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The Antiphospholipid Syndrome

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Abstract

The antiphospholipid syndrome (APS) is an autoimmune thrombophilic condition characterized by the presence in blood of antibodies that recognize phospholipid-binding proteins. The clinical manifestation of APS include arterial and venous thromboembolic events and/or obstetric complications (especially recurrent fetal losses). The antiphospholipid antibodies (aPLA) associated with the disease include the lupus anticoagulant (LA), anti-cardiolipin (a-CL), and anti-β2glycoprotein-I (a-β2GP-I). APS and aPLA can occur in isolation (primary) or in association with systemic lupus erythematosus (secondary).

Keywords

Antiphospholipid Antibodies; Coagulation; aPTT; dRVVT; Thrombosis; Pregnancy; Treatment

Introduction

The main antigens are β2-glycoprotein I (β2-GPI) and prothrombin although a number of autoantibodies recognize other PL-binding proteins like protein C (PC), protein S (PS), annexin V, complement factor H, high- and low- molecular- weight kininogen, prekallikrein, Factor IX, tissue factor pathway inhibitor (TFPI), Factor VII/VIIa. There are "anticoagulant" surface-mediated processes with which aPLA are thought to interfere. One anticoagulant pathway involves PC activated by thrombin on endothelial thrombomodulin, and PS. Activated PC in association with PS cleaves factor Va and factor VIIIa on the PL surface and thereby inactivates the intrinsic tenase and prothrombinase reactions. Occupancy of the surface by immune complexes could impede these interactions and thereby promote coagulative activation. Indeed, LAs can induce "activated protein C resistance". A second anticoagulant mechanism involves TFPI. This protein binds to negatively charged PL and to factor Xa on PL. This protein complex then links to the TF-factor VIIa complex, and shuts off further TF-mediated clotting. Occupancy of the PL surface by immune complexes may impede this interaction, leading to prolonged thrombin generation. The aβ2-GPI autoantibodies bind to and activate EC, monocytes, and platelets and induce endothelial microparticles release [5,7,8]. Activation of these cells results in a shift toward a prothrombotic state. Toll like receptor 2 (TLR2) and TLR1 or TLR6, and CD14 contribute to monocyte activation of aPLA. In particular, TLR2, TLR1, and TLR6 are involved in aPLA recognition by human monocytes. The CD14-dependent internalization of TLR2 by aPLA in monocytes triggers NF-kB activation inducing TF expression and upregulating TF activity [5,7,8]. Proteomic analysis has identified the vimentin (VIM) as a key antigen in the APS. VIM is an intermediate filament cytoskeletal protein, which is expressed by neuthrophils, T cells, monocytes and EC. Anti-VIM/CL antibodies were found in 92% of patients with APS [8]. Other target proteins are plasminogen activator inhibitor type-1 (PAI-1) linked to APS thrombogenesis. Immunoglobulin G isotype activates p38 mitogen-activated protein kinase (MAPK) causing the upregulation of TF activity and inducing the expression of vascular endothelial gowth factor (VEGF) [8]. The a-β2-GPI antibodies are associated with increased risk of thrombosis and are predominantly the IgG isotype, particularly IgG2 subclasses [5,6].

Diagnostic criteria for APS

The presence of aPLA alone does not constitute APS. Definitive APS is defined by the simultaneous presence of clinical and laboratory criteria as agreed upon International criteria for APS (Sapporo criteria) in 1998 and revised in 2006 [9] (Figure 1, [6] with permission). The clinical criteria are one or more objectively confirmed episodes of vascular thrombosis at any site and/or pregnancy morbidity defined as more than one unexplained death of a morphologically normal foetus, more than one premature birth of a morphologically normal neonate, or more than 3 unexplained consecutive spontaneous abortions before the 10th week of gestation [2,9]. The laboratory criteria are IgG and/or IgM aCL or aβ2-GPI or documentation of LA [9]. The laboratory abnormality must be present on two or more occasion at least 12 weeks apart [9] (Table 1, [1] with permission).

Laboratory Diagnosis of aPLA

According to the last revison of the "Sapporo" laboratory criteria [10], the APS requires the presence of at least one of the three aPLA (i.e. LA, IgG and/or IgM aCL and IgG and/or IgM aβ2-GPI antibodies) [9]. The revised criteria provided details about the titres (> 40 GPL or MPL or > the 99th percentile for aCL and > the 99th percentile for aβ2-GPI) and the persistence in time (presence on at least two occasion al least 12 weeks apart) of the antibodies [9,11]. Interestingly, LA is the strongest risk factor for thrombosis and recurrent fetal loss whereas aCL antibodies show some significant associations only at high titres. The G rather than the M isotype is significantly associated with the clinical events for both aCL and aβ2-GPI antibodies [11]. It has been reported that "triple LA positivity", defined by the presence of LA and high titres of aCL and aβ2-GPI antibodies, correlated with both thrombosis and pregnancy morbidity more strongly that single or double positivities [12].

Overview of the assays

The Lupus Anticoagulant/Phospholipid-Dependent Antibodies Subcommittee of the Scientific and Standardization Committee of the ISTH has recommended criteria for the diagnosis of LA [13]. The recommendation is to perform two different tests, such as the activated partial thromboplastin time (aPTT) and the diluite Russel's viper venom time (dRVVT) [13]. The LA assay system chosen has to comply with the 3-step strategy defined in the International Society of Thrombosis and Haemostasis criteria [14] (a) Screening test: demonstration of the prolungation of a phospholipid-dependent clotting time beyond the upper limit of the reference interval; (b) Mixing test: confirmation of the presence of an inhibitor and the exclusion of a coagulation factor deficiency.; and (c) Confirmation that the inhibitor is phospholipid-dependent and no directed against a specific coagulation factor. The mixing test involve combining the patient's plasma with normal plasma (1:1) and assessing the influence of this procedure on clotting time, the theoretical underpinning being that if prolongation of clotting time is the result of a coagulation factor deficiency, it will correct to normal, whereas with LA, correction requires larger volumes of normal plasma [6,14]. Although ELISA-based methods were developed to detect aPLA, LA detected by coagulometric tests has been shown to be strongly associated with thrombosis [4]. There is growing belief that β2-GPI-dependent aPLA are strongly associated with thrombosis [2,4]. For this reason, various attempts have been made to specifically detect β2-GPI-dependent LAs. Two methods of β2-GPI-dependent LA identification were described [15,16]. The aβ2-GPI antibodies may be divided into high and low avidity and the former is associate with thrombosis [6]. In the obstetric APS, testing positive on all 3 assays (LA, β2-GPI, and CL-ELISAs) is associated with a greater risk for thrombosis [17,18].

Clinical management Scenarios

Several studies have shown an important risk of thrombosis relapse in APS [17,18]. The prevention and treatment of thrombosis in patients with established APS is low molecular weight heparin (LMWH) followed by long-term oral anticoagulation [2,1]. The Canadian study [20] and the Warfarin in the Antiphospholipid Syndrome (WAPS) trial [21] established that the appropriate INR is 2.0 to 3.0 for thromboprophylaxis. High-intensity anticoagulation (INR 3.0- 4.0) is recommended after the first art

thromboembolic event, and in the recurrence of venous thrombosis [1]. There is significant debate regarding treatment of cerebrovascular events associated with aPLA, with some anticoagulating these patients as they would other patients with arterial or venous thrombosis, while others treat with aspirin alone [1].

Table 1. Summary of the Sydney Consenses Statement on Investigation Classififcation Criteria for the APS[13].

Anticoagulant treatment is generally not sufficient to treat the catastrophic APS (CAPS), a form of the disorder that is marked by the disseminated macro and microvacular occlusions resulting in multi-organ failure [1]. CAPS, which occurs in less 1% of patients presenting APS, is defined by thrombotic occlusions in at least three organ/tissues occurring within a week ("thrombotic storm"), with laboratory confirmation of aPLA. Even with optimal treatment, the mortality rate is approximally 48%. Patients with CAPS generally require supplementing anticoagulant treatment with plasma-pheresis and immunosuppression. Treatment approaches have included intravenous IgG, corticosteroids, cyclophosphamide, and azathioprine. Rituximab has been tried in patients who have been refractory to other treatments [1].

For the pregnant women with APS, the American College of Chest Physicians (ACCP) [22] evidenced-based guidelines recommendes low-dose aspirin (ASA) on confirmation of pregnancy [23,24]. The evidence that combined (LMWH+ASA) therapy improves outcomes is of modest quality. The optimal doses for LMWH and ASA are 75 to 100 mg of ASA per day plus prophylactic-dose LMWH. For women with obstetric APS and no history of thrombosis, thromboprophylaxis during the postpartum period should be considered [23]. If a woman has APS and is anticoagulated for prior thrombosis, it is suggested swithching to therapeutic-dose LMWH before six weeks gestation. Full-intensity anticoagulation is important during the pregnancy and the post partum period [23].

References

1. Rand JH. The antiphospholipid syndrome. Hematology. 2007; 136-142.

2. Arnout J, Jankowski M. Antiphospholipid syndrome. Hematol J. 2004, 5(Suppl 3): S1-S5.

3. Devreese KM, Pierangeli SS, De Laat B, Tripodi A, Atsumi T et al. Testing for antiphoshpholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014, 12(5): 792-795.

4. Swadzba J, Iwaniec T, Pulka M, De Laat B, De Groot PG et al. Lupus anticoagulant: performance of the test as recommended by the latest ISTH guidelines. J Thromb Haemost. 2011, 9(9): 1776 - 1783.

5. De Groot PG, Urbanus RT. Cellular signaling by antiphospholipid antibodies. J Thromb Haemost. 2014, 12(5): 773-775.

6. Giannakopoulos B, Passam F, Iannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. Blood. 2009, 113(5): 985-994.

7. Brandt KJ, Fickentscher C, Boehlen F, Kruithof EK, de Moerloose P. NF-kB is activated from endosomal compartments in antiphospholipid antibodies-treated human monocytes. J Thromb Haemost. 2014, 12(5): 779-791.

8. Ripoli VM, Lambrianides A, Pierangeli SS, Poulton K, Ioannou Y. Changes in regulation of human monocyte proteins in response to IgG from patients with antiphospholipid syndrome. Blood. 2014, 124(25): 3808-3816.

9. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006, 4(2): 295-306.

10. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. Arthritis Rheum. 1999, 42(7): 1309-1311.

11. Galli M. The antiphospholipid triangle. J Thromb Haemost. 2010, 8(2): 243-236.

12. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL et al. Update of the guidelinres for lupus anticoagulant detection. J Thromb Haemost. 2009, 7(10): 1737-1740.

13. Kumano O, Ieko M, Naito S, Yoshida M, Takahashi N et al. Index of circulating anticoagulant cut-off value establishment in activated partial thromboplastin time mixing test for lupus anticiagulant diagnosis. J Thromb Haemost. 2013, 11(10): 1919-1922.

14. Brandt JT, Barna LK, Triplett Da. Laboratory identification of lupus anticoagulants: results of the Second International Workshop for Identification of Lupus Anticoagulants. On behalf of the Subcommittee on Lupus Anticoagulants/Antiphospholipid Antibodies of the ISTH.. Thromb Haemost. 1995, 74(6): 1597-1603.

15. Simmenlink MJ, Derksen RH, Arnout J, De Groot PG. A simple method to discriminate between beta-2glycoprotein I and prothrombin dependent lupus anticogulants. J Thromb Haemost. 2003, 1(14): 740-747.

16. Pengo J, Biasiolo A, Pegoraro C, Iliceto S. A two-step coagulation test to identify anti beta-2glycoprotein I lupus anticoagulant. J Thromb Haemost. 2004, 2(5): 702-707.

17. Bouvier S, Cochert-Nouvellon E, Lavigne-Lissalde G, Mercier E, Marchetti T. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood. 2014, 123(3): 404-413.

18. Bouvier S, Cochert-Nouvellon E, Lavigne-Lissalde G, Mercier E, Fabbro-Peray P et al. Comparative incidence of pregancy outcomes in thrombophilia-positive women from the NOHAPS observational study. Blood. 2014, 123(3): 414-421.

19. Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2009, 68(9): 1428- 1432.

20. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithhrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost. 2005, 3(5): 848-853.

21. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosi in patients with the antiphospholipid antibody syndrome. N Engl J Med. 2003, 349(12): 1133-1138.

22. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM et al. VTE, thrombophilia,antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012, 141(Suppl 3): e691S736S.

23. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome inpregnancy: a randomized, controlled trial of treatment. Obstet Gynecol 2002, 100(3): 408-413.

24. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB et al. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med. 2014, 370(14): 1307-1315.

25. Gris J, Bouvier S, Molinari N, Galanaud JP, Cochery-Nouvellon E et al. Comparative incidence of a first thrombotic event in purely obstetric antiphospholipid syndrome with pregnancy loss: The NOH-APS observational study. Blood. 2012, 119(11): 2624-2632.