

## Antiphospholipid Syndrome

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The description of the antiphospholipid syndrome (APS) has been one of the most striking developments in the field of clinical immunology in the last 2 decades. APS is a systemic autoimmune disorder characterized by a combination of arterial or venous thrombosis and recurrent fetal loss, accompanied by elevated titers of antiphospholipid antibodies (aPL), namely the lupus anti-coagulant (LA) and anticardiolipin antibodies (aCL) [1,2]. The syndrome may occur in isolation (primary APS) or in association with an underlying systemic disease, particularly systemic lupus erythematosus (SLE) (secondary APS).

Because aPL-related thrombosis can occur anywhere in the body, the recognition of APS has had a major impact on several medical specialties, including pediatrics. The earliest descriptions of the association between a circulating anti-coagulant and vascular thrombosis in the pediatric population are those of Olive et al in 1979 [3] and St Clair et al in 1981 [4]. In recent years, the features of APS have been increasingly recognized in children [5,6]. Most information on APS in the pediatric population, however, comes from individual case reports or small patient series; large-scale multicenter studies are lacking.

The following case highlights some of the important clinical and laboratory features of the APS.

### Case report

A previously normal 6-year-old boy developed pain in the left lower limb, limping, and increasing calf swelling. One week after onset of symptoms, he was

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brought to the local hospital, where Doppler ultrasonography disclosed an extensive thrombosis in his left iliac and femoral veins. Family history was negative for autoimmune diseases or coagulation disorders. He was transferred to the authors' institute 1 day later for further examination.

On admission, the boy had low-grade fever but was in good general health. Physical examination revealed swelling, heat, and redness of the left calf, which had a circumference 3 cm greater than the contralateral one; there were mild cervical, axillary, and inguinal lymphadenopathy and slight spleen enlargement. Laboratory investigations were as follows: white blood cell count,  $9.6 \times 10^9/L$ ; hemoglobin, 103 g/L; platelet count,  $138 \times 10^9/L$ ; erythrocyte sedimentation rate, 32 mm/hour; C-reactive protein, 2.2 mg/dL; prothrombin time 65%; partial thromboplastin time, 64 seconds (normal, <32 seconds); and fibrinogen, 2.3 g/L. Liver and kidney function tests, viral serologies, serum complement fractions, rheumatoid factor, and urinalysis were normal or negative. Antinuclear antibodies (ANA) were positive at 1:160, whereas anti-DNA and anti-extractable nuclear antigen antibodies were negative. The direct Coombs test was weakly positive. IgG and IgM aCLs were detected, using ELISA, at a titer of 66 G phospholipid (GPL) (normal, <20) and 42 M phospholipid (MPL) (normal, <20), respectively, and LA was positive by kaolin clotting time. Protein C, protein S, antithrombin III, and homocysteine levels were within normal limits, and factor V Leiden mutation was absent. Based on the association of deep vein thrombosis with the presence of aPL, a diagnosis of APS was made.

The boy was treated with low molecular weight heparin for 2 weeks and then placed on long-term warfarin prophylaxis to maintain the international normalized ratio (INR) between 2.0 and 3.0. Repeated Doppler ultrasonography after 1 and 2 weeks showed progressive recanalization of involved vessels. Six months later, angiographic MRI revealed complete recovery of the vascular occlusion.

One year after the occurrence of thrombosis, several papular and plaque lesions were noted over the dorsal surface of the hands and the extensor aspect of both elbows and knees. The erythrocyte sedimentation rate was raised to 48 mm/hour, and ANA were still detectable at 1:320, but anti-DNA antibodies and urinalysis were negative, and serum complement fractions were within normal limits. Cutaneous biopsy led to a histologic diagnosis of lupus panniculitis. Treatment with prednisone (0.5 mg/kg/day) and hydroxychloroquine was started, which led to considerable improvement of skin disease.

After 18 months the patient was readmitted because of the development of a full-blown clinical and laboratory picture of SLE, with proteinuria (1.2–2.6 g/24 hours), microhematuria, decreased C3 (48 mg/dL; normal, 84–192 mg/dL) and C4 (4 mg/dL; normal, 10–42 mg/dL), and high-titer anti-DNA antibodies (1:2560).

This boy was diagnosed as having APS based on the association of vascular thrombosis with the presence of elevated titers of circulating aCL, a positive LA test, and the exclusion of other congenital or acquired thrombophilic conditions. In the early stages of his disease, no evidence of a systemic autoimmune

syndrome was found, except for the presence of low-titer ANA, weakly-positive Coombs test, and mild lymphadenopathy. The disease therefore was labeled as primary APS. After successful treatment of the acute thrombotic event, the boy was placed on long-term antithrombotic prophylaxis with intermediate-intensity warfarin, and no further vascular thrombosis was seen in the 2.5-year follow-up. One year after onset of symptoms, he presented with skin lesions consistent with lupus panniculitis, and 1.5 years later he developed full-blown SLE.

### **Laboratory detection of antiphospholipid antibodies**

The presence of aPL is the central serologic finding of APS [7]. aPL tests detect a heterogeneous group of antibodies, which possess different pathogenic properties. Those more strongly associated with clinical manifestations react predominantly against serum phospholipid-binding proteins (initially called “cofactors”) rather than against phospholipids per se. The most common of these proteins are anti- $\beta$ 2-glycoprotein I (a $\beta$ 2-GPI) and prothrombin, although other phospholipid-binding proteins, such as protein C, protein S, and annexin V, have been involved [8]. In addition to these antibodies, there are aPL that bind directly to negatively charged phospholipid themselves. They occur in patients with infections, such as syphilis, infectious mononucleosis, and HIV infection, and following exposure to certain medications and usually are not pathogenic. Routine assays, however, do not readily distinguish between these major antibody subsets.

The most commonly detected subgroups of aPL are LA, aCL, and a $\beta$ 2-GPI. Placement into these subgroups is based on the method of determination. LA is identified by coagulation assays, in which it prolongs clotting times. In contrast, aCL and a $\beta$ 2-GPI are demonstrated by immunoassays that measure immunologic reactivity against a phospholipid or a phospholipid-binding protein (cardiolipin and  $\beta$ 2-GPI, respectively). In general, LA is more specific for APS, whereas aCL is more sensitive. The specificity of aCL for APS increases with titer and is higher for the IgG than for the IgM and IgA isotype. There is no definitive association between specific clinical manifestations and particular subgroups of aPL, however. Therefore, multiple tests for aPL should be used, because patients may be negative according to one test but positive according to another.

aCL test results are reported according to isotype (IgG, IgM, or IgA) and level. Levels of IgG, IgM, and IgA aCL are reported in GPL, MPL, or A phospholipid (APL) units, respectively, as defined by the First International Workshop on aCL [9]. Because of the relatively wide error range of absolute levels, the use of semiquantitative measures to report results (normal or low positive, 20–80 units; moderate positive, 20–80 units; high positive, above 80 units) is preferable [1].

The LA test is a functional assay that measures the ability of this subgroup of aPL to prolong clotting tests such as the partial thromboplastin time, the

Russell viper venom time, or the kaolin clotting time. Inhibition of clotting *in vitro* is caused by blocking the conversion of prothrombin to thrombin in the presence of a phospholipid template. This process delays the formation of fibrin and, therefore, prolongs the time to clot formation, hence the name of LA. *In vivo*, however, the presence of LA is paradoxically associated with thrombotic events rather than with bleeding. Current criteria for the detection of LA require prolongation of coagulation in at least one phospholipid-dependent coagulation assay. According to established guidelines, two or more assays that are sensitive to this antibody must be negative to rule out the presence of LA [10].

The observation that many aCL are directed at an epitope on  $\beta$ 2-GPI led to the development of a $\beta$ 2-GPI immunoassays [11]. Although the use of these assays is not currently included in the criteria for APS, a $\beta$ 2-GPI are strongly associated with thrombosis and other features of APS. The clinical utility of aPL assays for autoantibodies other than aCL and of phospholipid-binding proteins other than  $\beta$ 2-GPI remains unclear. A significant minority of patients with APS have a biologic false-positive standard test for syphilis, which measures the ability of aPL to precipitate an antigen (eg, the VDRL antigen) containing a mixture of cardiolipin, phosphatidylcholine, and cholesterol.

### **Classification criteria and diagnostic issues**

In 1998, a set of criteria for classification of patients with APS (the Sapporo criteria) was proposed (Box 1) [7].

Although these criteria are intended to provide a basis for including patients with the syndrome in research protocols, they are used in practice as a guide to diagnosing the syndrome in individual patients. There are, however, patients with probable APS who do not meet the Sapporo criteria because of the presence of clinical and laboratory features that are not accepted universally as part of the syndrome. These manifestations include livedo reticularis, chorea, cardiac valve disease, transient cerebral ischemia, transverse myelitis, migraine, hemolytic anemia, and thrombocytopenia [12].

Because pregnancy morbidity is not a pediatric problem, and coincident thrombotic risk factors that are common in adults (as discussed below) have little or no impact in the pediatric population, it is likely that the sensitivity and specificity of the Sapporo criteria for aPL-related thrombosis is higher in children than in adults.

In clinical practice, a diagnostic workup for aPL should be considered in all children and adolescents with venous or arterial thrombosis for which there is no alternative explanation, particularly in the presence of recurrent manifestations. Likewise, unexplained thrombocytopenia, hemolytic anemia, chorea, livedo reticularis, and prolongation of any phospholipid coagulation test should lead to determination of aPL status.

**Box 1. Preliminary criteria for the classification of APS***Clinical criteria*

1. Vascular thrombosis: One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
  - A. One or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
  - B. One or more premature births of a morphologically normal neonate at or before the thirty-fourth week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency, or
  - C. Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

*Laboratory criteria*

1. aCL of IgG and/or IgM isotype in blood, present in medium or high titer, on two or more occasions at least 6 weeks apart, measured by a standardized ELISA for  $\beta$ 2-GPI–dependent aCL.
2. Lupus anticoagulant present in plasma, on two or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies), in the following steps:
  - A. Prolonged phospholipid-dependent coagulation demonstrated on a screening test (eg, activated partial thromboplastin time [aPTT], kaolin clotting time, dilute Russell's viper venom time, dilute prothrombin time, Texarin time)
  - B. Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma

- C. Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid
- D. Exclusion of other coagulopathies (eg, factor VIII inhibitor or heparin) as appropriate

Definite APS is considered to be present if at least one of the clinical criteria and one of the laboratory criteria are met.

### Pathogenetic mechanisms

Despite the strong association between aPL and thrombotic complications, the *in vivo* mechanisms responsible for thrombosis in patients with APS have not been fully elucidated. Proposed pathophysiologic mechanisms may be categorized in at least four types (reviewed in [13] and [14]). First, aPL may interfere with or modulate the function of phospholipid-binding proteins involved in the regulation of the coagulation cascade, leading to a procoagulant state. Examples include interference with  $\beta$ 2-GPI, inhibition of activated protein C and anti-thrombin III pathways and fibrinolysis, and increased tissue factor activity. Other proteins that are important in regulating coagulation, such as prothrombin, proteins C and S, and annexin V, may also be targeted by aPL. A second theory focuses on the activation of endothelial cells. Binding of aPL, which recognize  $\beta$ 2-GPI on resting endothelial cells, induces activation of the same cells, which is manifested by increased expression of cell-surface adhesion molecules and increased secretion of cytokines and prostaglandins. It is well known that activated endothelial cells promote coagulation. A third theory proposes an oxidant-mediated injury of the vascular endothelium. Oxidized low-density lipoproteins (LDL), which are leading contributors to atherosclerosis, are taken up by macrophages, causing macrophage activation and consequent damage to endothelial cells. Autoantibodies to oxidized LDL are known to occur in association with aCL, and some aCL have been shown to cross-react with oxidized LDL. A fourth route by which aPL may promote thrombosis is by platelet activation, leading to enhanced platelet adhesion or increased thromboxane synthesis. Thrombosis in APS has also been likened to that of heparin-induced thrombocytopenia, which may also induce vascular thrombosis [15].

Recent evidence in animal models indicates that viral and bacterial peptides, perhaps through a molecular mimicry mechanism, may induce aPL production, which in turn may promote thrombosis [16].

Whatever the pathogenetic mechanisms, it is likely that other factors play a role in determining whether patients develop the clinical manifestations of APS. Most patients with persistently elevated antibody levels never experience thrombosis. A second hit may, therefore, be necessary for thrombosis to occur. For instance, several other prothrombotic factors, such as smoking, contraception,

hypertension, obesity, and atherosclerosis, may increase the risk of vascular occlusion in aPL-positive patients. Notably, a recent study found that about half of patients with acute thrombosis that led to a diagnosis of APS had coincident risk factors for thrombosis [17]. Furthermore, an association between the number of prothrombotic risk factors and history of thrombotic events has been observed in individuals with positive IgG aCL [18].

Although the pathogenetic mechanisms involved in pediatric APS have not been thoroughly investigated, it is assumed that they are similar to those operating in adults. The frequency of vascular thrombosis is much lower in children than in adults, however, and other risk factors for thrombosis, such as cigarette smoking and atherosclerosis, are not applicable in the pediatric population. Therefore, children with aPL-associated thrombosis constitute a relatively “clean” sample to assess the clinical relevance of aPL and to provide pathogenic aPL to be studied for their specificity.

## Clinical features

With the obvious exception of pregnancy morbidity, most of the clinical features that can occur in adults with APS have also been described in children. The thrombotic process can involve virtually any organ, and a wide spectrum of

Table 1  
Sites of vascular thrombosis associated with aPL in children

Vessel involved	Clinical manifestations
<b>Veins</b>	
Limbs	Deep vein thrombosis Superficial vein thrombosis
Large veins	Superior or inferior vena cava thrombosis
Lungs	Pulmonary thromboembolism Pulmonary hypertension
Skin	Livedo reticularis
Brain	Cerebral venous sinus thrombosis
Liver	
Large vessels	Budd-Chiari syndrome
Small vessels	Hepatomegaly, enzyme elevation
Eyes	Retinal vein thrombosis
Adrenal glands	Addison's disease
<b>Arteries</b>	
Brain	Stroke, transient ischemic attacks
Kidney	
Large vessels	Renal artery thrombosis
Small vessels	Renal thrombotic microangiopathy
Limbs	Ischemia, gangrene
Heart	Myocardial infarction
Liver	Hepatic infarction
Gut	Mesenteric artery thrombosis

manifestations may be seen within any organ system. Thrombotic episodes associated with aPL may occur in vascular beds that are infrequently affected in other prothrombotic states. Some years ago, by reviewing the case histories of 50 pediatric patients with aPL-positive thrombosis reported in the literature [5], the authors found that this condition was more common in females, and that the age at first symptom ranged from 8 months to 16 years. Many patients had secondary APS associated with systemic autoimmune disease, particularly SLE, but some patients had primary APS. The clinical features, however, seemed to be the same in primary and secondary APS. Although most of the reported patients had involvement of the venous circulation, arterial thrombosis seemed relatively more common in younger children. A few patients had a family history of aPL-positive clinical events. The thrombotic manifestations reported in pediatric patients with APS are presented in [Table 1](#).

### *Venous thrombosis*

As in adults with APS, the deep and superficial veins of the lower limbs are the most frequently reported sites of venous thrombosis in children ([Fig. 1](#)). Some of these patients may develop pulmonary embolism. Thromboembolic pulmonary hypertension, caused by either recurrent pulmonary emboli or in situ thrombosis, is exceedingly rare in the pediatric population. Other reported sites of venous thrombosis in pediatric patients include the renal, mesenteric, hepatic, and retinal veins, as well as the superior and inferior vena cava ([Fig. 2](#)).

### *Arterial thrombosis*

Cerebral arteries are the most frequent site of arterial thrombosis in children, with most patients presenting with stroke or transient ischemic attacks, as discussed later. Other arterial sites of thrombosis include the retinal, coronary, hepatic, mesenteric, and peripheral arteries.

### *Nervous system manifestations*

Stroke and transient ischemic attacks are the most frequent neurologic complications of APS. Strokes occur more often in the region supplied by the middle cerebral artery ([Fig. 3](#)). Cerebral infarction may be silent, however, and when multiple events occur, patients may develop seizures or dementia secondary to widespread cerebral damage. Notably, a high prevalence of aPL has been reported in children with idiopathic cerebral ischemia, suggesting that these antibodies may play a major pathogenetic role in children who lack the other prothrombotic factors [19]. Thrombosis of the cerebral sinus has been observed in

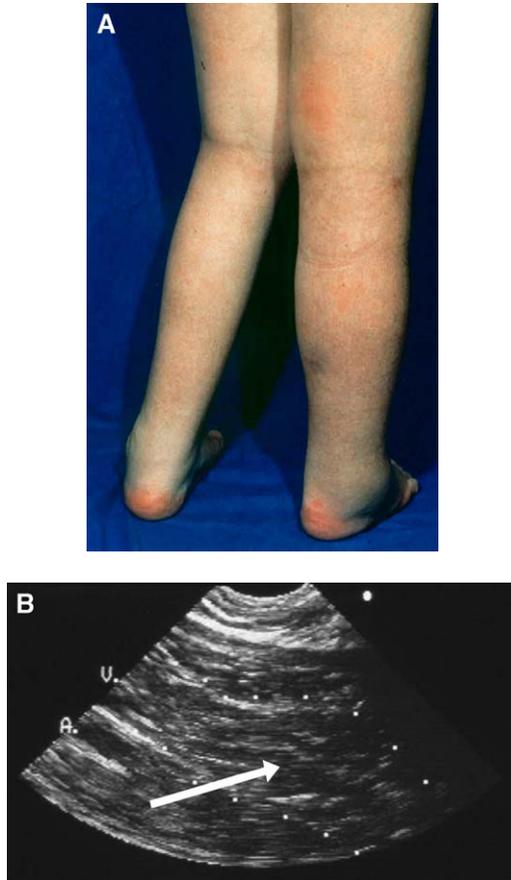


Fig. 1. Right limb deep vein thrombosis in a 16-year-old boy with systemic JIA who had circulating aPL and was exposed to another thrombophilic factor (a prolonged plaster immobilization for a tibial fracture). (A) Diffuse edema of the right limb. (B) Doppler ultrasonography showing complete occlusion of a popliteal vein by a thrombus (*arrow*).

both primary and SLE-associated APS [20]. Ocular ischemic events, including anterior ischemic optic neuropathy, central retinal artery occlusion, amaurosis fugax, and occlusion of retinal veins, and sensorineural hearing loss, often presenting as sudden deafness, have been described in patients with APS. Several other neurologic abnormalities have been linked to aPL but are not clearly related to thrombosis. They include chorea, transverse myelopathy, Guillain-Barré syndrome, psychosis, and migraine headaches. It has been suggested that these complications may result from direct interaction between aPL and the nervous tissue, or from immune complex deposition in cerebral or spinal cord vessels. Seizures have also been reported in association with aPL, but cerebral infarction should be excluded as a cause.

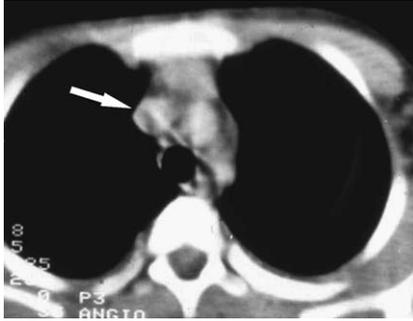


Fig. 2. Chest CT scan showing superior vena cava thrombosis (*arrow*) in a 13-year-old boy with primary APS.

### *Cardiac valve abnormalities*

Cardiac valve abnormalities resembling Libman-Sacks endocarditis can be observed by Doppler echocardiography in a number of adults with APS. Valvular thickening has been reported most commonly, but valvular vegetations, regurgitation, and stenosis may occur. Although any of the four heart valves may be affected, the mitral valve is most frequently involved, followed by the aortic valve; tricuspid and pulmonary valve involvement is uncommon. Valvular abnormalities in APS are different from those seen in rheumatic heart disease: valvular thickening is diffuse in the former condition, whereas in rheumatic carditis it is more localized, is detected at leaflet tips, and is often accompanied by thickening, fusion, and calcification of the chordae tendinae. The frequency of this complication in pediatric APS is unknown.

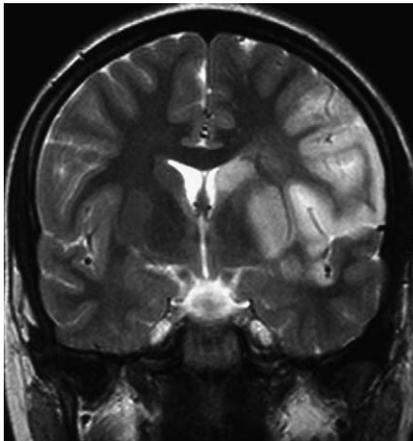


Fig. 3. Brain MRI revealing a stroke in the territory of the middle cerebral artery in a 12-year-old girl with SLE and antiphospholipid syndrome.

### *Skin manifestations*

Several cutaneous manifestations have been associated with APS, including leg ulcers, livedo reticularis, cutaneous necrosis, gangrene of the digits or extremities, thrombophlebitis, necrotizing purpura, and nailfold infarcts. Leg ulcers, which occur more often in the pretibial area and ankle, can be multiple and focal, are painful and sharply marginated, have a necrotic center or base, and leave a white atrophic scar on healing. Livedo reticularis is the most frequently reported skin manifestation of APS. Although its pathogenesis is unknown, it results from the stagnation of blood in dilated superficial capillaries and venules and primarily affects the skin of the thighs, shins, and forearms. The clinical triad of livedo reticularis, cerebrovascular disease, and hypertension (Sneddon's syndrome), which is frequently accompanied by the detection of aPL, is exceedingly rare in children.

### *Thrombocytopenia and hemolytic anemia*

A decrease in platelet count, usually in the range of  $100$  to  $150 \times 10^9/L$  is observed in about one third of patients with APS. Thrombocytopenia is rarely severe enough to cause hemorrhage (ie,  $< 50 \times 10^9/l$ ), however. The pathogenesis of thrombocytopenia in APS is unclear. Proposed mechanisms include binding of aPL to platelet membrane phospholipids,  $\beta_2$ -GPI/phospholipid complexes, or coexisting antibodies to platelet membrane glycoprotein. About 10% to 20% of patients with APS have a positive Coombs' test, but hemolytic anemia is relatively uncommon. The association of hemolytic anemia and thrombocytopenia (Evans' syndrome) has been reported occasionally in patients with APS. Differentiation of primary APS from classic idiopathic thrombocytopenic purpura is important to indicate closer follow-up for future manifestations related to the aPL or for progression to frank SLE (as discussed later).

### *Catastrophic antiphospholipid syndrome*

In most patients with APS, thrombotic events develop singly, and recurrence usually occurs months or years after the initial episode. Occasionally, however, aPL-positive patients may present with an acute and devastating syndrome characterized by multiple and simultaneous vascular occlusions throughout the body. This syndrome is termed "catastrophic APS" and is defined as clinical involvement of at least three different organ systems over a period of days or weeks with histopathologic evidence of multiple occlusions of large and small vessels [21]. Thrombosis of large vessels is less common in patients with this syndrome, who tend to develop an acute microangiopathy affecting small vessels of multiple organs. The kidney is the organ most commonly affected, followed by the lung, the central nervous system, the heart, and the skin. Disseminated intra-

vascular coagulation is observed in approximately 25% of cases. Patients may present with a medical collapse with severe thrombocytopenia, adult respiratory distress syndrome, and multiorgan failure, often accompanied by severe hypertension. The mortality rate is 50%, and death is usually caused by multiorgan failure. Precipitating factors of catastrophic APS include infections, surgical procedures, neoplasms, lupus flares, withdrawal of warfarin therapy, and the use of oral contraceptives [22]. Catastrophic APS, which has been occasionally reported in children [23,24], should be distinguished from severe lupus vasculitis, sepsis, thrombotic thrombocytopenic purpura, macrophage activation syndrome [25], and disseminated intravascular coagulation.

### Differential diagnosis

Thrombosis in children can be caused by many other conditions (Box 2).

Few clinical clues differentiate APS from other types of thrombophilia. A careful history, physical examination, and appropriate laboratory studies are, therefore, essential to make the proper diagnosis. Leukopenia, thrombocytopenia, livedo reticularis, arthralgia or a rheumatic illness, or a family history of rheumatic illness (particularly SLE) increases the likelihood that APS is the cause of the newly diagnosed thrombosis. In some patients with APS, however, the sole abnormality may be the existence of aPL. Because a normal aPTT does not exclude the presence of LA, a patient presenting with a first thrombotic event should be screened for aCL and with other assays that are sensitive to LA.

**Box 2. Disease states beside APS that should be considered in children and adolescents with unexplained venous or arterial thrombosis**

- Factor V Leiden (activated protein C resistance)
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Homocysteinemia
- Nephrotic syndrome
- Estrogen-containing oral contraceptives
- Myeloproliferative disorders
- Behçet's syndrome
- Systemic vasculitis
- Heparin-induced thrombosis

## Acquired coagulation factor inhibitors and antiphospholipid antibodies

### *The acquired hypoprothrombinemia–lupus anticoagulant syndrome*

Although the presence of LA confers an increased risk for thrombosis, this antibody has been occasionally associated with a bleeding tendency. This condition, which has been termed “acquired hypoprothrombinemia–LA syndrome” and is usually preceded by a viral infection, is characterized by serious bleeding, profound decrease of prothrombin level, and presence of circulating high-affinity antibodies that bind prothrombin without neutralizing its coagulant activity; hypoprothrombinemia probably results from the rapid clearance of prothrombin antigen-antibody complexes [26–28]. Prompt recognition of this syndrome is critical because corticosteroid therapy is effective.

### *The varicella-autoantibody syndrome*

Another condition in which aPL are associated with the presence of acquired coagulation factor inhibitors is a syndrome occasionally observed in children with acute varicella zoster virus infection [29]. It is characterized by purpura fulminans, thromboembolism, or disseminated intravascular coagulation secondary to an acquired, transient, isolated deficiency of protein S caused by the presence of circulating autoantibodies to the same protein. These antibodies have no direct inhibitory effect on the activity of protein S; the decrease of protein S antigen levels presumably results from rapid clearance of circulating immune complexes. In most children with this complication, the presence of LA and, less commonly, aCL has been identified, although the specificity of these aPL has not been demonstrated. Recently, significantly increased prevalence of LA and transiently reduced plasma level of free protein S have been demonstrated in children with varicella in the absence of thrombotic complications, suggesting that this common infectious disease is characterized by a marked hypercoagulability state [30].

## Neonatal antiphospholipid syndrome

It is well known that the presence of aPL during pregnancy is accompanied by a high incidence of obstetric and fetal complications, including first-trimester miscarriage, second-trimester pregnancy loss, preeclampsia, intrauterine growth retardation, and prematurity. Careful obstetric monitoring of pregnant women with circulating aPL and appropriate treatment can improve pregnancy outcome considerably, although fetal complications such as intrauterine growth retardation and prematurity may occur despite treatment.

Evidence exists that in pregnant women with APS, aCL can cross the placenta and can be detected in cord blood [31]. Follow-up of infants born to mothers with APS has shown that aCL levels are detectable in newborns' sera and decrease

progressively, disappearing within 6 months. However, neonatal thrombosis related to the transplacental transfer of aPL seems to be very uncommon. In general, vascular thrombosis in neonates is rare and, with the exception of spontaneous renal venous thrombosis, is usually associated with indwelling catheters. Several studies of the outcome of infants born to mother with APS have revealed that, except for prematurity and its complications, these neonates did not develop occlusive events (reviewed in [31]). This finding is surprising because it is known that the thrombotic risk is much greater in the first month of life than at any other age in childhood. Furthermore, thrombotic occlusions have been detected in experimental mouse models of aPL-induced fetal loss. Premature infants are also known to have diminished antithrombin III levels, which may further increase the risk of thrombotic events. It has been hypothesized that the unexpected low frequency of thrombosis in infants born to mother with APS may result from the different capacity of the aPL IgG subclasses to cross the placenta (ie, to the low placental transfer of the more pathogenic IgG2); alternatively, the intact neonatal vessel wall may not favor thrombus formation [31].

A few instances of thrombosis in infants born to aPL-positive mothers have been reported, however. In some cases aPL were not detected or looked for in the neonate, whereas in others the presence of aPL both in the mother and the baby has been documented (reviewed in [5] and [31]). These reports suggest that aPL acquired transplacentally may promote the development of neonatal thrombosis; however, these antibodies may simply constitute a second hit, leading to thrombosis in a neonate who is exposed to another thrombophilic factor, such as an indwelling catheter. In addition, these antibodies may explain the pathogenesis of renal venous thrombosis, which is a poorly understood disease, often with antenatal onset. Given the rarity of neonatal thrombosis, multicenter studies are needed to establish the true pathogenetic effect of transplacentally acquired aPL.

On clinical grounds, although the precise risk of thrombosis in infants born to mother with APS is unknown (and probably very low), it is advisable to monitor these infants closely for any possible aPL-related clinical manifestations, at least until transplacentally acquired aPL become undetectable [32]. Furthermore, the clinical evaluation of all neonates with vascular thrombosis should include testing for aPL, irrespective of the presence of other risk factors or a positive family history of thrombosis or autoimmune disease.

### **The clinical significance of antiphospholipid antibodies in juvenile systemic lupus erythematosus**

The reported prevalence of aCL and LA in juvenile SLE ranges from 19% to 87% and from 10% to 62%, respectively (reviewed in [33–43]) (Table 2). This wide variability may reflect either the different sensitivities and specificities of the assays used for the detection of aPL or a diversity in the clinical features of the patient populations. It may also depend, at least in part, on differences in the disease activity, because some investigators have observed a relationship between

Table 2  
Prevalence of aPL and frequency of thrombotic events in juvenile SLE

Authors (year)	No. of patients	aCL (%)	LA (%)	a $\beta$ 2-GPI (%)	Thrombosis (%)
Shergy et al (1988) [33]	32	50	ND	ND	0
Montes de Oca et al (1991) [34]	120	ND	19	ND	9
Molta et al (1993) [35]	37	19	11	ND	8
Ravelli et al (1994) [36]	30	87	20	ND	3
Gattorno et al (1995) [37]	19	79	42	ND	16
Seaman et al (1995) [38]	29	66	62	ND	24
Berube et al (1998) [39]	59	19	24	ND	17
Gedalia et al (1998) [40]	36	37	ND	ND	8
von Scheven et al (2002) [41]	57	53	23	48	5
Campos et al (2003) [42]	57	70	29	ND	9
Levy et al (2003) [43]	149	39	16	ND	9

*Abbreviations:* aCL, anticardiolipin antibodies; a $\beta$ 2-GPI, anti- $\beta$ 2-glycoprotein I antibodies; LA, lupus anticoagulant; ND, not determined.

the presence and titer of these antibodies and selected indicators of lupus activity: the lowest prevalence was observed in a cohort of samples obtained during periods of clinical remission. In some series, high levels of aCL have been associated with the occurrence of neuropsychiatric manifestations, but this association was not found in other series. The observed frequency of vascular thrombosis in juvenile SLE ranges from 0 to 24% (Table 2). As reported in adults, LA seems to be correlated more strictly with thrombotic events than aCL [43,44]. In the only study that investigated a $\beta$ 2-GPI in juvenile SLE, a prevalence of 48% was found [41]. These antibodies were not seen as frequently as aCL or LA and, with the exception of stroke, demonstrated weaker correlation with APS features than other aPL assays.

Recently, the presence of aPL in lupus patients has been associated with the development of ischemic microangiopathic nephropathy [45]. Clinically, this condition is manifested by hypertension (often malignant), proteinuria, and renal failure. Histopathologic study of kidney biopsy samples shows vaso-occlusive lesions of intrarenal vessels associated with acute thrombosis and intra-arteriolar lesions as well as with zones of cortical ischemic atrophy. Awareness of aPL-related nephropathy is important because its treatment may require anticoagulation instead of immunosuppressive medications. Because lupus nephritis and aPL-associated ischemic nephropathy cannot be distinguished clinically, renal biopsy is essential.

### Antiphospholipid antibodies in other systemic disorders

The presence of aCL in juvenile idiopathic arthritis (JIA) has been investigated in several cross-sectional studies, which found a prevalence ranging from 7% to 53% (reviewed in [5] and [31]). Most studies identified no association between the presence of aCL and disease activity, and no clinical manifestation of APS

was observed. Only two reports exist on the development of aPL-associated thrombosis in JIA patients [46,47]; one of these patients, however, was exposed to another thrombophilic factor (a prolonged plaster immobilization for a tibial fracture) (Fig. 1) [46]. It seems, therefore, that despite an apparently significant prevalence of aCL, thrombotic complications are rare in JIA, suggesting that these antibodies may have different pathogenetic potential and, possibly, antigen specificity as compared with SLE. On the other hand, the frequency of LA and a $\beta$ 2-GPI in JIA is much lower than that of aCL [31]. Notably, aPL have been preferentially found in serum of children with JIA who were previously infected with parvovirus B19 and had established, persistent infection [48].

The presence of circulating aPL has been observed in a variety of other pediatric autoimmune and nonautoimmune syndromes, including juvenile dermatomyositis, rheumatic fever, insulin-dependent diabetes mellitus, HIV infection, and atopic dermatitis. In most of these conditions, APS is uncommon, and the significance of aPL deserves further confirmation.

### **Outcome of primary antiphospholipid syndrome**

The relationship between primary APS and SLE is unclear. Although most authors agree that the primary syndrome is a distinct clinical entity with its own genetic, immunologic, clinical, and serologic characteristics, other investigators believe that primary APS, lupuslike disease, and SLE may represent three different facets of a unique clinical spectrum of disease [49]. In recent years, some cases of primary APS that evolved into SLE have been reported, and a survey of 90 adult patients with primary APS showed that 12 of them (13.3%) developed SLE or lupuslike disease during a median follow-up of 8.3 years [50]. The authors investigated the long-term outcome of 14 pediatric patients with primary APS who were followed for a median of 9 years in three Italian pediatric rheumatology centers [51]. At the time of the presenting clinical manifestation, no patient fulfilled more than one of the updated criteria for SLE [52], except for the presence of aPL and low-titer ANA. During follow-up, two patients developed 4 or more of the 11 1982 revised criteria for SLE [53] and were thus diagnosed as having a frank SLE, and one patient displayed the features of a lupuslike syndrome. The percentage of progression to SLE or lupuslike syndrome observed in the authors' pediatric cohort of primary APS (21.4%) was almost double than that found by Gomez et al [50] in the previously mentioned study on adult patients with primary APS. Of note, in the authors' two patients who developed SLE, the features of this disease occurred soon after the presentation of APS (after 9 and 14 months, respectively), and in the patient with lupuslike syndrome the more widespread clinical manifestations developed as early as 6 months after APS onset. These findings suggest that a significant proportion of children who present with the features of primary APS may progress in a relatively short time to SLE or to a lupuslike syndrome.

## Management

### *Asymptomatic antiphospholipid antibody-positive individuals*

Both aCL and LA can be found in children without any underlying disease. Such naturally occurring aPL are usually present in low titer and may result from previous infections or vaccinations. A wide range of frequency of aCL, from 2% to 82%, has been reported in healthy children [31]. This variability mainly results from methodological problems, including choice of inappropriate study groups, differently defined cut-off values, and lack of uniformity of the assays employed. Because aPL have been observed in association with various infections, and because postinfectious aPL tend to be transient, aPL positivity should always be verified with a further determination after the infection has cleared. The incidental discovery of LA usually is reported in children who undergo preoperative evaluations for tonsillectomy who are found to have prolonged aPTT. In most cases, no definite disease is found, and the aPTT corrects spontaneously within a few months.

Despite the established association between aPL and thrombosis, most asymptomatic persons who are found incidentally to have positive aPL tests do not develop thrombosis. The aCL test has been found to be positive in low titers in about 2% of a healthy obstetric population, but this finding does not seem to be associated with an adverse outcome [54]. A recent study has shown that no patient with asymptomatic aPL (that is, an aPL detected as a result of investigations for an unexpected prolongation of the aPTT) experienced thrombosis or pregnancy morbidity [17]. These findings suggest that screening-detected aPL in asymptomatic persons are of limited clinical relevance.

There is considerable controversy, however, as to whether prophylactic treatment is indicated for individuals with persistently positive aPL who have no history of thrombosis, because the thrombotic risk of these persons is unknown. At present, these patients generally receive either no treatment or prophylactic low-dose aspirin, although there is no evidence yet to support the usefulness of the latter. On the other hand, a panel of experts has recently recommended the use of low-dose aspirin for prevention of thrombosis in patients with aPL but without prior history of thrombosis [55]. Prospective studies that are under way should provide definitive, evidence-based answers. Hydroxychloroquine, which has modest anticoagulant properties and is widely used in SLE, may be useful in preventing thrombosis in asymptomatic aPL-positive patients with this disease [56].

Because children are less exposed than adults to coincident risk factors, the thrombotic risk in asymptomatic aPL-positive children is probably much lower than in adults. Nevertheless, secondary risk factors that increase the tendency to thrombosis should be pursued. For instance, prophylaxis of venous thrombosis with subcutaneous heparin should be considered to cover higher-risk situations, such as prolonged immobilization or surgery. Furthermore, particular attention should be paid to children who carry a heritable procoagulant state. Adolescents

with circulating aPL must be advised to avoid other risk factors, such as smoking and use of oral contraceptives.

Another unresolved issue concerns patients with aPL who do not have recurrent thrombosis but do have livedo reticularis, thrombocytopenia, hemolytic anemia, chorea, cardiac valve vegetations, or cognitive dysfunction and, thus, do not fulfill the criteria for APS. It is unknown whether anticoagulation treatment is indicated in these patients.

### *Antiphospholipid antibody-positive patients with thrombosis*

The management of acute thrombosis in patients with APS is no different from that of thrombosis arising from other causes.

Treatment with high-dose corticosteroids, cyclophosphamide, and plasmapheresis to reduce transiently the levels of circulating aPL, together with adequate anticoagulation, is indicated only in life-threatening situations such as the catastrophic antiphospholipid syndrome, as discussed later. Otherwise, immunosuppressive treatment, unless required for other accompanying features, is not advised, because aPL rapidly return to previous levels upon cessation of therapy, and these drugs do not prevent further thrombotic events.

Retrospective studies in adults have clearly shown that aPL-associated thromboses tend to recur. There is, therefore, consensus about the need to treat patients who experience an aPL-related thrombosis to prevent recurrences. The duration and intensity of antithrombotic therapy are not yet clearly established, however. Some authors suggest that it should be continued until aPL are present, whereas others believe that life-long prophylaxis is needed. A 1995 report of a retrospective study concluded that anticoagulant therapy producing an INR of 3.0 or higher affords better protection against recurrence than does less intense anticoagulant therapy [57]. Twenty-nine of the 81 patients with INR of 3 or higher had a significant hemorrhagic complication, however, and the complication was severe in 7 of them. A high rate of recurrent thrombosis (1.30 per patient/year), greater than that of untreated patients, was observed within 6 months after cessation of warfarin treatment, suggesting that, once established, warfarin therapy should be long-term. The results of this study led to the recommendation of using high-intensity warfarin prophylaxis (target INR  $\geq$  3.0) to prevent thrombotic recurrence in patients with APS.

These recommendations were recently challenged by two prospective, randomized, controlled trials in patients with APS who were assigned to moderate (target INR, 2.0–3.0) or high-intensity (target INR, 3.0–4.0) warfarin therapy [58,59]. Both studies found that the overall risk of recurrent thrombosis was very low and was unexpectedly lower in patients who received moderate-intensity warfarin than in those who were given high-intensity warfarin. Based on these results, it was suggested that warfarin administered with a target INR of 2.0 to 3.0 should be considered standard therapy in all patients with APS who have not had recurrent thrombosis while receiving warfarin prophylaxis [60]. Another recent large, randomized trial showed that the presence of aPL (either LA or

aCL) among patients with ischemic stroke does not predict increased risk for subsequent thrombotic events, and that warfarin therapy is not superior to aspirin therapy for secondary prevention of stroke in aPL-positive patients [61]. Other investigators, who expressed several concerns about the study methodology, questioned the results of this study [62–64]. These arguments demonstrate that consensus on the approach to prevent thrombosis associated with APS is far from being reached. In addition, the existing studies have failed to address several crucial questions, such as whether arterial and venous thromboses require the same intensity of anticoagulation, whether and when warfarin prophylaxis should be stopped, whether patients who develop thrombosis in the presence of other risk factors should be treated like those without any risk factor other than aPL, and how to manage patients with recurrent thrombosis despite high-intensity coagulation. Monitoring the level of anticoagulation in patients with APS is complicated by the lack of standardized reagents for the determination of the INR and the potential interference of aPL in this measurement.

Concerning APS in pediatric patients, only a few data are available on the recurrence rate of thrombosis or on the optimal anticoagulation regimen [43,51]. Thrombosis seems to be less common in juvenile than in adult-onset SLE, and the general risk of recurrence is probably lower in children than in adults. Specific problems with the use of warfarin in children are that the dose of this drug is age and weight dependent and that its administration requires close monitoring because of changing requirements. Furthermore, long-term anticoagulation at high therapeutic level may expose the younger patients to a high risk of bleeding during play and sport.

Based on these considerations, it is the authors' present policy to perform moderate-intensity anticoagulation therapy (target INR, 2.0–3.0) in children who had an aPL-related thrombotic event. A similar therapeutic approach has been proposed by other investigators [65]. In the authors' experience, this protocol has not been associated with recurrence of thrombosis or with bleeding.

Given the rarity of aPL-related thrombosis in childhood, the optimal therapeutic approach can be defined only through a large, controlled, prospective multicenter trial.

### *Catastrophic antiphospholipid syndrome*

Recommendations for treatment of catastrophic APS are based entirely on case reports or on expert consensus [66]. Because thromboses tend to be self-perpetuating, an aggressive therapeutic approach, including prompt treatment of any precipitating factor, is warranted. The use of a combination of anticoagulants and steroids plus either plasmapheresis or intravenous immunoglobulins and, in case of lupus flare, cyclophosphamide has been suggested. The fibrinolytic agents streptokinase and urokinase also have been used with varying success. Other reported management options include prostacyclin, defibrotide, danazol, cyclosporine, azathioprine, hemodialysis, and splenectomy.

## *Thrombocytopenia*

The thrombocytopenia of APS is usually mild and does not require treatment. For severe thrombocytopenia, the usual treatment is corticosteroid therapy. Anecdotal reports have shown improvement of corticosteroid-resistant thrombocytopenia with dapsone, danazol, chloroquine, warfarin, and low-dose aspirin. Aspirin administration is, however, potentially dangerous, especially in patients with very low platelet counts. Splenectomy is not advisable because theoretically the postsplenectomy thrombocytosis may increase the thrombotic risk; moreover, in some instances splenectomy has been ineffective in increasing the platelet count [67]. Intravenous immunoglobulins may raise the platelet count temporarily and may be useful before surgery.

## **Summary**

APS is recognized increasingly as a leading cause of vascular thrombosis in the pediatric population. With the obvious exception of pregnancy morbidity, most of the clinical features that may occur in adults with APS have been described also in children. Because the coincident prothrombotic factors that are common in adults have little or no impact in children, pediatric patients with APS constitute a suitable sample to investigate the relationship of aPL with the associated clinical manifestations, such as thrombocytopenia, hemolytic anemia, chorea, and livedo reticularis, and the specificities of aPL that are more linked to thrombosis. On the other hand, because of the high frequency of infectious processes in early life, children may have a greater prevalence of nonpathogenic and transient aPL. For these reasons, the diagnostic and therapeutic approach to APS in childhood may be different from that for adults. Because of the rarity of aPL-related thrombosis in children, the natural history and optimal management can be defined only through large, multicenter, controlled studies.

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