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Antiphospholipid Antibodies

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Antiphospholipid antibodies (APLAs) are proteins that may be present in the blood and may increase your risk for blood clots or pregnancy losses. If you have a history of blood clots or recurrent pregnancy losses, you may have been tested for the presence of APLAs in your blood. The purpose of this Cardiology Patient Page is to provide information for persons with APLAs about the disorder and appropriate treatment.

What Are APLAs?

Definition

Substances in the blood, called phospholipids, are required for the blood to clot. In some people, the body mistakenly identifies phospholipids, or proteins bound to the phospholipids, as foreign substances and forms antibodies against them. This reaction can be viewed as a confusion of the immune system, called an autoimmune process. These antibodies are called APLAs. Their presence can lead to blood clots and/or pregnancy loss. However, in some people, they do not cause any problems. Only if a person has had a blood clot or pregnancy loss and a test for APLAs that has been positive more than once, measured at least 6 weeks apart, does one refer to the person as

having the *antiphospholipid antibody syndrome (APLA syndrome)* (Table 1).

There are many subgroups of APLAs (Table 2). The ones most relevant to our discussion are *anti-cardiolipin antibodies (ACAs)* and lupus anticoagulant. The presence of these antibodies leads to an increased risk of blood clots and/or pregnancy loss. The significance of the other APLAs listed in Table 2 is unclear. They are, therefore, not part of the criteria (called the *Sapporo criteria*) for APLA syndrome (Table 1). Although some healthcare providers test their patients for these latter antibodies, it is not clear what positivity for these antibodies means for the patient.

How Do You Test for APLAs?

There are two ways to test the blood for the presence of APLAs. One test is a direct measurement of the amount of antibody present. Because the immune system can make APLAs against a variety of different phospholipids or proteins bound to phospholipids (for example, *cardiolipin, beta₂-glycoprotein-1*), a variety of tests can be performed (Table 2). Furthermore, because our immune system can make three different forms of antibodies, referred to as immunoglobulins (immunoglobulin

G=IgG, M=IgM, and A=IgA), three different tests can be performed for each phospholipid. These tests are poorly standardized, which causes problems when interpreting the results or comparing results from one laboratory to those of another.

The other way to look for the presence of APLAs is by measuring the effect that the antibodies have on the clotting system in the test tube (*lupus anticoagulant test*). A variety of clotting tests are used for this purpose, most commonly the *DRVVT*-based test and the *LA-PTT*-based test. Lupus anticoagulants are detected by mixing the patient's blood with phospholipids and measuring the time that it takes the blood to clot in the tube. The lupus anticoagulant test is one of the most error-prone tests performed in coagulation laboratories. A prudent approach to a report of a positive test may be to obtain copies of the test results and have them reviewed by a physician knowledgeable about APLAs.

A person can be positive for APLA with only one subcategory of the APLA tests, two categories, or several, as indicated by the individual circles and the overlapping of the circles in Figure 1. Although anticardiolipin antibodies are more common than lupus anticoagulants, the presence

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TABLE 1. Sapporo Criteria for Diagnosing APLA Syndrome

Presence of 1 Clinical Event AND a Repeatedly* Positive Lab Test	
Clinical Events	Lab Tests
Blood clot (=thrombosis)	
<i>Venous</i>	
<ul style="list-style-type: none"> ● Deep vein thrombosis (DVT)=clot in leg or arm ● Pulmonary embolism (PE)=clot in lung ● Other (in eye=retinal vein thrombosis; around brain=sinus vein thrombosis; in abdomen=mesenteric, portal, or hepatic vein thrombosis; etc) 	<ul style="list-style-type: none"> ● Lupus anticoagulant confirmed with clotting tests that depend on phospholipids OR ● Medium or high levels of anticardiolipin IgG or IgM antibodies
<i>Arterial</i>	
<ul style="list-style-type: none"> ● Stroke ● Heart attack ● Leg or arm arterial clot (=ischemia or gangrene) ● Other (in eye=retinal artery thrombosis; in abdomen=mesenteric artery thrombosis, etc) 	
Pregnancy loss, defined as one of the following†:	
<ul style="list-style-type: none"> ● Three or more losses before the 10th week of pregnancy ● One or more losses at or after the 10th week of pregnancy ● One or more premature deliveries at or before the 34th week of pregnancy because of eclampsia, preeclampsia, or placental insufficiency 	

*Tested at least 6 weeks apart.

†Other possible causes of pregnancy loss or premature delivery should be excluded, such as birth defects, chromosomal abnormalities, and abnormalities of the mother's uterine anatomy or hormone levels.

of a lupus anticoagulant puts a person at a higher risk of having a clot than does the presence of anticardiolipin antibodies alone. For a person who has anticardiolipin antibodies, the higher the antibody level, the greater the risk of developing a blood clot.

History

It should be noted that the term "lupus anticoagulant" was coined because these antibodies were originally dis-

covered in people with lupus. However, it is not an appropriate name, because at least 50% of people with lupus anticoagulants do not have lupus. Also, the use of the word anticoagulant (meaning blood thinner) would lead one to believe that people with lupus anticoagulants bleed, but they actually tend to develop blood clots.

How Does Blood Clot Normally?

Small injuries to blood vessels occur many times every day. The body's

method of responding to small injuries in blood vessels is to form small clots to prevent bleeding. Clots form when proteins and platelets in the blood interact with one another and with the blood vessel wall at the site of injury. Certain substances, such as phospholipids, must also be present in the blood for the clotting proteins to function properly and form a clot. The body forms small blood clots in the blood vessels all the time, and there is a delicate balance in place that prevents overwhelming clot formation while also allowing the body to break down the small clots that are formed so that they do not cause problems.

How Do APLAs Lead to Blood Clots?

We know that APLAs in a test tube cause blood to take a longer than normal time to clot. This is because the antibodies decrease the number of phospholipids available to help the clotting proteins form a clot. On the basis of this information, one would think that people with APLAs would have trouble forming clots (that is, they would have a bleeding disorder). However, APLAs within the body actually cause the opposite reaction and increase the tendency toward clotting.

The mechanisms by which APLAs lead to blood clots are not well understood. APLAs may interact with the cells on the inner surface of blood vessels, making them more prone to form clots. They may interact with blood platelets, making them stickier and more likely to cause clots. Moreover, the APLAs may prevent the body's natural ability to break up blood clots by interfering with substances in the blood that normally prevent excessive clotting (protein C and S).

Who Gets APLAs?

How Often Do Positive APLAs Occur?

The frequency of APLAs is not well known. However, in the general population, 1% to 5% of people have positive APLAs. Of people with spon-

TABLE 2. APLA Subgroups

Detected by Clotting Test (=Functional Test)	Lupus Anticoagulant
Detected by tests that measure the level of antibody (IgG, IgM, or IgA) in the blood	Anticardiolipin
	Anti-beta-2-glycoprotein I
	Anti-phosphatidyl-serine
	Anti-phosphatidyl-ethanolamine
	Anti-phosphatidyl-inositol
	Anti-prothrombin

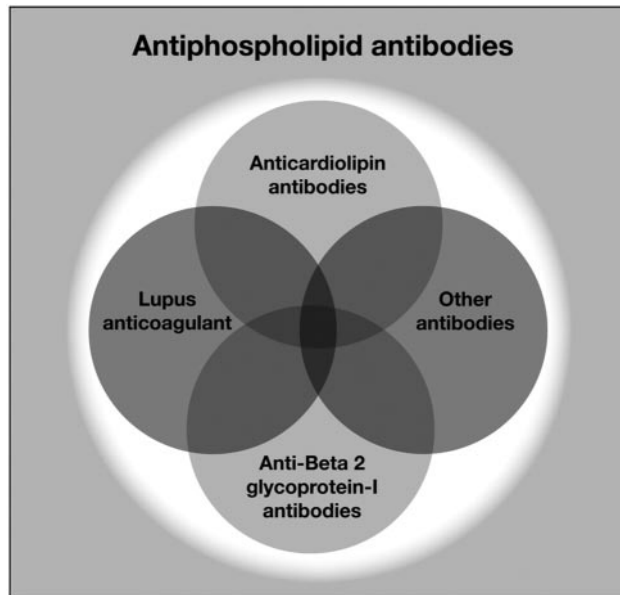


Figure 1. Categories of APLAs.

taneous blood clots in the veins (deep vein thrombosis [DVT] or pulmonary embolism [PE]), up to 10% have elevated APLAs at the time of the clot. Of people with stroke or heart attack, as many as 42% and 17%, respectively, may have some level of positive APLAs at the time of the event. In many people, the antibody in their blood disappears (for unclear reasons) over the subsequent several weeks, and thus they do not have the APLA syndrome.

Primary and Secondary APLA Syndromes

APLAs can be present in people with autoimmune disorders, such as lupus or rheumatoid arthritis. Approximately 12% to 34% of people with lupus also have APLAs. However, only a fraction of them will develop blood clots or pregnancy loss. When people with autoimmune disorders have APLAs and clots or pregnancy loss, they are said to have secondary APLA syndrome.

Some people without known autoimmune disorders can have APLAs. If these people develop clots or pregnancy loss, they are said to have primary APLA syndrome. The reasons why these people develop APLAs are not known.

Inherited Component

APLAs are typically not inherited from family members. Instead, they are acquired, meaning that the body simply starts making antibodies at some point, possibly in response to some sort of trigger or a disturbance of the immune system. The children of someone with APLAs are no more likely to develop APLAs than are children of people without APLAs. However, a few families have been reported in which APLAs appear to be hereditary. Nothing is known about the genetic mechanism associated with such heredity.

What Problems Do APLAs Cause?

Venous Clots

One of the complications of APLAs can be clots in the veins, most commonly either a DVT in the leg or a PE in the lung. Less common locations for venous clots include the superficial veins (superficial thrombophlebitis), the eye, the abdomen, in or around the brain, and in or around the liver.

Arterial Clots

APLAs may also cause clots in the arteries, such as stroke, heart attack, and clots in the arteries of the arm, leg,

eye, kidney, or abdomen. Suspicion for the presence of APLAs in a person with an arterial clot is higher if the person has no obvious risk factor for arterial disease (such as diabetes, high blood pressure, high cholesterol), does not smoke, or is relatively young.

Pregnancy Complications

APLAs are present in approximately 10% to 20% of women with recurrent miscarriage. Women with APLAs have a higher risk of pregnancy loss at or after 10 weeks of pregnancy. This is in contrast to pregnancy loss in the general population, which occurs more commonly before 10 weeks of pregnancy. Additionally, APLAs are associated with other pregnancy complications, including eclampsia, preeclampsia, and placental insufficiency.

A woman is considered to have had a clinical event that meets the Sapporo criteria (Table 1) if she has had one of the following: (1) three or more losses before the 10th week of pregnancy, (2) one or more losses at or after the 10th week of pregnancy, and (3) one or more premature deliveries at or before the 34th week of pregnancy because of eclampsia, preeclampsia, or placental insufficiency. Other possible causes of pregnancy loss or premature delivery should be excluded before testing for the presence of APLAs.

Other Clinical Presentations

Many studies show that APLAs can be associated with a variety of other clinical findings, including low platelets, anemia, heart valve disease, skin rashes, mini-strokes, joint pain, joint inflammation, dry eyes, and dry mouth.

Catastrophic APLA Syndrome

Most patients with APLAs who develop clots will develop them as individual events and possibly have recurrent clots at a later time. However, a very small group of people with APLAs develop multiple clots in different organ systems throughout the body within a matter of days. This is called *catastrophic APLA syndrome*.

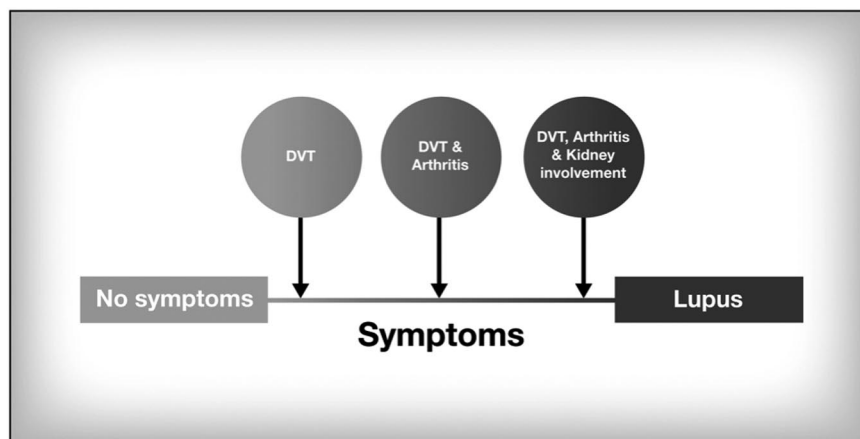


Figure 2. Spectrum of associations with APLAs.

Clots may occur at the same time in the kidney, the brain, the heart, the extremities, the lungs, and/or other organs, with resultant multi-organ failure and a high risk of dying. The treatments are blood thinners, steroids, plasma exchange, and possibly suppression of the immune system.

The Asymptomatic Individual With APLAs

Some people with APLAs will never develop blood clots or experience pregnancy loss. Few data are available on the risk of a blood clot or pregnancy loss in an asymptomatic individual with APLAs. One percent of people may develop a blood clot every year. There are presently no recommendations that support the routine use of blood thinners in asymptomatic people. However, one aspirin per day appears to be beneficial.

Asymptomatic individuals should take the following precautions: (1) Inform healthcare providers that they have APLAs; (2) consider use of short-term blood thinners to prevent a clot during situations that increase the risk of developing a clot (such as surgery or immobilization); (3) know the symptoms of DVT (swelling and pain throughout the leg, leg warmth, and discoloration) and PE (sudden chest pain and shortness of breath); (4) seek medical care immediately if symptoms of DVT or PE develop and inform physicians of the presence of APLAs

in their blood; and (5) modify their other risk factors for arterial and venous blood clots, including avoiding hormone therapy, not smoking, normalizing weight, and controlling blood pressure, cholesterol, and blood sugar.

Who Should Be Tested for APLA and How Often?

People who have had one of the clinical events listed in the Sapporo criteria (Table 1) and who do not have other identifiable reasons for blood clots or pregnancy losses should be tested for APLAs. If they are found to have APLAs, the test should be rechecked at least 6 weeks later. If the second test is again positive, they can be categorized as having APLA syndrome.

It is not known whether people who have had an APLA-associated blood clot lose their risk for a recurrent clot if the APLAs disappear over time or whether their blood thinner can be discontinued if the APLAs disappear. If a person has one positive APLA test followed by a negative APLA test 6 weeks later, the test should be repeated again in 3 to 6 months. If the test is negative twice, the person does not have APLA syndrome, and consideration can be given to stopping blood thinners (depending on the other clinical circumstances surrounding the blood clot).

In the person with APLA syndrome (by repeatedly positive tests), the au-

thors of this article take the approach to recheck APLAs once every 6 to 12 months. If APLAs are negative on two consecutive tests, then discussion about discontinuation of blood thinners can be held, depending on the other circumstances surrounding the previous clot. This is always an individualized decision.

In general, if the APLA test at the time of the clinical event is negative, there is no need to recheck for APLAs unless the person later has another clinical event.

Time Course of Antibodies and Symptoms

The body may make more or fewer antibodies over time. For example, the number of APLAs in the blood may diminish over time and eventually become undetectable, or they may wax and wane over time. The presence of APLAs does not mean that a person will go on to develop lupus or other autoimmune disorders. People with APLAs may experience a progression or regression of their symptoms related to APLAs, but they often remain consistent in their symptom complex from the time of APLA detection (Figure 2).

Treatment

Anticoagulants (Blood Thinners)

Treatment for blood clots in people with APLA syndrome is similar to treatment for clots in people without APLAs. Venous clots are typically treated with blood thinners. Intravenous heparin or subcutaneous low-molecular-weight heparins may be used at the time of the acute clot and, in a few cases, for long-term anticoagulation.

Most people on blood thinners take oral medications called coumarins (warfarin=Coumadin; phenprocoumon=Marcumar, Falithrom; acenocoumarol=Sinthrome). When these drugs are taken, the thinness of the blood needs to be closely monitored with a blood value called the international normalized ratio (INR). In the past, it was thought that all people with APLAs and a history of a

clot should be maintained with an INR greater than 3.0. However, two clinical trials now suggest that, in most people with APLAs and venous clots, the INR value should be maintained between 2.0 and 3.0.

In some people with APLAs, the antibodies may interfere with the method of measuring the INR. For this reason, the INR may not be a reliable method of monitoring warfarin therapy in these people. In those instances, it may be necessary for your healthcare professional to order special tests such as factor II activity, chromogenic factor X activity, or the prothrombin-converting time to measure the level of blood thinning.

The risk of having another clot in people with APLAs is higher than in people without APLAs. With blood thinners, people with APLAs have a risk of 3% to 10% over three years of having another clot. If blood thinners are stopped, people with APLAs have a 10% to 29% risk per year of having another clot. For this reason, blood thinners are often continued long term in people with APLAs who have had a venous clot.

Antiplatelet Agents

Arterial clots are typically treated with medications that interfere with platelets in the blood. These medications essentially make the blood less sticky and can reduce the risk of future clots in the arteries. Examples of such medications are aspirin, clopidogrel (Plavix), and aspirin combined with dipyridamole (Aggrenox). Antiplatelet medications should be continued long term in people with APLAs who have had a previous arterial clot. It is not clear whether people with APLA syndrome and arterial clots have fewer recurrent clots on long-term aspirin or warfarin. Other risk factors for arterial clots should also be modified, such as controlling blood pressure and cholesterol, losing weight, and stopping smoking.

Prevention of Pregnancy Loss

Women with APLAs who have recurrent pregnancy loss may be given blood thinners with aspirin during

pregnancy. This would include injections of heparin or low-molecular-weight heparin (such as enoxaparin [Lovenox] or dalteparin [Fragmin]) plus low-dose aspirin during future pregnancy. Treatment increases the live birth rate to about 80%. Women whose only clinical event associated with APLA syndrome has been pregnancy loss may benefit from long-term daily aspirin therapy after pregnancy to decrease their risk of future clots.

Immunosuppressants and Other Therapy

Because APLAs are produced by a reaction of the immune system, some people have used drugs that interfere with the immune system to treat patients with APLAs. Examples include cyclophosphamide (Cytoxan), azathioprine (Imuran), hydroxychloroquine (Plaquenil), rituximab (Rituxan), and steroids (eg, prednisone). This approach may be more beneficial for people who have secondary APLA syndrome, such as that associated with lupus.

Immunoglobulin (IVIG) is a preparation of proteins that is given as an infusion directly into the veins. The benefits of this treatment for people with APLAs have not been well proven. For some people with APLA syndrome that is difficult to manage or in cases of catastrophic APLA syndrome, it may be necessary to periodically remove the APLAs from the blood. This process is called plasmapheresis.

Research and Resources

Research is ongoing regarding APLAs and blood clots in general. This research may reveal new insights into the clinical management of people with APLAs and blood clots. For this reason, it is important for people with APLAs, particularly those taking long-term anticoagulation, to have regular follow-up with a physician to discuss new data and future plans for medical therapy.

APSCORE

The Antiphospholipid Syndrome Collaborative Registry, or APScore, is a national registry of people with APLAs. Two thousand people with APLA syndrome will be enrolled over a 5-year period to research the causes and treatment of APLA syndrome. Becoming involved in APScore is a good way to promote research into the disorder. More information about the registry can be found at <http://www.apscore.org>.

Rare Thrombotic Diseases Consortium

The Rare Diseases Clinical Research Network is an effort sponsored by the National Institutes of Health (NIH) to facilitate research on rare diseases, including APLA syndrome. Information on the research activities and further information can be found on the Web at <http://www.rarediseasesnetwork.org/rtdc/learnmore/index.htm#aps>.

National Alliance for Thrombosis and Thrombophilia (NATT)

The National Alliance for Thrombosis and Thrombophilia (NATT) is a nationwide, non-profit patient advocacy group representing the interests of people with blood clots and clotting disorders, including people with the APLA syndrome. NATT's mission is to address major treatment issues, such as preventing thrombosis and its complications, and reducing death and illness related to thrombosis. NATT wants patients to get involved. Their Web site is www.nattinfo.org.

Drugs in Development

Although coumarins (warfarin, etc) are presently the only oral blood thinners available, there are several oral blood thinners at various stages of development and testing (warfarin is the only oral blood thinner available in the United States presently). The hope is that some of these drugs will be found to be safe and effective for treatment of blood clots and will become available for use in patients, including those with APLAs.



Abbreviations Used

- *APLAs*—antiphospholipid antibodies
- *DRVVT*—dilute Russell viper venom time
- *DVT*—deep vein thrombosis
- *INR*—International Normalized Ratio
- *NATT*—National Alliance for Thrombosis and Thrombophilia
- *PE*—pulmonary embolism

Additional Resources

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