

Antiphospholipid syndrome in children: review of pathogenesis, diagnosis and treatment

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Antiphospholipid syndrome in children is a complex problem. Active investigation continues into its pathogenesis and the role of anticardiolipin antibodies, anti- β_2 glycoprotein 1 antibodies and other autoantigens. Despite these ongoing questions, there is substantial new information available regarding the differential diagnosis, clinical features and current and potential treatment options.

Antiphospholipid syndrome (APS) is characterized by venous, arterial thrombosis and/or recurrent pregnancy loss, associated with a distinct autoantibody profile. The association of recurrent clotting abnormalities with autoantibodies arose from recognition that these problems were associated with false-positive biologic tests for syphilis. In the early 1950s, the association was expanded with recognition of the increased prevalence in patients with systemic lupus erythematosus (SLE). Studies of the false-positive biologic test for syphilis established the association of thromboembolic events with the presence of antiphospholipid antibodies (aPL).

Key to understanding this syndrome was recognition that lupus patients with clotting abnormalities were not simply deficient in one of the clotting factors, but in fact possessed a circulating factor that slowed the clotting of normal serum. In 1972, Rapaport and Feinstein proposed the term 'lupus anticoagulant' [1]. The earliest use of the term APS was proposed by Harris in 1987 [2,3]. The first pediatric description in the literature was made by Olive in 1979 [4].

Historically, patients with APS have been distinguished as having primary or secondary disease on the basis of the presence or absence of concomitant illness. The international consensus statement on classification of APS advises against the use of the term 'secondary APS'. They were unable to find differences on the clinical consequences of aPL in these groups. Most patients, including children with 'secondary' disease, have an underlying diagnosis of SLE. The unknown is if APS and SLE occur together coincidentally, as two elements of the same disease process, or if SLE provides a setting for APS to develop [5].

Definition of APS

It is important to recognize that the presence of aPL does not define APS. The updated Sapporo criteria for the classification of patients with APS were proposed in 1998 and recently revised.

Updated Sapporo criteria summary

Clinical criteria

- Vascular thrombosis: one or more arterial, venous or small-vessel thrombosis in any organ or tissue.

Pregnancy morbidity

- One or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation;
- One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia or recognized features of placental insufficiency;
- 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

- Anticardiolipin antibody (aCL) of immunoglobulin (Ig)G or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 IgG phospholipid units or IgM phospholipid units, or more than the 99th percentile) measured by a standardized enzyme-linked immunosorbent assay (ELISA);
- Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis;
- Anti- β_2 glycoprotein (GP)1 antibody of IgG or IgM isotype in serum or plasma (in titer more than the 99th percentile), measured by a standardized ELISA;
- Laboratory criteria must be positive on two or more occasions, at least 12 weeks apart;

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- At least one clinical and one laboratory criteria must be met. Since recurrent pregnancy failure is not a usual feature of pediatrics, diagnosis of APS in childhood requires the child to have had documented thrombosis and not simply laboratory abnormalities.

Although they are important, the nonthrombotic features of the disease do not define its presence. These features include livido reticularis, cardiac involvement (including valvulopathy), chorea, seizures and a multiple-sclerosis-like condition. Associated laboratory findings include: antibodies in low titer that do not fulfill the updated Sapporo criteria, thrombocytopenia and hemolytic anemia [6]. Antibodies to annexin, prothrombin and neutral phospholipids have been detected in patients with APS [7]. The clinical significance of their presence is as yet unclear. A false-positive venereal disease research laboratory was the finding that gave rise to the discovery of the condition; however, it is no longer a criterion for classification. Although consensus criteria were developed for adult patients, they apply equally to children as to adults. As with adults, children may present with a nonclassical aPL-related manifestation and then go on to develop APS with thrombosis.

Antiphospholipid antibodies

aPL are heterogeneous and different antibodies react against different phospholipids or serum phospholipid-binding proteins. There are three main groups of aPL: lupus anticoagulants (LAs), aCL and other antibodies against specific phospholipid-binding proteins. Specific phospholipid binding protein targets include, most importantly β_2 GP1, but also protein C, protein S, prothrombin and annexin V. These aPL occur in varied titers and frequencies in different populations and circumstances. In general, APS is more common in patients with anti- β_2 GP1 antibodies than in those with other laboratory findings [8].

LAs are hexagonal immunoglobulins that interfere with the conversion of prothrombin to thrombin. The resultant laboratory abnormalities may include altered activated partial thromboplastin time, kaolin clotting time and/or the Russell viper venom time. Because of their heterogeneity, the detection of LA is by a three-step functional assay, and no single functional assay is adequate to reliably detect their presence.

Routine coagulation studies – specifically the activated partial thromboplastin time, are the most commonly used method of screening for

LA. However, the kaolin clotting time is a more sensitive measure (it does not require the addition of exogenous phospholipids, thus maximizing the effect of the LA if present). The dilute Russell viper venom test may detect additional cases [8]. Failure to correct a prolonged clotting time in mixing studies with normal plasma is key to the definition of the LA even in the absence of aPL detected by routine ELISA.

aCL and anti- β_2 GP1 antibodies are measured using conventional ELISA techniques. The most common aPL isotype is IgG. IgA and IgM isotype antibodies are less common. Approximately a third of patients have aPL of more than one isotype [8].

The anticoagulant, β_2 GP1 binds to negatively charged phospholipids, inhibiting platelet aggregation via an adenosine diphosphate-dependant pathway. β_2 GP1 also inhibits prothrombinase. Paradoxically, antibodies to this glycoprotein may accelerate clotting or decrease platelet inhibition and prolong the coagulation cascade [8].

Pathogenesis of APS

The mechanism(s) by which aPL increase the incidence of thrombosis is uncertain. The probability is that development of clinical APS is dependent on the multiple-hit hypothesis, with both genetic susceptibility and environmental triggers playing a role. Potential mechanisms are discussed below.

Interference with the coagulation cascade

aPL may induce a procoagulant state by altering the interaction of phospholipid-binding proteins throughout the coagulation cascade. This may include inhibition of protein S or the thrombomodulin–thrombin complex. Alternatively, aPL may cause downstream inhibition of protein C substrates or annexin V. Additionally, aPL may act by disrupting activation of platelets, leading to increased thromboxane production and platelet adhesion.

Activation of endothelial cells

Endothelial cell activation stimulates coagulation via cytokine secretion, increased surface adhesion molecule expression and increased tissue factor production. Binding of aPL, to β_2 GP1 expressed on the endothelial cell surface has been shown to increase cellular activation *in vitro*. An alternative mechanism of activation may relate to the development of antibodies to low-density lipoprotein (LDL), which results in

macrophage activation. In the presence of aCL, autoantibodies to oxidized LDL develop. Antibody-linked oxidized LDLs are taken up by macrophages at the endothelial surface. Subsequent activation of these macrophages may lead to endothelial cell activation and damage [9,10].

Clinical features of APS & aPL in childhood

APS and aPL have a broad spectrum of clinical manifestations. Many children with aPL antibodies are picked up coincidentally and do not fulfill criteria for APS. Even if a child is documented to have circulating LA, by definition, they do not have APS if there has never been a thrombotic episode (see aforementioned updated Sapporo criteria). However, careful attention to the history and physical examination are required to ensure that an episode of thrombosis has not been overlooked. Additionally, catastrophic APS (Asherson's syndrome) may occur in children with no antecedent events. Nonetheless, in the absence of a thrombotic episode, these children should be noted to have aPL, but not diagnosed with APS. The long-term prognosis of such children is under study.

A number of studies have attempted to assess the prevalence of aCL in healthy children, but they have reported widely divergent results [11]. In a group of 61 children tested at well visits, aPL were detected in 11%, with anti- β_2 GP1 antibodies in 7%. Blood was drawn at a single time point for each child, giving a prevalence of aPL positivity, but not fulfilling laboratory criteria for APS [12]. Levels of β_2 GP1 antibodies were highest in babies. Some have questioned whether oral food items may induce a transient production of anti- β_2 GP1 antibodies [12].

Thrombosis

Ravelli and Martin suggest that APS in the pediatric age group is more common in females [13]. APS occurring in the context of another autoimmune condition, usually SLE, is recognized more commonly than primary APS in childhood. Associated thrombotic events may occur in any vascular bed. However, the relative frequency of arterial thrombosis in children appears to be greater. Children have few underlying thromboembolic risk factors. In general, they are nonsmokers, do not use the oral contraceptive pill and, although an increasing number have sedentary lifestyles and are overweight, their vasculature has incurred fewer years of cumulative

atherosclerotic damage. Thrombosis in children with aPL is rare over the relatively short periods for which they have been followed.

In childhood, deep vein thrombosis occurs more frequently than superficial. Pulmonary emboli and pulmonary artery hypertension resulting from multiple microthromboemboli have been reported [14]. Additional complications reported include infarction of the adrenal glands resulting in Addison's disease [15], as well as thrombosis of the inferior vena cava, renal, hepatic and mesenteric veins. The retinal vein thrombosis with visual loss and cavernous sinus thrombosis may also occur.

The CNS is the most common site of arterial thrombosis in childhood, with stroke being the most commonly reported event. aPL are a risk factor for pediatric stroke. Of 58 children with ischemic stroke, 53% had at least one marker of thrombophilia compared with 25% of controls [16]. As well as an increased stroke risk [16], an increase in transient ischemic events has been reported in children with aPL [17]. Any child presenting with thrombosis in the absence of other recognized predispositions should be evaluated for APS.

Nonthrombotic

Although thrombosis is the causative pathological mechanism in most cases, there is increasing evidence that there are several nonthrombotic mechanisms at play in the etiology of the various symptoms of APS. A direct role for autoantibodies is postulated in the development of transverse myelitis and of the chorea and epilepsy observed in APS patients [18]. It has been suggested that a vasculopathy of the major vessels may have a causative role in avascular necrosis [18]. Subendothelial immune complex deposition has been demonstrated in APS valve disease [19]. The mechanism of recurrent fetal loss, although infrequently a problem in pediatrics, has been demonstrated to have a complement-driven component [20].

Other CNS manifestations

Multiple neurological symptoms not clearly linked to thrombosis have been reported in children with aPL. aPL interact directly with cells of the neurological system or cause deposition of immune complexes on the cell surface, leading to cellular activation. Reported clinical presentations include seizures, Gullian–Barre syndrome, chorea, psychosis and migraine [14]. aPL may also cause transverse myelitis [17]. A potential role for aPL in Tourette's syndrome has also been postulated, but not yet established [21].

Cardiac

A valvulopathy similar to Libman–Sacks endocarditis has been reported in adults with aPL. The vegetations are composed of platelets and fibrin. Most commonly the mitral and aortic valves are affected. This valvulitis is more diffuse than that seen in other rheumatic diseases and often involves the chordae tendinae. Other cardiac pathology associated with aPL includes ventricular hypertrophy and dysfunction, intracardiac thrombosis and pulmonary hypertension [22].

Dermatologic

Livido reticularis is the most common dermatologic manifestation in children. Digital gangrene, purpura, skin ulceration and necrosis have all been reported [14]. Pretibial lesions are more common in childhood, perhaps because of the nature of their activities. Healing can be slow and painful with extensive scarring.

Hematologic

Thrombocytopenia is common in patients with APS, with up to a third of children affected. Platelet counts are usually in the $100\text{--}150 \times 10^9/l$ range, rarely dropping to less than 50×10^9 . This may occur because aPL (particularly anti- β_2 GP1 antibodies) interact with platelet membrane phospholipids [14]. Hemolytic anemia occurs and up to 20% of patients may be Coombs-positive. Evans syndrome (hemolytic anemia and thrombocytopenia) is reported [14].

The acquired hypofibrinogenemia–lupus anticoagulant syndrome occurs when antibodies to prothrombin lead to profound hypofibrinogenemia and severe bleeding [23]. Becton and colleagues have reported on six children, in whom the most common presentation was epistaxis. The children responded to corticosteroids [24].

Catastrophic antiphospholipid syndrome (Asherson's Syndrome)

The catastrophic antiphospholipid syndrome (CAPS) is now referred to as Asherson's syndrome [25]. It is defined as the clinical involvement of at least three organ systems with histopathologic evidence of multiple thrombi occurring over a period of days to weeks. Acute microangiopathy in the small vessels is more common than large-vessel involvement. The kidneys are affected most frequently, but CNS, lung, heart and skin may also be affected. Multiorgan failure results in a mortality rate of 50%. Disseminated intravascular coagulopathy occurs in approximately 25%. Although rare, reported cases have occurred in

children who fulfill adult criteria with rapid onset of organ failure in the setting of positive aPL. Most often reported is acute renal failure, but cardiopulmonary embolism, cerebral infarction and deep vein thrombosis are also suffered [26–28]. Asherson's syndrome may occur in the setting of infection, surgery, lupus flare or other events. Lupus vasculitis, sepsis, disseminated intravascular coagulation (DIC) and macrophage-activation syndrome should be considered in the differential diagnosis [29–31].

Neonatal

Infants delivered to aPL-positive mothers often have detectable antibodies resulting from transplacental passage. The most common perinatal complications are intrauterine growth retardation (IUGR) and prematurity. As expected, aPL diminish over the first 6 months of life. Thrombotic complications are rare. Renal vein thromboses in association with in-dwelling catheters and cerebral ischemia have been reported.

It is postulated that thrombotic complications are rare in aPL-positive neonates because their vessel walls lack atherosclerotic or other antecedent damage to serve as a point of initiation. Alternatively, the antiphospholipid IgG subclasses transferred transplacentally may be less effective [32].

Nonetheless, children of aPL-positive mothers should be monitored for thrombosis at least until the aPL titers have diminished. Recent work confirms a low rate of aPL transplacental passage for mothers with aPL-positive autoimmune disease, with none of 22 infants testing positive for aCL IgG or IgM. There was a high percentage of positivity for anti- β_2 GP1 antibodies (15 out of 22 infants) at 1 year of age. It is postulated that the antibody may be stimulated by infection or nutritional exposure. The authors conclude that measuring aCL is the more reliable assay for monitoring the disappearance of maternal antibody [33].

APS associated with other autoimmune conditions

The clinical manifestations of the APS in these children are similar to those with primary disease. In a recent, well-conducted study of long-term outcomes in 14 children with primary APS, fulfilling updated Sapporo criteria followed for a median of 6 years, two had developed SLE, one lupus-like syndrome and one non-Hodgkin's lymphoma [34]. In 12 combined series of children with SLE, 48% were positive for aCL and 23% for lupus anticoagulant. However, the reported positive percentage varied

widely between studies [11]. Children with SLE and aPL may be at a greater risk of thrombosis than those with either alone [35]. The relationship of specific aPL subsets to risk of thrombosis and specific disease manifestations remains uncertain, although symptoms of APS occur more commonly in patients with positive anti- β_2 GP1 antibodies [8]. Associations between aPL and cerebrovascular disease, chorea and microangiopathic nephropathy have been reported in childhood. A study of 137 children with lupus, of whom 26% (22 out of 84) had LA and 65% (23 out of 137) had aCL, demonstrated a statistically significant association between the presence of aPL and that of cerebrovascular disease. They also showed an association between persistently positive aCL and chorea [36]. An association has also been observed between aCL positivity in patients with SLE and ischemic microangiopathic nephropathy [37].

aPL can be found in children with a variety of other autoimmune conditions, including juvenile idiopathic arthritis (JIA), dermatomyositis, diabetes and rheumatic fever. In JIA, APS has been reported to occur in anything from 7 to 53% [14]. Serra and colleagues report a prevalence of aPL in JIA of 32.5%, similar to the percentage of antibody-positive juvenile SLE patients (37.5%). However, no association between the presence of antibodies and clinical manifestations was observed [38]. Only two reports appear in the literature of thrombosis occurring in aPL-positive JIA patients. One of these patients developed a bilateral femuropopliteal vein thrombosis but had the additional risk factor of a prolonged immobilization in plaster for a tibial fracture. The second patient had a central retinal vein occlusion [39,40]. An association has been observed between the presence of aPL and the development of persistent parvovirus B19 infection in children with JIA [41].

aPL often occur following infections, for example HIV and Epstein–Barr virus (EBV) and the use of some medications. These aPL differ by binding to negatively charged phospholipids. They are less often associated with complications, but are not distinguished from pathogenic aPL by normal testing. Children who test positive for aPL following an infection should have repeated positive tests before a definitive aPL-positive label is applied [14]. There is some evidence in murine models to suggest that the presence of viral or bacterial peptides may induce the presence of aCLs through a molecular mimicry model [42].

The varicella-autoantibody syndrome occurs rarely in children following varicella infection. DIC, purpura fulminans or thrombosis may occur as the result of a transient reduction in protein S. Levels are decreased when autoantibodies to protein S bind, forming immune complexes that are rapidly cleared. The autoantibodies aCL and LA have been seen in many children with this condition, although their specificity has not been defined [43].

More recently, Kurugol and colleagues have demonstrated the presence of LA along with decreased protein S in children with typical varicella infection, suggesting that this virus mediates a transient hypercoagulable state [44].

Differential diagnosis

Because thrombotic events occur rarely in children without heart disease or arteriovenous malformations, thorough search for the cause is necessary. In addition to testing for aPL, one should consider deficiency of protein C or S, Factor V, Leiden or antithrombin III. Other known risk factors, such as homocystine levels, should also be assessed.

A careful history and physical examination are essential to the detection of unrecognized rheumatic disease, heart defects or atrio-ventricular (AV) malformation. A family history of recurrent thromboses may be associated with inherited deficiencies or predisposition to rheumatic disease. A family history of recurrent pregnancy loss or rheumatic disease increases the likelihood of APS. Medication use, including contraceptives and anticoagulants, and illicit drug use must be evaluated. The presence of thrombocytopenia and leucopenia suggests rheumatic disease, but may also occur in children with malignancies. Infections may both cause thrombosis and be associated with the appearance of aPL. A schema for the detection and confirmation of the presence of aPL is suggested in Figure 1.

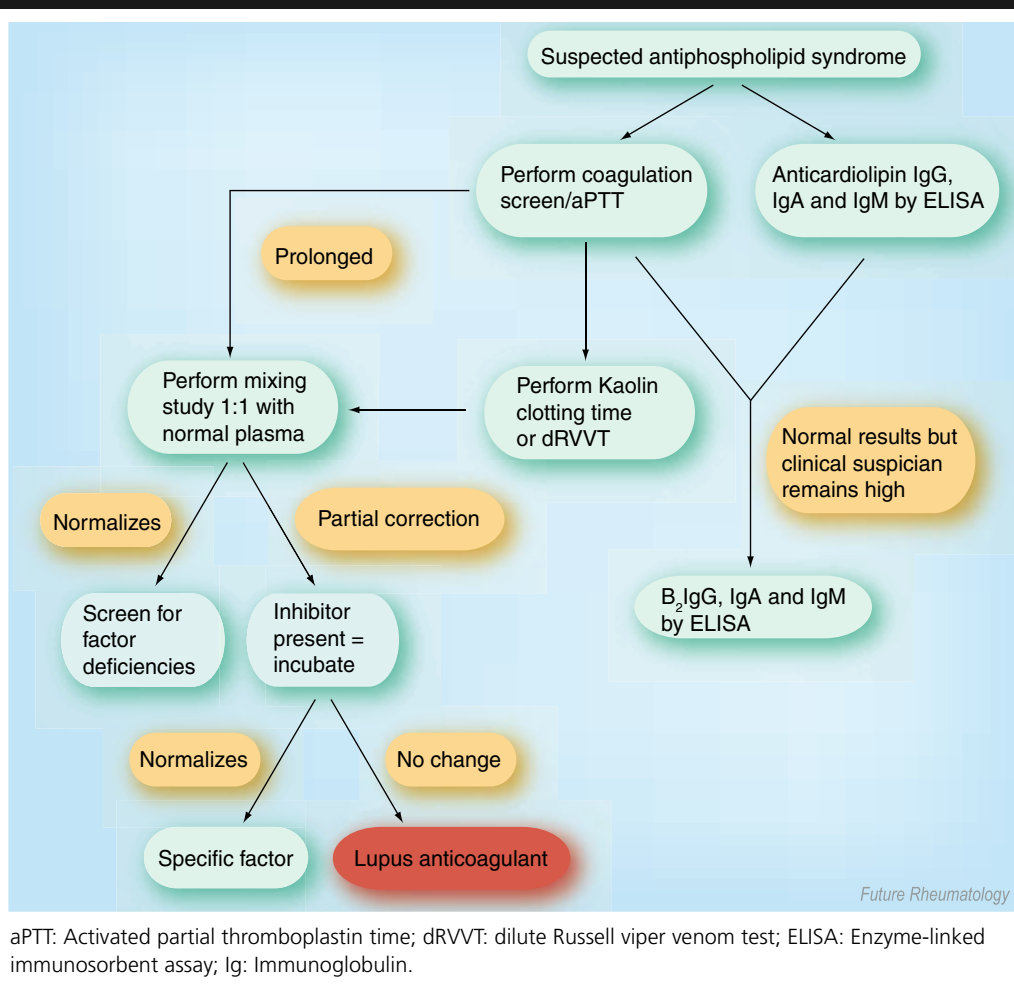
Treatment

The treatment of children with aPL or APS is controversial.

Asymptomatic children with aPL

aPL are found in a significant percentage of the healthy population. Their presence alone may not be associated with an increased risk of thrombosis in the absence of secondary factors [45]. In children with persistent positive tests for aPL, consideration may be given to treatment with an antiplatelet dose of aspirin. Some clinicians argue that no therapy is

Figure 1. A schema for the detection and confirmation of the presence of antiphospholipid antibodies.



necessary as the risk is low and the reduction in risk associated with aspirin use is unproven. Large-scale studies evaluating the use of aspirin in adults with aPL are ongoing. In our practice, children with significant aPL titers are advised to take 81 mg of aspirin daily. While there is a suggestion that aspirin may have a protective role in APS, substantive data are needed [46]. In addition, we advise strongly against other known risk factors, such as tobacco use and oral contraceptives.

Children with APS

Significant thrombosis in children with aPL requires initial treatment with heparin followed by oral anticoagulation. There is no consensus regarding duration of therapy or the appropriate degree of anticoagulation. Thrombosis in APS patients tends to reoccur, hence treatment should be maintained at least until aPL are undetectable, and many authorities recommend continued anticoagulation. In adults, a higher

degree of anticoagulation did not appear more effective at preventing recurrence [47]. Since children are at lower risk of recurrence and a higher risk of trauma with athletic activity, moderate anticoagulation may be best for pediatric APS patients. However, the severity of the problem and degree of risk must be considered for each child individually.

Thrombocytopenia

Although commonly present, thrombocytopenia is usually mild. Thrombocytopenia in the presence of aPL is not treated differently from idiopathic thrombocytopenic purpura (ITP) or thrombocytopenia associated with any recognized underlying condition, unless there has been an episode of thrombosis. Use of aspirin in patients with low platelets may increase the risk of bleeding. Splenectomy is not advised in patients with APS as the subsequent thrombocytosis may increase the risk of thrombosis [14].

Catastrophic antiphospholipid syndrome (Asherson's syndrome)

CAPS (Asherson's syndrome) is an emergency that must be aggressively treated. The treatment regimen for adults is based on the consensus statement from the international congress [48]. No independent pediatric recommendations exist. Key steps in treating a child with Asherson's syndrome are identification of precipitating factors and control of ongoing thrombosis. Intravenous anticoagulation may be combined with corticosteroids, intravenous immunoglobulin, plasma exchange and, in children with rheumatic diseases, additional immunosuppression [49,50]. Any child with CAPS should be anticoagulated indefinitely.

Future perspective

Optimal therapy for adults and children with aPL, APS or CAPS remains to be determined. Many treatments have been used in uncontrolled studies with reported success. These include hydroxychloroquine (HCQ), which has not only anti-inflammatory, but immunomodulatory effects, and an inhibitory effect on

platelets. Aspirin or HCQ may have a protective role in a cross-sectional review of asymptomatic aPL-positive patients [46].

Statins are known to downregulate cytokines, inhibit platelet function and interfere with the interaction between leukocytes and the endothelium [51]. They may benefit patients with aPL through any of these mechanisms or simply by reducing the severity of atherosclerotic damage. The lupus Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study investigating the effects of statin use in these children is currently ongoing; this will give us safety and efficacy data in a group of children with autoimmune disease.

Prostaglandin E1 and prostacyclin infusions have been used in patients with CAPS. These drugs act as potent vasodilators and inhibit platelet aggregation. The risk of rebound thrombosis must be carefully evaluated when considering their use [52].

Reports of rituximab (anti-CD20 monoclonal antibody) use in aPL-positive patients have shown some positive results, particularly in patients with thrombocytopenia [53].

Executive summary

Antiphospholipid syndrome

- Antiphospholipid syndrome (APS) is characterized by venous, arterial thrombosis and/or recurrent pregnancy loss, and is associated with a distinct autoantibody profile.
- APS may occur alone or as a clinically identical syndrome seen in association with concomitant autoimmune disease.
- In children, as in adults, the most common concomitantly occurring autoimmune condition is systemic lupus erythematosus.

Definition of APS

- The Sapporo criteria for the classification of patients with APS were proposed in 1998 and recently revised.
- Diagnosis of APS in childhood requires the child to have had documented thrombosis and not simply laboratory abnormalities, since recurrent pregnancy failure is not a usual feature in pediatric patients.
- Nonthrombotic features of the disease are important but do not define the presence of APS.
- Consensus criteria were developed for adult patients, but they may be equally applied to children. Children may present with a nonclassical manifestation and then go on to develop APS with thrombosis.

Pathogenesis of APS

- The mechanism(s) by which antiphospholipid antibodies (aPL) increase the incidence of thrombosis are uncertain.
- The probability is that development of clinical APS is dependant on the multiple-hit hypotheses, with both genetic susceptibility and environmental triggers playing a role.
- aPL may induce a procoagulant state by altering the interaction of phospholipid-binding proteins throughout the coagulation cascade.
- Antibody-linked oxidized low-density lipoproteins are taken up by macrophages at the endothelial surface. Subsequent activation of these macrophages may lead to endothelial cell activation and damage.

Future perspective

- Optimal therapy for adults and children with aPL, APS or catastrophic APS remains to be determined.
- Many treatments have been used in uncontrolled studies with reported success, these include hydroxychloroquine and rituximab (anti-CD20 monoclonal antibody).
- Current areas of research include complement inhibition, the inhibition of protein kinases in the platelet and inhibition of tissue-factor expression.

Many additional therapeutic avenues are undergoing exploration as the molecular basis of aPL and APS becomes more clearly understood. Current areas of research include complement inhibition, the inhibition of protein kinases in the platelet and inhibition of tissue-factor expression. In a murine model system, tumor necrosis factor- α blockade confers protection against pregnancy loss in mice with aCLs. This has not been explored in humans [54].

Synthetic proteins that mimic regions of β_2 GP1 and block its thrombogenic properties are under investigation, as is a β_2 GP1 toleragen [55].

Conclusion

aPL are surprisingly common in children without manifestations of disease and their significance is uncertain. By contrast, APS in childhood is rare but potentially devastating. Both APS and aPL are more commonly seen in children with rheumatic diseases, but occur in isolation. Any child presenting with LA or unexplained thrombosis should be vigorously evaluated for aPL, and children with APS should be vigorously treated.

Disclosure

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