC or both. In general, antibodies causing LAC are more specific for APS, whereas aCL are more sensitive. The specificity of aCL for APS increases with titre and is higher for the IgG than for the IgM isotype.[13] However, multiple tests for aPL should be applied since patients may be negative according to one aPL test and positive in another.

Table 1

Preliminary classification criteria for antiphospholipid syndrome[12]

Vascular thrombosis
a) One or more clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ AND
b) Thrombosis confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis AND
c) For histopathological confirmation, thrombosis present without significant evidence of inflammation in the vessel wall.
Pregnancy morbidity
a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus OR
b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or severe placental insufficiency OR
c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal, anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
a) Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titre on at least two occasions at least six weeks apart, measured by standard ELISA for β_2-glycoprotein-1 dependent anticardiolipin antibodies OR
b) Lupus anticoagulant present in plasma on two or more occasions at least six weeks apart, detected according to the guidelines of the international Society on Thrombosis and Haemostasis.[23]

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

Clinical criteria include objectively verified vascular thrombosis and well-described pregnancy complications. APS-related thrombotic events occur in both arterial and venous vessels and may comprise both large and small vessels. APS-related thrombosis has been described for almost any vascular bed of the human body and reported clinical manifestations are consequently very diverse. Deep vein thrombosis in the legs, pulmonary emboli and ischaemic stroke are the most frequent APS-related thrombotic manifestations.[14] APS-related thrombosis tends to recur. The vascular pattern of thrombotic recurrences seems fairly consistent in APS. Retrospective studies found that venous thrombosis is followed by another venous thrombosis in more than 70% of cases, and an arterial thrombosis by another arterial event in more than 90% of cases.[15,16] Additional risk factors are often present in patients with aPL-related thrombosis. This holds in particular for pregnancy, surgical procedures, hypertension and smoking.[17]

The term catastrophic APS refers to a life-threatening condition in which aPL-positive patients develop progressive thrombosis in at least three different organ systems in a period of days to weeks. In this accelerated form of APS, vascular occlusion afflicts predominantly small vessels, although in a minority of patients thrombosis also occurs in large vessels.[18] The condition resembles thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome and diffuse intravascular coagulation.

The APS criteria differentiate between pregnancy complications that occur before and after ten weeks gestation (viz. 70 days from conception), which implies a segregation between the (pre-)embryonic and foetal periods of pregnancy. This is based on observations in the general population where (pre-)embryonic loss is frequent (occurring in 10 to 15% of recognised pregnancies) and foetal loss after 14 weeks gestation is rare (2%). More than half of sporadic (pre-)embryonic losses are related to chromosomal abnormalities of the conceptus and in many cases a visible embryo never forms. Therefore, epidemiological evidence dictates that the definition of recurrent miscarriage should include three or more consecutive (pre-)embryonic losses.[19] Furthermore, the APS criteria recognise that a preterm live birth accompanied by severe pre-eclampsia or severe placental insufficiency is comparable with a loss late in pregnancy.

Apart from thrombosis and pregnancy complications, the presence of aPL also relates to thrombocytopenia (often mild), livedo reticularis, heart valve abnormalities, movement disorders (chorea), myelitis transversa and

microangiopathic nephropathy.[14] With this last complication, histological examination of a kidney biopsy characteristically shows vascular occlusions, cellular intima fibrosis, fibroelastic intima hyperplasia, ischaemic glomeruli and signs of cortical ischaemic atrophy.[20] The prevalence of APS nephropathy in patients with primary APS is not exactly known. In the original paper by Nochy *et al.*[20] the 16 described patients came from a database from three university hospitals in Paris comprising seven years. However, it is likely that with increasing awareness of this complication the real prevalence will be higher than these data suggest. The frequency of APS nephropathy in patients with SLE is about 30%.[21] In SLE patients the characteristic histopathological abnormalities of APS nephropathy may be isolated or occur together with classical findings of lupus nephritis. The most frequent renal manifestations in primary APS are hypertension (93%), renal insufficiency (87%) and proteinuria (75%).[20] In the series from Nochy *et al.*[20] hypertension was malignant in two patients (12.5%). Patients with SLE and histological proof of APS nephropathy have significantly more often hypertension (60 *vs* 28%) and significantly higher initial serum creatinine levels compared with SLE patients with renal involvement in absence of microangiopathic nephropathy. For the prevalence and extent of proteinuria no significant differences were found.[21]

EPIDEMIOLOGY

Because assays for aPL are poorly standardised and there are no generally accepted cut-off levels that discriminate negative from low-positive results and low-positive from clinically relevant aCL levels as determined in ELISA, the range in reported frequencies of aPL in different studies is wide. Among young, apparently healthy control subjects the prevalence lies between 1 and 5%.[22] In the elderly, the frequency of aPL increases.[22] Similar to what is found in conditions as infection, cancer, haemodialysis and the use of certain drugs, these aPL are usually of IgM isotype, present at low levels and not associated with thrombotic events.[13] Among patients with SLE, reported prevalences for aPL range from 12 to 34% and in women with recurrent (pre-)embryonic pregnancy loss from 10 to 20%.[13] Although prospective studies have shown an association between aPL and the first episode of venous thrombosis, the first myocardial infarction and recurrent stroke,[13] there are insufficient data to determine what percentage of healthy subjects with aPL will eventually have a thrombotic event or a complication of pregnancy consistent with APS. In patients with SLE, APS may develop in 50 to 70% of patients with aPL over 20 years of follow-up.[13] Traditional risk factors for venous and arterial thrombosis are associated with aPL-related thrombosis[17] supporting the importance of a second-hit theory. However, in daily practice we still do not know what the characteristics are of asymptomatic aPL-positive persons with high risks for APS.

WHO SHOULD BE TESTED FOR APL?

Accepted conditions for aPL testing in patients are the presence of SLE, an obstetric history that meets the criteria for obstetric APS (*table 1*), arterial or venous thrombosis before the age of 45 years, recurrent thrombosis, thrombosis in an unusual site and an association of both venous and arterial events.

INTERPRETATION OF AN APL TEST

At first glance the laboratory criteria for APS (*table 1*) are simple: a positive test for LAC and/or a medium to high IgM and/or IgG titre. However, many laboratories still use insensitive coagulation tests to diagnose LAC and do not adhere to the international guidelines for testing LAC.[23] As no single assay is 100% sensitive for LAC at least two different tests should be used for screening. False-negative results occur when platelets are not sufficiently removed from the test sample and presence of heparin in the test sample causes false-positive results. With respect to the aCL ELISA, it is widely recognised that the assay is difficult to standardise. With the same samples tested, different (commercial) tests often give discordant results.[24-26] Despite many efforts at standardisation, cut-off levels for negative, low, medium and high titres remain a matter of dispute, especially at the lower ranges. A good dialogue between the clinic and the laboratory is essential. Furthermore, in the interpretation of test results, clinicians should take into account the age of the patient, use of aPL-inducing drugs, presence of infection, use of immunosuppressive drugs and if the patient has SLE the degree of disease activity at the time of blood sampling.[27] A positive test should always be repeated after six to eight weeks with a second sample to establish persistent positivity.

CONSEQUENCES OF A POSITIVE TEST

The incidental presence of a positive aPL test or a low titre aCL has no clinical consequences. At present, most authorities agree that there is no indication for chronic primary prophylactic treatment in asymptomatic persons with persistently positive aPL tests.[13] However, it seems justified to offer thromboprophylaxis to these persons during high-risk situations such as immobilisation, surgery and the postpartum period, and to consider the

aPL status when a method of contraception is chosen.
In the general population, standard treatment for patients with venous thrombosis and embolic cerebrovascular events is oral anticoagulation targeting an international normalised ratio (INR) of 2.0 to 3.0. After the first venous thrombotic episode treatment is continued for three to six months. Longer duration of anticoagulation implies less recurrences, but the risk for bleeding apparently outweighs the benefits. For patients with nonembolic ischaemic stroke, antiaggregants, notably aspirin, are the standard treatment. The clinician has to decide whether these strategies also hold if the thrombotic patient has aPL. The retrospective study by Khamashta *et al.*[16] including 147 patients with a median follow-up of six years suggested that all patients with thrombosis who fulfil the laboratory criteria for APS should receive life-long high-intensity oral anticoagulants (target INR ≥3). Lower intensities of anticoagulation and aspirin were found to be significantly less effective and the period of six months following cessation of oral anticoagulation had an extraordinarily high risk for recurrent thrombosis. The conclusions of this paper were adopted by many centres worldwide, despite the notion that the study had many methodological shortcomings, such as its retrospective design, treatment according to physicians' and patients' choices, thrombosis taken as the endpoint without discrimination between arterial and venous events and that single patients contributed to different strategies evaluated.[28]
Recent data indicate that the conclusions from the study by Khamashta *et al.* can not be generalised[16] and that prophylaxis with intermediate-intensity anticoagulation and even aspirin may be effective in selected patients. The best evidence comes from a randomised, double-blind trial on anticoagulant treatment of patients with persistently positive aPL tests and thrombosis (over 75% venous).[29] This study, which excluded among others patients with a recurrent event while anticoagulated at an INR of 2.0 or greater, concluded that high-intensity anticoagulation (target INR 3.1 to 4.0) was not superior to anticoagulation at moderate intensity (INR 2.0 to 3.0). This prospective study found a recurrence rate of 2.6 per 100 patient years with anticoagulation. The study supported similar conclusions from some previous small studies.[28]
For current clinical practice this implies that prophylaxis with intermediate-intensity anticoagulation can be provided to most aPL patients with venous thrombosis. The optimal duration of treatment is an open question. In particular questions on whether treatment can be stopped earlier when thrombosis is triggered by surgery, use of oral contraceptives, or by other nonrecurring triggers, or in case traditional aPL tests become negative are important but await further studies. Most authorities currently advise continuation for years if not lifelong. There may also be a role for aspirin for secondary prophylaxis in patients with aPL-related nonembolic stroke.[30] The prospective randomised AntiPhospholipid Antibody in Stroke Study (APASS) found similar rates of recurrence when aPL-positive patients received 325 mg aspirin or low-dose oral anticoagulation (target INR 1.4 to 2.8).[31] Of note, patients in the APASS did not by definition have APS as patients with low titre aCL were included and the aPL status was based on the test result with a single sample.
Because of the rarity of the condition, there are no prospective studies on treatment of catastrophic APS. From an analysis of case histories and small series, guidelines for treatment have been published.[18] These include for all cases treatment of known precipitating factors (in 35% infections), treatment with effective anticoagulation and high-dose corticosteroids. With a life-threatening condition administration of intravenous γ-globulins and/or plasma exchange with fresh frozen plasma is indicated. Treatment should be extended with cyclophosphamide if the condition is associated with a lupus flare. The survival rate of catastrophic APS is about 50%. Poor prognostic factors are older age and a higher number of involved organs. About 60% of patients who survive initial catastrophic APS remain symptom-free with anticoagulation during a follow-up of more than 5.5 years. About a quarter of patients will have further APS-related events during follow-up.[32]
Based on results from retrospective studies, pregnancy outcome in aPL-positive patients who meet the obstetric APS criteria is poor without pharmacological treatment, as there is about a 60% chance of recurrent loss. In considering the literature on pharmacological treatment of obstetric APS, it should be realised that obstetricians will consider a pregnancy a high risk for complications if aPL are found and consequently optimise obstetric care. This in itself will increase the chances of a live birth.[33]
The first pharmacological treatment widely applied in APS pregnancies was the combination of prednisone and low-dose aspirin. When a small randomised study showed similar outcome (over 70% live births) with aspirin and heparin and less side effects, the enthusiasm for prednisone waned. In women with primary obstetric APS randomised studies compared heparin plus aspirin with aspirin alone, aspirin with placebo and heparin plus aspirin with heparin plus aspirin and intravenous γ-globulin. In general, outcome was relatively good with in most studies 70% or more live births in treated pregnancies. Superiority of heparin plus aspirin over aspirin alone in terms of live birth rates was found in some,[34,35] but not in other[36] controlled trials. It is supposed that differences in patient selection, notably on laboratory criteria for obstetric APS, are important denominators for these discrepant results.[13] At present most authorities believe that a combination of low-dose aspirin and a prophylactic dose of low-molecular-weight heparin is the preferred treatment for pregnant women with obstetric APS. This conclusion

was also reached in a recent meta-analysis.[37]

It should be noted that patients with SLE or previous thrombosis were excluded from all previous randomised trials. Whether a history of thrombosis characterises a subset of patients with worse prognosis for pregnancy is unknown. Most physicians will advise use of (low-molecular-weight) heparin in APS patients with a thrombotic history. The dose should be individualised based on the circumstances at which thrombosis occurred, its location and its severity. We advise starting (low-molecular-weight) heparin before conception or, at the latest, within two weeks of the missed period, because oral anticoagulants cross the placenta, are teratogenic when given between 6 and 12 weeks' gestation and may cause intracranial bleeding in the foetus. As pregnancy progresses the volume of distribution for heparin increases and dose-adjustments in proportion to weight gain or based on APTT or anti-factor Xa levels can be considered. In selected cases a switch from heparin to oral anticoagulants may be practical between 15 and 34 weeks' gestation[33]

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