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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Antiphospholipid antibody syndrome: Recent findings on managing this challenging condition

ABSTRACT

Patients with antiphospholipid syndrome can suffer recurrent thrombosis that is very difficult to manage. Recent research has demonstrated that high-intensity anticoagulation is not superior to standard therapy. Basic questions about the nature and treatment of this syndrome remain unanswered.

KEY POINTS

The diagnosis of antiphospholipid antibody syndrome requires both a laboratory finding (anticardiolipin antibody or lupus anticoagulant) and a clinical finding (unexplained thrombosis or pregnancy loss).

Patients with arterial or venous thrombosis and persistently positive antiphospholipid antibodies should be treated indefinitely with warfarin (INR 2–3). Adding aspirin may benefit patients with arterial thrombosis.

Patients on warfarin who have recurrent thromboses should receive either high-intensity warfarin (INR 3–4) or therapeutic doses of low-molecular-weight heparin.

For patients with transiently positive antiphospholipid antibodies, thrombosis should be treated with an appropriate therapeutic course of warfarin.

There is no evidence that a patient with antiphospholipid antibodies but no history of thrombosis should be treated prophylactically. Aspirin is appropriate if other risk factors for vascular disease are also present.

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FIRST DESCRIBED in detail by Hughes,[1] the antiphospholipid antibody syndrome is a hypercoagulable state that poses the risk of recurrent thrombi (arterial, venous, or both) and pregnancy morbidity.

The best way to treat this syndrome remains unclear. Recent research shows that high-intensity treatment with warfarin is not superior to standard therapy, and much remains to be understood about the nature and treatment of this disease.

CHALLENGES IN TREATMENT

Although hypercoagulability is associated with antiphospholipid antibodies, not all patients with elevated titers experience symptoms. And in some patients, anticoagulation is not effective.

The following three cases show how difficult the syndrome can be to manage.

Case1: Recurring coronary occlusions

A 42-year-old woman presents to the emergency department with chest pain. She has no risk factors for coronary artery disease and no clinical history of autoimmune conditions.

Laboratory testing reveals a highly elevated troponin level, mild thrombocytopenia, and lupus anticoagulant. Coronary angiography shows occlusion of the right coronary artery and critical stenosis of the circumflex artery. Stents are placed, and she begins aspirin and clopidogrel treatment.

This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

Two days later, while in the coronary care unit, she has an asystolic cardiac arrest. On repeat angiography, both stents are found to be 100% occluded. Stenting is repeated. Two days after that, she develops chest pain, and the stents are again found to be occluded.

After her condition stabilizes, she is discharged home receiving aspirin, clopidogrel, and therapeutic-dose warfarin.

Two weeks later, she presents to her family physician with petechiae and bruising and is found to have a dangerously low platelet count (20,000/mm^3). Anticoagulants are withheld and prednisone 50 mg/day is started. Three days later, her platelet count has risen to 69,000/mm^3, and aspirin and clopidogrel are restarted.

Two days later, she has chest pain again, and angiography reveals complete occlusion of the right coronary circumflex artery and 40% proximal occlusion of the left anterior descending artery. Her cardiologists feel that further stent replacement is futile.

Case 2: Arterial thromboses leading to amputation

A 48-year-old woman with nephrotic syndrome gradually develops arterial ischemia of the right leg. She has no clinical history of systemic lupus erythematosus, but she tests positive for lupus anticoagulant.

She presents to the hospital with a painful, cold leg and is found to have arterial thrombosis. The clot is removed, and angioplasty of the stenosis is performed.

One month later she develops bilateral leg ischemia. She is treated with anticoagulation therapy, but her condition rapidly worsens. Aortic angiography reveals that her distal aorta is occluded, despite an otherwise normal aorta and heart. Bilateral amputations above the knees are required for therapy of gangrene.

The diagnosis requires at least one clinical and one laboratory criterion

Case 3: Recurring pulmonary emboli

A 35-year-old woman presents with hemoptysis and is found to have a pulmonary embolism. She has a history of five separate incidents of pulmonary emboli, despite therapy with an inferior vena cava filter and high-intensity warfarin therapy (INR 3.6).

ANTIPHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies are a group of autoantibodies directed against specific complexes of glycoproteins (often cell-associated) and anionic phospholipids. These antibodies occur spontaneously or may be associated with a number of factors, eg:

- Autoimmune conditions (systemic lupus erythematosus)
- Drugs such as procainamide, hydralazine, quinidine, and chlorpromazine
- Other conditions (human immunodeficiency virus, hepatitis, chronic bacterial infections, malaria).

The antiphospholipid antibodies can be divided into two general groups: anticardiolipin antibodies and lupus anticoagulants.

Anticardiolipin antibodies were first described during World War II in servicemen with falsely positive VDRL tests. Most anticardiolipin antibodies are directed against beta-2 glycoprotein-1, which forms a complex with cellular phospholipids.

Lupus anticoagulants, a group of antibodies also known as nonspecific inhibitors, which can prolong the partial thromboplastin time, were first noted in 1952 in two patients with systemic lupus erythematosus and a bleeding disorder. In 1963, lupus anticoagulants and thrombosis were found to be associated, and the term "lupus anticoagulant" was formally proposed in 1972.

CLINICAL MANIFESTATIONS

Clinical manifestations of the antiphospholipid antibody syndrome can be broadly divided into major, minor, and "other" categories.

Major manifestations include:

- Thrombocytopenia due to autoimmune platelet destruction
- Recurrent fetal loss
- Macrovascular or microvascular arterial or venous thrombosis.

Minor manifestations include:

- Livedo reticularis
- Migraines.

Other. A number of other conditions are also included in the syndrome:

- Catastrophic antiphospholipid antibody syndrome (life-threatening thromboses in

multiple organs developing simultaneously or over a short period)
- Microvascular variants
- Renal manifestations.

DIAGNOSIS

The Sapporo criteria offer a standardized definition of the antiphospholipid antibody syndrome.[2] At least one clinical criterion and one laboratory criterion are required to make the diagnosis.

Clinical criteria are:
- Vascular thrombosis (ie, at least one episode of a blood clot occurring without any clear explanation)
- Pregnancy morbidity (ie, a single unexplained pregnancy loss after 10 weeks of gestation; three or more consecutive, unexplained losses at less than 10 weeks of gestation; or a premature birth at less than 34 weeks of gestation, when delivery is because of severe preeclampsia, eclampsia, or severe placental insufficiency).

Note that thrombocytopenia and other clinical manifestations are not included in this definition.

Laboratory criteria include the presence of either anticardiolipin antibody or lupus anticoagulant on at least two occasions at least 6 weeks apart. The anticardiolipin antibody must be immunoglobulin G (IgG) or IgM in a medium or high titer, detected using a standardized enzyme-linked immunosorbent assay.

Some researchers argue that the diagnosis should be determined by the detection of anti-beta-2 glycoprotein-1-dependent antibody instead of a simple anticardiolipin antibody assay. However, the evidence is unconvincing that this method is better.

The major disadvantages of anticardiolipin antibody testing are that many laboratory diagnostic kits are used, they have varying sensitivities, and no standard threshold exists for abnormal values. In a study in Europe, samples from 12 patients suspected of having antiphospholipid antibody syndrome and from 12 controls were sent to 56 expert laboratories. A total consensus was reached of whether anticardiolipin antibodies were present in only 25% of the samples. Even a general consensus (ie, agreement between 90% of the laboratories) on whether anticardiolipin antibody was present was reached in less than half the cases.[3]

Lupus anticoagulant should be identified using the guidelines of the International Society of Thrombosis and Hemostasis.[4] Clotting times are measured in phospholipid-dependent assays in which the lupus anticoagulant interferes with complex formation. Lupus anticoagulant is determined to be present if specific clotting times are prolonged, do not correct when mixed with normal plasma (which excludes a factor deficiency), then normalize after excess phospholipid is added. Other coagulopathies such as a specific coagulation factor inhibitor must be excluded.

Because no target epitope has been determined, only the presence or absence of lupus anticoagulant can be ascertained. Titers cannot be measured. Despite this, and unlike with an anticardiolipin antibody, lupus anticoagulant testing is reliable.

ANTIBODY-DISEASE CONNECTION?

Although patients with a lupus anticoagulant have an increased risk of recurrent deep vein thrombosis, there is no direct evidence that the antibody actually causes the disease.

Laboratory testing for anticardiolipin antibodies is not standardized

For example, the Antiphospholipid Antibodies and Stroke Study (APASS),[5] a large, prospective cohort study, found that patients with antiphospholipid antibodies (either lupus anticoagulant or anticardiolipin antibodies) had no greater risk of subsequent thrombo-occlusive events over 2 years after an initial stroke. Only a small subgroup of patients who had both types of antibodies had a trend towards a higher event rate compared with patients who tested negative for both antibodies (unadjusted relative risk 1.36; 95% confidence interval 0.97–1.92; $P = .07$).

In addition, lupus anticoagulant and anticardiolipin antibodies are often transiently positive or can vary dramatically over time, not necessarily coinciding with the clinical picture. A waxing and waning picture (typical of autoimmune diseases) is often seen but makes a diagnosis of the disease difficult. Serial follow-up is critical to determine if a patient is positive for antibodies only tran-

siently or over the long term, which may affect treatment decisions.

Furthermore, researchers have not been able to create animal models of thrombocytopenia or thrombosis with antiphospholipid antibodies. Only one animal model of antiphospholipid antibody syndrome exists: Sherer and Schoenfeld[6] have induced or injected antiphospholipid antibodies into mice, which reduced the mice's ability to reproduce but did not cause thrombosis.

HOW MIGHT THROMBOSIS DEVELOP?

How thrombosis develops in antiphospholipid antibody syndrome is still poorly understood. Several mechanisms have been proposed.

Rand et al[7] suggested that thrombosis may be induced by antiphospholipid antibodies displacing a protective substance, annexin V, that normally covers the phospholipid bilayer on the placental vasculature. Without annexin V, the endothelial surface becomes thrombogenic, causing placental insufficiency and fetal loss.

Another proposed mechanism is analogous to heparin-induced thrombocytopenia: antiphospholipid antibodies activate platelets, which release large amounts of highly thrombotic platelet-associated microvesicles, contributing to thrombosis. Activation of the complement cascade may also be involved.[8]

If thrombosis recurs, look for treatable causes, eg, lipids, homocysteine, or factor V Leiden

TREATMENT: RECENT FINDINGS

Early retrospective studies of the treatment of antiphospholipid syndrome[9,10] suggested that patients treated with standard-intensity warfarin (INR 2–3) had an unacceptably high risk of recurrent thrombosis. Thus, the investigators recommended that patients be treated with high-intensity therapy.

High-intensity warfarin not superior

Recent studies, however, show that while a small group of patients with antiphospholipid antibody syndrome are resistant to warfarin, most patients can and should be treated with standard-intensity warfarin.

Our team[11] randomized 114 patients with antiphospholipid antibodies and either arterial or venous thrombosis to receive either standard-intensity (INR 2–3) or high-intensity (INR 3–4) warfarin therapy. Contrary to our expectations, the rate of recurrent thrombosis was no lower in the high-intensity warfarin group.

Our study has been criticized for excluding patients with any tendency to significant bleeding, a contraindication to warfarin, or previous failure of warfarin therapy. However, we believe it would have been unethical to include these patients. Furthermore, it is standard practice in studies of atrial fibrillation and deep vein thrombosis to exclude patients with previous or recurrent deep vein thrombosis. I would argue that how to treat patients for whom warfarin has failed is a completely separate research area.

Finazzi et al[12] conducted a similar study, which confirmed our findings.

Warfarin and aspirin equivalent after stroke

The Warfarin vs Aspirin Recurrent Stroke Study (WARSS)[5] enrolled about 1,600 patients and evaluated warfarin (INR 1.4–2.8) vs aspirin to prevent recurrent strokes. There was no significant difference in outcome with either therapy, regardless of antiphospholipid status, and the event rate was high.

TREATMENT RECOMMENDATIONS

The best way to treat antiphospholipid antibody syndrome is still unclear. My recommendations are based on a review of the literature combined with my clinical experience.

Positive antibodies and thrombosis. For a patient with a persistently positive antiphospholipid antibody test:

- Treat venous thrombosis with moderate-intensity warfarin (INR 2–3)
- Treat arterial thrombosis with moderate-intensity warfarin plus aspirin (based on recommendations from analogous cardiovascular studies).

No data exist on the optimal duration of therapy. In general, I recommend anticoagulation treatment for as long as it is tolerated.

Thrombotic event and transiently positive antibodies. For a patient who has a thrombotic event and has an antiphospholipid antibody test that is positive at the time and becomes negative shortly afterwards, treat with an appropriate therapeutic course of war-

farin, depending on the type of clot. Stroke can be treated with aspirin. Thus, for example, a secondary deep vein thrombosis that occurred in the setting of a risk factor that is completely resolved might be treated with as little as 3 months of warfarin.

Positive antiphospholipid antibodies and no history of thrombosis. Evidence is insufficient to treat this group of patients prophylactically. However, for a patient with multiple risk factors, eg, an extremely prolonged clotting time during lupus anticoagulant testing, heavy smoking, and high cholesterol, I recommend prophylaxis with aspirin.

Recurrent thrombosis and warfarin failure. A small group of patients with antiphospholipid antibodies have recurrent thromboses despite warfarin therapy. For such patients, it should be first be established that the target INR was actually reached when the recurrent thrombus developed. If so, one of the following treatments should be used:

- Long-term high-intensity warfarin therapy (INR 3–4)
- Long-term therapeutic doses of low-molecular-weight heparin.

In addition, one should aggressively search for additional treatable conditions that might cause hypercoagulation, such as high cholesterol, high triglycerides, high homocysteine, or factor V Leiden.

(I first saw the patient in case 3 in 1996. She has been treated since then with low-molecular-weight heparin in therapeutic doses and has had no further pulmonary emboli.)

Anticoagulation in patients with thrombocytopenia. Antiphospholipid antibody syndrome is often associated with thrombocytopenia, which increases the risk of anticoagulation therapy. For patients with a high risk of a thrombus, I recommend standard warfarin therapy despite platelet counts as low as 30,000/mm^3, and I warn patients of their increased risk for bleeding. If warfarin therapy is needed, I try to increase platelets with steroids, intravenous immunoglobulin, and perhaps splenectomy. Thrombocytopenia in patients with antiphospholipid antibodies is treated analogously to thrombocytopenia in patients who do not have antiphospholipid antibodies.

Pregnancy. Specific recommendations for the prevention of obstetrical complications are beyond the scope of this manuscript.

FURTHER RESEARCH DIRECTIONS

Basic questions remain unanswered about the nature and treatment of this syndrome. An important focus is identifying which patients are destined to fail standard anticoagulant therapy and how best to treat them. New anticoagulant medications are expected to be available soon, promising further research in optimal treatment.

REFERENCES

1. **Hughes GRV.** Hughes Syndrome: A Patient's Guide. London, New York: Springer; 2001.
2. **Wilson WA, Gharavi AE, Koike T, et al.** International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999; 42:1309–1311.
3. **Favaloro EJ, Silvestrini R.** Assessing the usefulness of anticardiolipin antibody assays: a cautious approach is suggested by high variation and limited consensus in multilaboratory testing. Am J Clin Pathol 2002; 118:548–557.
4. **Brandt JT, Triplett DA, Alving B, Scharrer I.** Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995; 74:1185–1190.
5. **Levine SR, Brey RL, Tilley BC, et al.** Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. JAMA 2004; 291:576–584.
6. **Sherer Y, Shoenfeld Y.** Antiphospholipid syndrome: insights from animal models. Curr Opin Hematol 2000; 7:321–324.
7. **Rand JH, Wu XX, Andree HA, et al.** Pregnancy loss in the antiphospholipid-antibody syndrome—a possible thrombogenic mechanism. N Engl J Med 1997; 337:154–160.
8. **Girardi G, Redecha P, Salmon JE.** Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nature Med 2004; 10:1222–1226.
9. **Rosove MH, Brewer PM.** Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992; 117:303–308.
10. **Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR.** The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993–997.
11. **Crowther MA, Ginsberg JS, Julian J, et al.** A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349:1133–1138.
12. **Finazzi G, Marchioli R, Barbui T.** A randomized clinical trial of oral anticoagulant therapy in patients with antiphospholipid antibody syndrome: the WAPS study. J Thrombo Haemost 2003 Jul; 1(s1):OC365.

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