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Review/ Derleme

Antiphospholipid syndrome in terms of cardiovascular surgery

Kalp damar cerrahisi açısından antifosfolipit sendromu

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ABSTRACT

Antiphospholipid syndrome (APS) is a rare syndrome mainly characterized by several hypercoagulation disorders. Clinical findings of this syndrome include arterial or venous thrombosis, recurrent pulmonary embolism, valve diseases, intracardiac thrombus formations, pulmonary hypertension, coronary artery disease, and dilated cardiomyopathy. A definitive diagnosis can be made in a patient with history of arterial or venous thrombosis or recurrent abortions and positive for anticardiolipin antibodies, anti-beta 2-glycoprotein-1 antibodies -also known as antiphospholipid antibodies- and/or lupus anticoagulants. The incidence of thrombosis is highest during the following periods: 1) preoperative period due to the withdrawal of warfarin; 2) postoperative period due to potential hypercoagulability despite warfarin or heparin therapy; and 3) postoperative period before the start of adequate anticoagulation treatment. Irregular thickening of the valve leaflets due to deposition of immune complexes may lead to vegetation and valve dysfunction. The most commonly affected valve is the mitral valve, followed by the aortic and tricuspid valves. Anticoagulation dosage should be adjusted carefully during cardiopulmonary bypass due to the high risk of thrombosis in patients with APS. Multidisciplinary approaches are needed to reduce risk of bleeding and thrombosis during peri- and postoperative periods by adequate anticoagulation adjustment. Further prospective studies are required on anticoagulation adjustments in patients with APS during cardiovascular surgery.

Keywords: Antiphospholipid syndrome; cardiovascular surgery; intracardiac mass.

ÖZ

Antifosfolipit sendromu (APS) temelde çeşitli hiperkoagülasyon bozuklukları ile karakterize nadir bir sendromdur. Bu sendromun klinik bulguları arasında arteriyel veya venöz trombozlar, tekrarlayan pulmoner embolizm, kapak hastalıkları, intrakardiyak trombüs oluşumları, pulmoner hipertansiyon, koroner arter hastalığı ve dilate kardiyomiyopati sayılabilir. Arteriyel veya venöz tromboz veya tekrarlayan düşük öyküsü olan ve antikardiyolipin antikorları, antifosfolipit antikorlar diye de bilinen anti-beta 2-glycoprotein-1 antikorları veya lupus antikoagülan antikorları pozitif olan bir hastada kesin tanı konulabilir. Tromboz insidansı şu dönemlerde en yüksektir: 1) varfarinin kesilmesi nedeniyle ameliyat öncesi dönem; 2) varfarin veya heparin tedavisine rağmen potansiyel hiperkoagülabilite nedeniyle ameliyat sonrası dönem; 3) uygun antikoagülasyon tedavisi başlanmadan önce ameliyat sonrası dönem. İmmün komplekslerin birikimi sonucu kapakçıkların düzensiz kalınlaşması vejetasyona ve kapakçık disfonksiyonuna neden olabilir. En yaygın etkilenen kapak mitral kapak olup bunu aortik ve triküspit kapaklar takip eder. APS'li hastalarda tromboz riskinin yüksek olması nedeniyle kardiyopulmoner baypas sırasında antikoagülasyon dozu dikkatli ayarlanmalıdır. Ameliyat sırası ve sonrası dönemde antikoagülasyonun iyi ayarlanması ile kanama ve tromboz riskinin azaltılması için multidisipliner yaklaşımlar gereklidir. Antifosfolipit sendromlu hastaların kalp damar cerrahisi sırasında antikoagülasyon ayarlamaları hakkında daha fazla prospektif çalışmaya ihtiyaç vardır.

Anahtar sözcükler: Antifosfolipit sendrom; kalp damar cerrahisi; intrakardiyak kitle.

Antiphospholipid syndrome (APS) is a systemic, acquired heterogeneous autoimmune disorder. It has been described by Hughes[1] as a combination of the various clinical symptoms of arterial and venous thromboembolism combined with the presence of autoantibodies. Antiphospholipid antibodies (aPLs) are a heterogeneous group of antibodies that interact with anionic phospholipids, cardiolipin, and other phospholipid-binding protein cofactors, especially serum protein β_2-glycoprotein-1 (β_2GP1). The circulating aPLs include anticardiolipin antibodies (aCL), anti-β_2-glycoprotein-1 (anti-β_2GP1), and the lupus anticoagulant (LA), and these are associated with an increased risk of arterial and venous thromboembolism. Antiphospholipid syndrome is seen in about 2% of the general population; however, the

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antibodies occur in approximately 5% of the healthy population.

If there is no underlying disorder, the syndrome is called "primary". Primary APS is frequently associated with young age, and there are no vascular risk factors related to this condition. Secondary APS is one of the primary indicators of systemic lupus erythematosus (SLE), and this autoimmune disease is present in approximately 40% of all APS patients. The prevalence of aPL antibodies is much higher in patients with SLE, ranging from 12% to 30% for aCL, and 15% to 34% for LA.[2,3]

This syndrome can manifest with a variety of clinical presentations, including vascular thrombosis and various obstetric complications, with deep venous thrombosis (DVT) often seen in pregnant women However, valvular heart disease and cutaneous disorders such as livedo reticularis, leg ulcers, and superficial macules mimicking vasculitis can also be found. In two-thirds of the patients with APS, the cardiovascular system is affected. Furthermore, APS may also cause restenosis of the coronary artery conduits and stents that can lead to morbidity and mortality in patients with coronary heart disease.[4] Thus, this syndrome is challenging for both cardiologists and cardiac surgeons alike. The goal of this review is to focus on some recent aspects of the pathogenesis, clinical manifestations, and treatment of APS from the perspective of a cardiovascular surgeons.

PATHOGENESIS

The mechanism of thrombosis in patients with APS is not fully understood, but several possibilities have been proposed. Some data[5] has suggested that aPLs induce thrombosis through different mechanisms. They then interfere with endogenous anticoagulant mechanisms as well as the binding and activation of platelets and the interaction with endothelial cells. Antiphospholipid antibodies also induce the expression of adhesion molecules and tissue factors and activate the complement cascade. Recent investigations have also suggested that these antibodies, in particular LA and aCL, are directed predominantly against negatively charged phospholipids and that they play a role in thrombosis because of the affect they have on platelet membranes, endothelial cells, and clotting proteins such as prothrombin, protein C, and protein S.[5]

The targets of pathogenic antibodies in APS are vascular and/or plasma cell proteins. Indeed, aPLs generally act against a wide variety of phospholipid-binding proteins (also known as cofactors), specifically serum protein β_2GP1, prothrombin, and annexin V. The aPL-induced endothelial proinflammatory response takes place through adhesion molecule upregulation. At the end of this process, proinflammatory cytokine and chemokine synthesis and secretion occur, and the activated complement fragments themselves have the capacity to bind and activate inflammatory and endothelial cells.[6] With this in mind, Pierangeli et al.[5] demonstrated that complement activation mediated two important effectors of aPLs: the induction of thrombosis and the activation of endothelial cells.

The exact mechanism of intracardiac thrombus formation in APS is unclear. When in the presence of other hemostatic defects, circulating aPLs disrupt the balance between thrombosis and fibrinolysis and might also change the endocardial surface factors, thereby contributing to clot formation. In addition, previous studies have speculated that an abnormal intracardiac blood flow pattern possibly contributes to thrombosis and that diffuse ventricular dysfunction may be predisposed to intracardiac thrombus formation. However, the underlying abnormalities are only rarely identified in these cases.[7,8]

The pathogenesis of Libman-Sacks endocarditis has generally been assumed to involve the formation of fibrin-platelet thrombi on the altered valve, the organization of which leads to valve fibrosis, distortion, and subsequent dysfunction.[9,10] In addition, Hedge et al.[11] also proposed that aPLs mediate valvular damage merely by promoting thrombus formation on the injured valve endothelium rather than by playing a more direct pathogenic role.

CLINICAL PRESENTATIONS

Antiphospholipid syndrome has various clinical features, with arterial and venous thromboses being seen the most. In patients with APS, cardiovascular involvement, such as valvular heart disease (Libman-Sacks endocarditis), coronary artery disease (CAD), intracardiac thrombus formation, pulmonary embolism (PE), pulmonary hypertension (HT), and dilated cardiomyopathy, have also been identified.[11,12] Cardiac valvular pathology includes irregular thickening of the valve leaflets due to the deposition of immune complexes, and these can lead to vegetation and valve dysfunction. These lesions occur frequently and may be a significant risk factor for stroke.[13] The most commonly affected valve is the mitral valve, although the aortic and tricuspid valves are sometimes affected as well. In APS patients with mitral valve disease, the incidence of arterial embolization is 77%,[14] and clinical studies have suggested a link between aPLs

and heart valve lesions. The baseline characteristics of patients with APS are shown in Table 1.[3]

Approximately one-third of patients with primary APS exhibit valvular abnormalities, which is considerably more than the general population, and valvular thickening, nonbacterial vegetation on the left heart valves, and unknown intracardiac masses have been seen on echocardiography. Most patients develop a mild form of valvular regurgitation, but 4-6% progress to severe valvular regurgitation that requires valve surgery.[15,16] Primary APS patients tend to be rather young; therefore, mechanical valve replacement is often the first surgical treatment option since they will require long-term anticoagulation. Bili et al.[17] studied 1,150 acute myocardial infarction (AMI) patients and reported that elevated aCL-immunoglobulin G (IgG) and decreased aCL-IgM antibodies are independent risk factors for recurrent cardiovascular events. Moreover, Zuckerman et al.[18] suggested that the presence of elevated aCLs is a marker for an increased risk for myocardial reinfarction and thromboembolic events after AMI. However, Hamsten et al.[19] demonstrated that the presence of aCL can sometimes indicate a high risk of recurrent cardiovascular events in young people. In contrast, in a study involving 597 AMI survivors, Sletnes et al.[20] failed to prove via multivariate analysis that aCL is an independent risk factor for mortality, cerebral thromboembolism, or recurrent MI. Furthermore, Ciocca et al.[21] retrospectively analyzed patients with APS who underwent cardiac or vascular surgical procedures and reported a postoperative thrombosis or bleeding incidence of 84.2% and a mortality rate of 63.2%. In all of the aforementioned series, we identified only thirteen patients who underwent cardiac surgery.

Although an intracardiac mass caused by APS is uncommon, this syndrome should still be kept in mind when these masses occur. In their study, Buyuksirin et al.[22] found an intracardiac mass in a patient with no apparent cause, such as infective endocarditis or genetic disorders, and we previously presented the case of a patient with APS who also had an intracardiac mass.[23] That patient underwent an operation for the mass, and moderate thrombocytopenia was detected. However, we found no underlying or coexisting cardiac abnormalities. The mass was located on both mitral valve leaflets and mimicked infective endocarditis vegetation. It was subsequently removed by surgical intervention. A histopathological investigation was then carried out, and the results showed bloody fibrin, mesothelial cells, organized necrotic thrombus formation, and vegetation-like lesions.

Table 1. The most common manifestations of antiphospholipid syndrome

Manifestations	%
Peripheral thrombosis	
Deep vein thrombosis	38.9
Superficial thrombophlebitis in the legs	11.7
Arterial thrombosis in the legs	4.3
Venous thrombosis in the arms	3.4
Arterial thrombosis in the arms	2.7
Subclavian vein thrombosis	1.8
Neurological manifestations	
Migraine	20.2
Stroke	19.8
Transient ischemic attack	11.1
Epilepsy	7.0
Multi-infarct dementia	2.5
Chorea	1.3
Acute encephalopathy	1.1
Pulmonary manifestations	
Pulmonary embolism	14.1
Pulmonary hypertension	2.2
Pulmonary microthrombosis	1.5
Cardiac manifestations	
Valve thickening/dysfunction	11.6
Myocardial infarction	5.5
Angina	2.7
Myocardiopathy	2.9
Vegetations	2.7
Coronary bypass rethrombosis	1.1
Intra-abdominal manifestations	
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	2.7
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	1.5
Splenic infarction	1.1
Cutaneous manifestations	
Livedo reticularis	24.1
Ulcers	5.5
Pseudovasculitic lesions	3.9
Digital gangrene	3.3
Cutaneous necrosis	2.1
Osteo-articular manifestations	
Arthralgia	38.7
Arthritis	27.1
Avascular necrosis of the bone	2.4
Ophthalmologic manifestations	
Amaurosis fugax	5.4
Retinal artery thrombosis	1.5
Hematological manifestations	
Thrombocytopenia (<100,000/μL)	29.6
Hemolytic anemia	9.7
Obstetric manifestations in pregnancy	
Pre-eclampsia	9.5
Eclampsia	4.4
Abruptio placentae	2.0
Fetal manifestations in pregnancy	
Early fetal los (<10 weeks)	35.4
Late fetal los (≥10 weeks)	16.9
Live births	47.7
Premature births	10.6

Patients with APS are at an increased risk for thrombosis; hence, adequate anticoagulation is of vital importance during cardiopulmonary bypass (CPB). Many reports have described thrombotic or hemorrhagic complications, including early graft occlusion, hemothorax,[24,25] pulmonary emboli, and limb ischemia, in cardiac surgical patients.[26,27] In their study, Gorki et al.[28] reported a high mortality rate in their valvular surgery patients. Early death occurred in 7% of their cases and late death in 12% after a mean follow-up period of less than three years. In addition, Colli et al.[29] presented the results of a retrospective

Table 2. Revised classification criteria for the antiphospholipid syndrome*

1. Vascular thrombosis	One or more clinical episodes of arterial, venous, or small vessel thrombosis must be present in any tissue or organ, and rhrombosis must be confirmed via objectively validated criteria (i.e., unequivocal findings using appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity	1. One or more unexplained deaths of a morphologically normal fetus must have occurred at or beyond the 10^{th} week of gestation with normal fetal morphology documented by ultrasound or direct examination of the fetus. 2. One or more premature births of a morphologically normal neonate before the 34^{th} week of gestation must have occurred because of either *(i)* eclampsia or severe pre-eclampsia (according to standard definitions) or *(ii)* the presence of recognized features of placental insufficiency. 3. Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation must have occurred, the cause of which cannot be maternal anatomic or hormonal abnormalities or paternal and maternal chromosomal abnormalities.
3. Laboratory criteria	1. Lupus anticoagulant, as defined by the guidelines of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis, must be present in the plasma on two or more occasions that occurred at least 12 weeks apart. 2. The anticardiolipin (aCL) antibody of IgG and/or the IgM isotype must present in the serum or plasma, and medium or high titers (>40 GPL or MPL or > the 99^{th} percentile), as measured by a standardized enzyme-linked immunosorbent assay (ELISA) test, must have occurred on two or more occasions that were at least 12 weeks apart. 3. 3. The anti-β_2 glycoprotein-I antibody of IgG and/or the IgM isotype must be present in the serum or plasma (titer > the 99^{th} percentile as measured by a standardized ELISA test) and must have occurred on two or more occasions that were at least 12 weeks apart. In addition, recommended procedures must be followed.

* Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria are met. However, a diagnosis of APS should be avoided if less than 12 weeks or more than five years separate a positive aPL test from the clinical manifestation.

analysis of nine patients with APS who underwent heart valve surgery using CPB, and they observed high morbidity (50%) and mortality (22%) rates. Furthermore, their patients also exhibited an abnormal coagulation profile with prolonged activated partial thromboplastin time (aPTT).

DIAGNOSIS

The persistent presence of aCL, LA, and/or anti-β_2GP1 antibodies (the so-called aPLs) on laboratory tests in patients with arterial or venous thrombosis or recurrent abortions points toward APS. This diagnosis may be suspected at first, but it must be confirmed by laboratory investigations that include the clinical criteria for thromboembolism and/or pregnancy, morbidity, and positive laboratory findings such as lupus anticoagulants, anti-β_2GP1, and/or aCL. Antiphospholipid syndrome can only be diagnosed when there is the presence of at least one clinical and one laboratory criterion. The diagnostic criteria are summarized in Table 2.[27]

TREATMENT

The optimal management for patients with APS remains unclear. Because of the high risk of recurrent thromboembolism, the first treatment choice is usually antithrombotic therapy. In cases of APS, the consensus opinion is that patients should be treated with oral anticoagulants after the first venous thrombosis attacks in order to achieve the desired international normalized ratio (INR) of between 2.0 and 3.0. However, Ruiz-Irastorza et al.[30] recommended a target INR of >3.0 in patients with APS and arterial thrombosis.

Retrospective studies have shown that patients with APS who are left untreated or who discontinue their oral anticoagulant therapy after the first episode of venous thromboembolism have a high risk of recurrence. Nowadays, warfarin (or another vitamin K antagonist) is the gold standard for the long-term treatment of patients with APS. The recommended target INR is between 2.0 and 3.0[31] based on randomized controlled studies that have demonstrated that high-intensity warfarin (INR >3.0) is not superior to standard-intensity warfarin (INR=2.0-3.0) for preventing recurrent thrombosis in patients with APS.[32,33] On the other hand, Khamashta et al.[34] suggested that high-intensity oral anticoagulant therapy (INR ≥3) is actually more effective than low-intensity anticoagulation (INR <3) for preventing further venous and arterial thrombotic events associated with aPL high titer levels. In fact, for patients with recurrent and/or arterial events, the target INR can indeed be above 3.0. Furthermore, Bulkely and Roberts[35] determined that for the secondary prevention of aPL-associated thrombosis, low-dose aspirin (75 mg daily) either alone or in combination with warfarin provided no therapeutic benefits after adjusting for other risk factors related to thrombosis. Moreover, there is no evidence that shows that corticosteroid treatment can prevent valvular damage in APS patients. Although the basic disease process and presence of tissue injury are not altered by steroid therapy, the inflammatory reaction may be dramatically suppressed. Thus, corticosteroid treatment may contribute to the healing of valvular vegetation, but it may also result in marked scarring and deformity of the valve, which would most likely lead to valve dysfunction.[34,36]

We also do not know the optimal duration for anticoagulation for preventing recurrent venous thromboembolism in patients with APS. However, it is safe to say that because of the high risk of recurrent venous thromboembolism and the comparatively lower risk of major bleeding in these patients, they should receive long-term anticoagulation based on the current data.[31,37]

Thus, since patients with APS are prone to repeated thrombotic episodes, especially in the first few months after the withdrawal of oral anticoagulants, long-term or even possibly lifelong anticoagulation is needed in the presence of persistently elevated aPL titers.[34,37]

ALTERNATIVE THERAPIES

The new oral anticoagulants dabigatran etexilate and rivaroxaban are rapidly absorbed and have been shown to be effective in the management of venous thromboembolism. These drugs function by directly inhibiting thrombin and factor Xa, respectively, with the inhibition of upstream factor Xa causing the early termination of the clotting cascade. Additionally, another advantage of these anticoagulants is that they do not require laboratory monitoring.[38]

Additionally, recent consensus guidelines have advocated the use of statins as adjuvant therapy, with the rationale for their use being secondary to their pleiotropic effects. Besides having a lipid-lowering effect, they also possess anti-inflammatory and antithrombotic characteristics. Moreover, statins may also play a role in the primary prophylaxis of venous thromboembolism and cardiovascular disease.

Another treatment option is hydroxychloroquine (HCQ), an antimalarial drug commonly used in the management of SLE because of its anti-inflammatory

and antithrombogenic properties. A recent systematic review[39] revealed that HCQ is well tolerated and can be used effectively at any stage of SLE. and these findings form the basis for recommending that it be used to treat APS.

Rituximab is a CD-20 monoclonal antibody that is frequently prescribed for rheumatoid arthritis (RA) patients. It targets B cells and prevents the formation of autoantibodies. The rituximab in APS (RITAPS) pilot study suggested that this drug was safe for APS patients and that even without inducing a substantial change in aPL profiles, it may be effective for controlling some non-criteria manifestations of aPL.

PRE- AND POSTOPERATIVE APPROACHES

Patients with APS may be taking preoperative anticoagulation therapy such as aspirin, warfarin, or heparin. However, the discontinuation of this medication before surgery as well as inadequate intraoperative anticoagulation either intraoperatively or prior to the postoperative institution of anticoagulation exposes these patients to the risk of vaso-occlusive complications, cerebrovascular accidents, MI, and venocaval thrombosis. Even today, the perioperative management of patients with APS who are also undergoing CPB is especially challenging for both surgeons and patients. The incidence of thrombosis is highest in the early postoperative period perhaps because of the hypercoagulability state of the disease with warfarin being withdrawn preoperatively until the adequate anticoagulation is achieved in the postoperative period. Beginning the anticoagulation in the early postoperative period via heparin and warfarin is recommended.

PROGNOSIS

DeMarco et al.[39] reported that there is an increase in the risk of venous thromboembolism in patients with APS. They also noted that thrombotic complications may cause death in many of these patients, and this syndrome is responsible for 10% of all deaths in many non-industrial countries. Patients with LA, aCL, and IgG concentrations at high titers, or anti-β_2GP1 antibodies plus LA or aCL have the highest thrombotic risk.[40,41] Furthermore, Espinosa et al.[42] demonstrated that in patients with APS, those that were LA-positive were at a much greater risk for both arterial and venous thrombosis, although patients who were LA-negative but persistently tested positive for aCL in more than two-thirds of the determinations had an increased risk of thrombosis, especially in the arterial system.

Conclusion

There is an obvious association between aPL and thrombus formation as well as heart valve lesions, and aPL may also play a pathogenic role in endocardial damage. In addition, well-organized prospective and randomized controlled clinical trials are needed to further define the optimal management for patients with APS. More trials are also necessary to determine the role of APS in thrombus formation and to assess the effects of aPL on the coagulation cascade so that the best treatment option can be determined in order to prevent APS along with its potential clinical consequences.

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