Pediatric Antiphospholipid Syndrome

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Antiphospholipid syndrome is a multisystem autoimmune disease, characterized by arterial and venous thrombosis, recurrent fetal loss, and persistent circulating antiphospholipid antibodies [1]. This syndrome with protean clinical manifestations can be either primary or secondary to other autoimmune disease, mainly systemic lupus erythematosus. Whereas APS in adults has been well characterized, only a few studies of children with APS have been reported, most of them case reports [2-5]. The first pediatric series, published in 1996, included nine patients [6]. In a review of 50 case reports of children with APS, Ravelli and Martini [7] concluded that pediatric APS is similar to adult APS. Later it was shown that patients with childhood-onset APS presented with significantly more episodes of chorea and jugular vein thrombosis than did adults [8].

Pediatric primary APS is very rare, and disease onset before age 15 occurred in only 2.8% of patients from a large APS cohort [8]. The prevalence of secondary APS in children with SLE is 9–14% [9,10]. The recently revised criteria for the diagnosis of APS in adults are currently used for pediatric patients, but there is no validation of these criteria for children [5].

Laboratory tests

The aPL antibodies, directed against phospholipids and phospholipid-binding proteins, are tested by coagulation or immunologic assays. The aPL antibodies have both pro- and anti-coagulant properties; they alter coagulation tests, causing inhibition that is not corrected by addition of normal plasma. Several tests for aPL are available. The prolonged activated partial thromboplastin time test has a low sensitivity; kaolin clotting time is too complicated to assay. dRVVT (Russell viper venom time) is very sensitive to phospholipid interference and is currently the preferred test for lupus anticoagulant detection. Other tests for measuring aPL antibody are immunological, namely, the enzyme-linked immunosorbent assay, which detects different isotypes of anticardiolipins and antibodies to many other phospholipids (phosphatidylserine, phosphatidylinositol, phosphatidylcholine) [11]. Their specificity increases with the titer, and immunoglobulin G anticardiolipin is more specific than immunoglobulin M. Another group of antibodies is directed against protein co-factors that bind the phospholipids, such as beta-2 glycoprotein-1 and annexin. Although there is some overlap between all these antibodies, it is important to use more than one test to detect them.

Definition of pediatric APS

The revised criteria for the definition of APS include a combination of one of two clinical (thrombosis/recurrent abortions) and one of three laboratory features. The laboratory criteria are positive lupus anticoagulant test or a medium or high titer anticardiolipin or anti-β2GP1 IgG and IgM antibody, present on two occasions at least 12 weeks apart. These criteria are not valid for the pediatric population for several reasons. Obstetric morbidity, one of the two clinical criteria, is not relevant to the pediatric population. Children are less prone to vascular thrombosis, due to rarity of additional thrombophilic risk factors such as atherosclerosis, pregnancy and use of oral contraceptives [12]. On the other hand, other important and common manifestations of the syndrome are not included in these criteria, such as livedo reticularis, chorea and thrombocytopenia. Nonetheless, these criteria are applied for the diagnosis of pediatric APS, despite the lack of validation in children.

Epidemiology

Low titer anticardiolipin and anti-β2GP1 antibodies have been reported in 11% and 7% of healthy children respectively [13]. Increased prevalence of anti-β2GP1 antibodies in infants with atopic dermatitis and in children with juvenile idiopathic arthritis has also been observed [13]. The prevalence of aPL antibodies correlated to previous infections and vaccinations in these cases [14]. In the majority of these cases, antibodies were transient and non-pathogenic. Serum levels of IgA anticardiolipins are lower in children than in adults, while anti-β2GP1 IgG levels were found highest in preschool children [15,13].

Persistent aPL antibodies are associated with an increased risk of arterial thrombosis (mainly cerebrovascular events) [16,17] and contribute to a higher risk of CVA in children [18]. However, the

APS = antiphospholipid syndrome
aPL = antiphospholipid
β2GP1 = beta-2 glycoprotein-1
Ig = immunoglobulin
CVA = cerebrovascular accident

association of aPL antibodies with pediatric sinus vein thrombosis is controversial [19,20].

The prevalence and levels of aPL antibodies in children with SLE are higher than in healthy controls, with anticardiolipin antibodies ranging from 27 to 57% [21,22] and lupus anti-coagulant in 16–29% [10,22]. Thrombosis, central nervous system disease, cytopenia [22], leukopenia and osteonecrosis are associated with increased aPL antibody level in pediatric SLE patients [23].

Clinical features

The clinical manifestations of APS are similar in adults with primary and secondary APS forms [24]. An increased prevalence of livedo reticularis, thrombocytopenia and leukopenia and a higher prevalence in females have been reported in the APS in SLE patients. However, there is an overlap between these related autoimmune diseases, and hemolytic anemia, thrombocytopenia, cardiac valvular lesions and chorea occur both in SLE and in primary APS.

The major clinical manifestation of the syndrome is vascular thrombosis. Thrombosis on the venous circulation is found in 59% of adult cases, arterial vessels in 28%, and in both systems in 13% [25]. The thrombotic event may be spontaneous or triggered by a predisposing factor, such as vascular stasis, trauma, surgery, use of oral contraceptives and inherited thrombophilia.

Deep vein thrombosis of the lower limbs is the most common thrombosis in pediatric APS patients and tends to recur if proper long-term anticoagulation is not applied [5]. Superficial and upper extremity veins are less commonly involved; more rare are thromboses occurring in the inferior and superior vena cava, hepatic (Budd-Chiari syndrome) and portal veins, renal, adrenal, retinal and intracranial veins [5,26]. Arterial thrombosis, resulting mainly in stroke (20%) and transient ischemic attacks (11%), are less common [5,8]. Other less commonly involved vessels include coronary, subclavian, mesenterial, renal, retinal and pedal arteries. The arterial thrombosis is much more common in children than in adults [5]. A great variety of central nervous system symptoms in APS has been described, including chorea, dementia, migraine, intracranial hypertension, neurocognitive deficits, psychosis and depression, epilepsy, Guillain-Barré syndrome, transverse myelopathy and optical neuritis [27].

Cardiac manifestations comprise valvulopathy, intracardiac thrombosis, coronary artery disease and cardiomyopathy [28]. Rarely, adult APS patients develop severe valvular disease that requires surgical treatment and is associated with significant morbidity and mortality [29]. Cardiac disease is rare in children with APS [5]. In our cohort of pediatric APS, thrombocytopenia and hemolytic anemia were found in 20% and 10% of patients respectively [5]. Livedo reticularis, the reticular cyanosis caused by vascular stasis of deep dermal vessels, is the commonest skin manifestation of the syndrome and appears in 15% of adult cases, yet this phenomenon is rare in children [5]. Renal and pulmonary involvement, increasingly reported in adult APS, is also scarce in pediatric patients. Various gastrointestinal manifestations have been reported in APS patients, including Budd-Chiari syndrome, intestinal and esophageal ischemia and infarction, ischemic colitis, colonic ulceration, infarction of the liver, cholecystitis, and mesenteric and portal vein thrombosis [26]. These manifestations are rare, and are mostly secondary to large vessel thrombosis.

A retrospective study from three Italian referral centers reported 14 children with primary APS [4]. They differed from adult series in gender distribution (male majority) and the predominance of arterial over venous thromboses. The most common manifestations were CVA and leg deep vein thrombosis. During follow-up, four patients had at least one recurrence of trombosis and another disease appeared in four cases (SLE and Hodgkin's lymphoma).

In our cohort of 28 pediatric APS patients, the most common initial APS manifestations were venous thrombosis, stroke and thrombocytopenia. Lupus anticoagulant was detected in almost all patients. A high rate of progression to lupus was found in girls with primary APS. Neither renal nor heart or skin disease has been observed during follow-up. Recurrent thrombotic events were less common in patients who received anticoagulant therapy. A high rate of inherited thrombophilias (45% of patients) was found in our series, implying that aPL antibodies may serve as a "second vascular hit" in children [5].

Catastrophic APS

Catastrophic APS, an acute widespread small vessel coagulopathy resulting in multi-organ disease (mainly renal, pulmonary, central nervous system, cardiac) with high mortality, occurs in 0.8% of adult patients [8]. Various triggers, such as infection, medication, anticoagulation withdrawal, surgery, neoplasm or flare of SLE within a few day, were found in 60% of cases [30,31]. In a review of 115 patients with catastrophic APS, only 3 were children [32].

Perinatal APS

Rare cases of perinatal thrombosis in infants born to mothers with APS or mothers with aPL antibodies have been reported [33]. Positive aPL tests were observed in most infants, and the clinical presentation consisted of arterial and venous thromboses in multiple localizations similar to adult APS patients. In our cohort of children with APS, five patients presented with perinatal stroke. Although patients in this subgroup have diagnostic criteria of APS, their disease behaves differently, is transitory and does not recur, similar to patients with neonatal SLE. Thus, perinatal stroke in children with APS deserves special consideration and may not require anticoagulant therapy unless other risk factors prevail [5].

Conclusions

APS in children has unique features, manifesting commonly with central nervous system and rarely with skin, heart, or kidney disease. SLE may develop in a significant percentage of girls presenting with primary APS. aPL antibodies may serve as a "second hit" in children with hereditary thrombophilic risk factors, and children with APS may benefit from thrombophilia analysis.

Infants with APS present perinatal stroke, had monophasic disease, and other manifestations of APS did not develop later. Due to the rarity of APS in children, multicenter prospective studies are warranted.

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When the power of love overcomes the love or power the world will know peace

Jimi Hendrix (1942-1970), musician, singer and songwriter. Hendrix is considered one of the greatest and most influential guitarists in rock music history.