



Editorial

Antiphospholipid syndrome: coming of age

El síndrome antifosfolípido: alcanza la mayoría de edad

J.M. Gray and M.A. Khamashta*

Lupus Research Unit, King's College London. School of Medicine. London, UK

Antiphospholipid syndrome (APS) is a relatively “new” disease entity. First proposed in 1983,¹ it has since received recognition and interest from a diverse range of specialties, resulting in the rapid development of a large knowledge base. There is now an improved understanding of many this condition's aspects. However, numerous elusive aspects continue to cause a great deal of head scratching for both researchers and clinicians and provide a continuous platform for heated debate.

Antiphospholipid syndrome is described as a form of autoantibody induced thrombophilia which is characterized by thromboses and recurrent obstetric complications.² As well as these main features there are numerous other less well recognized clinical manifestations. The condition was first recognized in sufferers of systemic lupus erythematosus (SLE)¹ It was some ten years later when the term primary APS was coined for situations where the classic signs and symptoms of APS are seen in the patient without the clinical features of SLE.³

In the decades following the recognition of APS as a distinct entity, there came increasing calls for a consensus on the criteria required for accurate diagnosis of these patients. In response, an International workshop was held in Sapporo Japan⁴ with the sole aim of producing classification criteria that would allow further investigation and study into the syndrome. This expert workshop's result was a group of criteria divided into clinical and laboratory findings. The stated requirements were that patients must meet at least one clinical and one laboratory criteria in order to be classified as having APS. The clinical manifestations focused on vascular thrombosis and obstetric complications whilst the lab criteria required the presence of either Lupus Anticoagulant (LA) or Anticardiolipin antibodies (aCL). These antibodies had to be present on two separate testings at least six weeks apart. The Sapporo criteria were revised and updated in 2006.⁵ These updates resulted in two important amendments. Firstly, the addition of a new laboratory criteria, anti- β_2 glycoprotein-I antibody.

This antibody is now recognised as being crucial to APS pathogenesis and is in fact an independent risk factor for thromboses.⁵ Secondly, it was advised that the time delay between serological testing should be extended to twelve weeks instead of the original six so as to avoid positive results caused by transient rises in autoantibody titres.

It should be noted that these criteria were not developed with clinical situations in mind but were specifically aimed at encouraging clinical trials in the area. Despite this, there remains no alternative for clinicians who simply need accurate guidance in providing valid diagnoses for their patients.

As previously mentioned the potential APS clinical manifestations are numerous and widespread. This can be illustrated by listing a myriad of clinical specialities that can be involved in a patient's management- rheumatology, neurology, cardiology, nephrology, endocrinology, gastroenterology, dermatology, surgery, haematology, intensive care and finally obstetrics. The hallmarks of APS, as defined by the Sapporo criteria, are however limited to thromboses and obstetric complications.²

APS is different from other recognized thrombophilias because there is a risk of thrombosis in both venous and arterial systems.² Of the two, venous thromboembolism is the most common and may result in recurrent DVTs or less commonly, thrombosis of the internal organ vasculature such as the kidney, liver, lung or brain.² Arterial thrombosis can present as a stroke or transient ischaemic attacks² but may also be the cause of limb ischaemia or infarction of internal organs.⁶

Within the Sapporo criteria pregnancy morbidity is defined by either unexplainable death of a healthy foetus after 10 weeks gestation, premature birth of a healthy baby before 34 weeks gestation or three or more consecutive unexplainable miscarriages before 10 weeks gestation.² Recurrent miscarriage is considered the most common obstetric manifestation but complications such as severe pre-eclampsia and placental insufficiency are also recognised.⁶

As well as the now well-recognised main manifestations there are a number of less common but still important ones, clinical features that may nudge a clinician towards APS diagnosis in the appropriate clinical setting. These include thrombocytopenia, epilepsy, migraine, Livedo Reticularis (LR), haemolytic anaemia, heart valve disease and coronary artery disease.² The majority of the features could

*Corresponding author.

E-mail address: munther.khamashta@kcl.ac.uk (M.A. Khamashta)

be considered frustratingly vague and associated to many clinical diagnoses. However, the concurrent presence of LR, alongside any fellow features should heighten a clinician's suspicion sufficiently to warrant further investigation. The easily recognizable skin mottling of LR has been noted in up to a quarter of APS sufferers⁶ and is considered indicative of those patients who are at higher risk of arterial thrombosis.²

The most severe and fortunately infrequent form of APS is catastrophic APS. This form is characterised by widespread small vessel thrombosis with multi-organ failure and more than 50% mortality.⁷

Following the recognition of important APS clinical features, the identification of different antibodies to the condition is required to confirm suspicion through appropriate serological testing. The three classes of antibody now recognised as necessary for a firm diagnosis of APS are LA, aCL and, most recently Anti β_2 Glycoprotein-I antibody (Anti β_2 -GPI) has been added.⁵ Each class of antibody is considered an independent risk factor and so any one found to have reproducible serological positivity is sufficient for diagnosis.⁸

It is apparent that testing positive for all three of these antibodies is associated with both increased risk of thromboses and obstetric complication and that these triple positive patients may have a higher risk of recurrence following an initial event.⁸ However, despite ongoing research it remains difficult to distinguish whether or not positivity to a single antibody increases specific risks. LA appears to have the most distinct correlation to clinical manifestations.

Despite the fact that the updated classification criteria continues to demand the demonstration of antiphospholipid antibody positivity for valid diagnosis there is a growing body of clinicians who support the seronegative concept. Since it was first proposed in 2003,⁹ 'seronegative antiphospholipid syndrome' has gained little momentum in its attempt to become an accepted and valid diagnostic option. Unlike seronegative rheumatoid arthritis and seronegative lupus, which have both been recognised as disease variations for some time now.¹⁰ Eight years since the initial seronegative proposal this is still surrounded by heated debate. The fact that patients exist, who demonstrate the clinical APS features but who consistently produce negative serological samples, is a source of frustration for clinicians. Without the ability to provide a clear diagnosis in such cases means that both patients and their doctors are left floundering and unable to decide on future management plans.

A greater understanding of this curious condition is possible with knowledge of how the autoantibodies involved exert their different effects. Thrombotic and obstetric manifestations are preceded by a complicated cascade of events initiated by the activation of endothelial cells, monocytes and platelets.² It appears that these events are mediated by both nuclear factor κ B and p38 mitogen-activated protein kinase.² Direct activation of endothelial cells and monocytes leads to the production of adhesion molecules and crucially, upregulation of tissue factor production. Simultaneously, activated platelets upregulate their glycoprotein IIb-IIIa expression and thromboxane A2 production.

The increased presence of key thrombotic components, thromboxane A2 and tissue factor, means that a prothrombotic state is favoured. Further exacerbation of this may be provided by factors commonly associated with traditional cardiovascular risk such as smoking, inflammation and oestrogenic therapies.²

It is also now recognised that complement activation plays an important role in APS pathogenesis, with proof provided by the fact that additional factors have been found in the placentas of APS patients.² The natural anticoagulant annexin A5 is more specifically involved in foetal loss. It is considered that without this factor's action placental thrombosis may occur resulting in miscarriage. Pregnancy may also be threatened when antiphospholipid antibodies bind the cytotrophoblast cells of the placenta. This can result in reduced secretion of human chorionic gonadotrophin and inflammatory damage.²

This greater pathogenic mechanism understanding, which acts at a cellular level has permitted considerable treatment progression. Earlier in APS history it was thought that many of the now recognisable symptoms were best treated with immunosuppression, as in SLE.³ It is now accepted that successful treatment regimes are tailored around anticoagulation principles. However, despite a growing knowledge base, questions remain regarding how these regimes should differ depending on the exact presentation mode. These uncertainties are exacerbated by a scarcity of high quality randomized control trials in the area, owing to inherent recruitment difficulties. As a result, knowledge is mainly based on weak retrospective or observational studies.

In an aim to simplify evidence evaluation authors have divided APS into different groups to allow each potential presentation to be considered in turn.^{11,12} Each patient group carries a differing morbidity risk. There are three groups to consider: those who are positive for antiphospholipid antibodies but remain asymptomatic, those who have had single or multiple thrombotic events, and those with obstetric APS.

Asymptomatic APS carriers are rare, simply due to the fact that most patients are diagnosed following an initial thrombotic event.¹² Carriers identified through serological testing prior to any event should be considered for treatment on an individual basis depending on concurrent risk factors. Those with low risk profiles (low titres of antibodies without co-morbidities) do not require treatment but should be followed up if antibody titres are persistently positive.¹² High risk profiles (persistently positive moderate to high titres or SLE co-morbidity) are at significantly higher risk of thromboses and should be treated more aggressively.¹² Aspirin should be given as primary thromboprophylaxis in this patient group with hydroxychloroquine providing possible additional benefit for those with SLE.¹²

Those patients who have already suffered thromboses as a result of APS present complicated treatment decisions. It is now accepted that long term thromboprophylaxis is required. However, debate exists as to whether those who have suffered either a venous or arterial thrombotic event gain most benefit from high intensity anticoagulation (INR 3.1-4) or moderate intensity anticoagulation (INR 2-3).¹¹ Those with one previous venous thrombosis are considered low risk in this patient group and it is advisable that they should be treated indefinitely with warfarin aiming for an INR of 2.0-3.0.¹² Those with arterial thrombosis or recurrent thrombotic events are considered high risk and should receive indefinite warfarin therapy with INR of 3.0-4.0.¹² Both of these patient groups will benefit from counseling aimed at reducing traditional cardiovascular risk factors.¹²

Obstetric APS management may be the most complicated. In-depth pre-pregnancy counseling and strict antenatal care is required in order to maximize the chances of a successful outcome for these women. There may be the added complication of multiple previous miscarriages or stillbirths and the resulting psychological remnants of these events. Women should be advised to only consider pregnancy if there have been no recent thrombotic events, blood pressure is well controlled and they are free of pulmonary hypertension.¹² For those who do successfully become pregnant - the gold-standard treatment is combined therapy with heparin and aspirin.^{2, 12, 13} Again regimes need to be tailored to individuals and depend on previous thrombotic events and pregnancy morbidity.¹² Close foetal monitoring throughout pregnancy is required with the involvement of both obstetricians and physicians. The post partum period is also a considerable increased risk period and therefore treatment should be continued for 4-6 weeks following delivery. Women on warfarin prior to pregnancy should recommence therapy as soon as possible following delivery.¹²

It is easy to see how APS management can appear like a minefield for the inexperienced clinician. There are numerous issues that lack clarity and, unfortunately, current research appears to provide only conflicting advice.¹⁴

APS patients vary widely in prognosis terms, depending on their autoimmune profile and presentation mode as well as the presence of co-morbidities and independent cardiovascular risk factors. Each clinical situation requires individual consideration and as we have seen, specific tailoring of treatment regimes so that the best possible outcome is achieved. Certain immune profiles appear to confer a higher risk of significant morbidity. Patients considered low risk with no previous thrombotic events and no co-existing SLE have a thrombotic risk of 0%-2.8%.¹² SLE patients who are also positive for antiphospholipid antibodies and those with obstetric APS are at a significantly higher risk of developing thromboses. Those patients who have already suffered an event are said to have an increased risk of recurrent thromboses of between 22% and 69%.¹²

Women who have suffered recurrent pregnancy losses are those who are most likely to seek reassurance regarding their future health and chances of reproducing successfully. It is estimated that with tight therapeutic control these women stand a 70%-80% chance of achieving full gestation and having a healthy, live baby.^{2, 12}

The body of knowledge continues to grow for APS, but numerous avenues for research and investigation remain. Developments include the recently proposed vimentin/cardioliipin complex as a new antigenic target.¹⁵ Proposals such as this, and seronegative APS, must fight against the rigid inflexibility of current diagnostic criteria in order to be considered seriously. Specific ELISA for antibodies directed against the domain I of β_2 -glycoprotein-I is one of the new awaited tests that will need assessment. These antibodies, with LA activity, are strongly associated with thrombosis.¹⁶ There is wide acceptance that high quality, multi-centre trials are required to improve treatment development. Several proposals regarding potential new therapies have been made including clopidogrel, dipyridamole, hydroxychloroquine, statins and rituximab.² New oral Antifactor Xa (Rivaroxaban) and Anti-factor IIa (Dabigatran) drugs have not been tested in patients with APS. Both drugs have been licensed for primary thromboprophylaxis after orthopaedic surgery in many settings. Evidence from clinical trials using Dabigatran or Rivaroxaban is suggestive of its potential role as an alternative thromboprophylaxis to low molecular weight heparin or warfarin. Additionally, both agents do not require laboratory monitoring and that contributes their array of advantages further when compared to conventional anticoagulation.¹⁷ A trial with Rivaroxaban in patients with APS and venous thrombosis is currently being organised in the

UK. The results from this trial and any future trial with Dabigatran are paramount in defining its use as an alternative treatment modality in APS. Potential exists for greater clinician understanding and improved patient outcome with continued enthusiastic input into these areas of uncertainty and interest.

References

1. Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *BMJ*. 1983;287:1088-9.
2. Ruiz-Irastorza G, Crowther M, Khamashta MA. Antiphospholipid syndrome. *The Lancet*. 2010;376:1498-1509.
3. Hughes GRV. The antiphospholipid syndrome: ten years on. *The Lancet*. 1993;342:341-4.
4. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum*. 1999;42:1309-11.
5. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306.
6. Cervera R, Plette JC, Font J, et al. Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002;46:1019-27.
7. Cervera R, Asherson RA. Síndrome antifosfolipídico: nuevas perspectivas clínicas y terapéuticas. *Reumatol Clin*. 2005;1:183-6.
8. Giannakopoulos, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. *Blood*. 2009;113:985-94.
9. Hughes GRV, Khamashta MA. Seronegative antiphospholipid syndrome. *Ann Rheum Dis*. 2003;62:1127.
10. Joseph A, Brasington R, Kahl L, Ranganathan P, Cheng TP, Atkinson J. Immunologic rheumatic disorders. *J Allergy Clin Immunol*. 2010;125:S204-S215.
11. Giannakopoulos B, Krilis SA. How I treat the antiphospholipid syndrome. *Blood*. 2009;114:2020-30.
12. Tuthill JI, Khamashta MA. Management of antiphospholipid syndrome. *J Autoimm*. 2009;33:92-8.
13. Fernandez-Llanio N, Alegre-Sancho C, Chalmeta-Verdejo C, et al. Terapias hormonales, fertilidad y embarazo en el síndrome antifosfolipídico. *Reumatol Clin*. 2006;2:90-106.
14. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arzuza I, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody positive patients: Report of a task force at the 13th International Congress on antiphospholipid antibodies. *Lupus*. 2011;20:206-18.
15. Ortona E, Capozzi A, Colasanti T, et al. Vimentin/cardioliipin complex as a new antigenic target of the antiphospholipid syndrome. *Blood*. 2010;116:2960-7.
16. De Laat B, Derkson RH, Urbanus RT, De Groot PG. IgG antibodies that recognise epitope Gly40- Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. *Blood*. 2005;105:1540-5.
17. Cohen H, Machin S. Antithrombotic treatment failures in antiphospholipid syndrome: the new anticoagulants? *Lupus*. 2010;19:486-91.