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Diagnosis and treatment of antiphospholipid syndrome in childhood: A review

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ABSTRACT

The antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by recurrent fetal loss and thromboembolic events associated with the presence of elevated titres of antiphospholipid antibodies (aPL). The purpose of this review is to summarize what is currently known about the diagnosis and treatment of pediatric APS, to highlight key differences between APS presenting in adults versus children throughout, and to identify areas where future research is needed.

1. Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease process characterized by recurrent fetal loss and thromboembolic events that occur in the presence of elevated titres of antiphospholipid antibodies (aPL) and has been reported in children. It may involve pregnancy morbidity, hematologic, neurologic, dermatologic, and other manifestations [1]. It occurs either as an isolated (primary) clinical syndrome or secondary to another disease, mainly systemic lupus erythematosus (SLE) or any other process that perturbs the vascular endothelial microenvironment (e.g. inflammation). In childhood, APS can occur any time from the neonatal period through to adolescence. Neonatal APS in babies born to mothers with aPL is a very rare syndrome. APS can occur due to de novo production of aPL in the neonate, child, or adolescent. Catastrophic APS (CAPS) can also occur in children. This is a severe form of APS involving the rapid development of multiorgan thrombosis characterized by a small vessel microangiopathy and may coincidentally involve large vessel thrombosis. There are several unique features of pediatric APS to consider. The objectives of this review are to summarize current knowledge concerning the diagnosis and treatment of APS in childhood, to discuss key differences between APS presenting in adults versus children throughout, and to point out gaps in our knowledge in this area.

2. Definition and classification

There are no currently validated criteria for the diagnosis of APS in childhood. Preliminary classification criteria for adults were developed by consensus in 1998 and updated in 2006. These criteria were specifically designated for research purposes for use in study design to assure uniform cohorts and not for clinical care. A patient would be classified (by these updated Sapporo criteria) as APS with the occurrence of vascular thrombosis or recurrent fetal losses (clinical criterion) associated with the persistent presence of one or more of the anti-phospholipid antibodies (aPL), namely the lupus anticoagulant (LA), anti-cardiolipin (aCL) of immunoglobulin G (IgG) and/or IgM subtype, or anti-ß$_2$ glycoprotein I (anti-ß$_2$ GPI) of the IgG and/or IgM subtype in medium or high titres. Experts have suggested that the Updated Sapporo criteria [2] be adapted for children by removing the pregnancy morbidity criterion, as this is rarely applicable in the pediatric age group (Table 1) [3].

3. Epidemiology and clinical characteristics

There are currently no reliable data on the incidence and prevalence of pediatric APS because of the lack of validated clinical criteria. The diagnosis is made by applying adult criteria in combination with clinical judgement. What is known about pediatric APS had largely come from case reports and case series. However, in 2004, an international registry of pediatric patients with APS (the Ped-APS Registry) was initiated as a collaborative project of the European Forum on Antiphospholipid Antibodies and the Juvenile Systemic Lupus Erythematosus Working Group of the Paediatric Rheumatology European Society (PRES). The

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Table 1
Adaptation of the updated Sapporo criteria for pediatric APS patients (3).

Clinical criterion
- Vascular thrombosis: 1 or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ confirmed objectively by validated criteria.
Laboratory criteria
1. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart
2. Anticardiolipin of IgG and/or IgM isotype, in medium or high titre (>40 GPL or MPL, or >99th percentile), on 2 or more occasions, at least 12 weeks apart
3. Anti-ß$_2$ glycoprotein I antibody of IgG and/or IgM isotype, in medium or high titre (>99th percentile), on 2 or more occasions, at least 12 weeks apart

APS is said to be present if the clinical criterion and at least one of the laboratory criteria are present. These are the adult criteria minus the pregnancy morbidity criterion for the pediatric population. These classification criteria are meant for research purposes, not for diagnostic purposes, per se.

demographic characteristics of 121 of these patients were described in 2008. This revealed a mean age of 10.7 years (range 1.0 to 17.9 years) [4]. Studies have revealed a female-to-male ratio of pediatric APS patients ranging from 1.2:1 to 3:1 [4–6]. This differs from adult studies, in which the female-to-male ratio is typically > 5:1 [7–8].

3.1. Primary APS

Those with primary APS (i.e. not associated with another underlying autoimmune disease) account for 40–50% of the cases of pediatric APS [4,6]. However, a number of those initially diagnosed with primary APS eventually meet criteria for SLE or another autoimmune diagnosis if followed over time. In the Ped-APS Registry cohort, 30% of those with SLE initially presented with primary APS but, during the 6.1 years of follow-up, progressed to full blown SLE [9]. This is more than four times the rate found in adult patients with SLE [10]. In general, children with primary APS are more likely to be younger and to have arterial thrombotic events, while those with secondary APS are more likely to present at an older age and to have venous thrombotic events and hematologic and dermatologic manifestations [4].

3.2. Secondary APS

APS secondary to autoimmune disease represents about 50–60% of pediatric APS [9]. The underlying disease is SLE or SLE-like disease in 80–90% of these cases. Often, the clinical distinction between primary and secondary APS is difficult to make, given that there are several overlapping features between APS and SLE, such as hematologic abnormalities, skin manifestations, neurologic features, and kidney involvement [11]. A high percentage of patients with juvenile idiopathic arthritis (JIA) have also been found to have aPL, but very few ever develop thrombosis. Several cross-sectional studies have reported a prevalence of aCL ranging from 7% to 53% in patients with JIA. However, LA and anti-ß$_2$ GPI, which are known to be more specific for risk of thrombosis, were found in <5% of these patients [12–18]. Most of these studies found no association between the presence of these antibodies and disease activity and no clinical manifestations of APS were observed [14, 18]. In a prospective study of 28 patients with JIA, persistent aCL was observed in 6 patients (21%). Of these, 4 (14%) had persistently medium or high titre antibodies. In spite of this, none of these patients had any clinical manifestations related to the aPL. Only one patient in this study was persistently positive for anti-ß$_2$ GPI and this was at low titre. None of the patients were persistently positive for LAC (14). Thus, the aPL found in patients with JIA seem to have limited pathogenic potential. This likely explains the very low incidence of thrombosis in JIA patients and the fact that aPL are not routinely screened for in these patients. There have also been reported cases of APS in various other childhood autoimmune diseases, including Henoch-Schonlein purpura [19–20], Behcet's disease [21], polyarteritis nodosa [22], immune thrombocytopenic purpura [6,23], hemolytic uremic syndrome [HUS, [24]], and rheumatic fever [25]. Patients with idiopathic thrombocytopenic purpura (ITP) and aPL need to be monitored for progression to SLE. There is a clear difference between cases of APS in patients with these other autoimmune diseases and the finding of mildly elevated/transient titres of APLA in children with JIA and other diseases.

3.3. Infection and aPL

Infections are quite common in the pediatric population. Several bacterial and viral infections have been known to induce the production of aPL in previously negative patients. For example, children going for tonsillectomy are sometimes incidentally found to have LA after a work-up for prolonged aPTT. These patients often have recurrent Group A Streptococcal (GAS) infections prior to being referred for surgery. Many other infections of childhood, such as varicella, parvovirus B19, staphylococcal, and Mycoplasma have been known to induce the production of aPL, as well. The etiology of this phenomenon is thought to be molecular mimicry between the infectious agent(s) and the antigenic targets of the aPL and/or the unmasking of cryptic antigenic determinants of naturally occurring aPL [26–27].

3.4. Malignancy and aPL

Malignancy is a known risk factor for thrombosis in children. However, there have only been rare case reports of the association of aPL with thrombosis in pediatric patients with various malignancies, including solid tumors, lymphoproliferative cancers, and hematologic malignancies [28–30]. In a Turkish study of 37 consecutive children with thrombosis and malignancy, aPL were found as one of the acquired risk factors for thrombosis in only one case [29]. In the Ped-APS registry, only a single patient (0.8% of all patients) had APS secondary to malignancy [4]. However, APS associated with malignancies are more common in elderly patients, particular those with solid tumors [30–32].

3.5. Healthy children with aPL

In studies, up to 25% of otherwise healthy children have been found to have low levels of aPL, which is higher than the reported rate of aPL in asymptomatic adults [33–37]. These aPL, however, are present in lower titre than those typically associated with thrombosis and are usually transient (i.e. are not present with repeat testing 12 or more weeks later). Given the fact that children are exposed to more infections and vaccinations than adults, these aPL could be triggered by environmental factors. There is also increasing evidence that the developing immune system may produce non-pathogenic anti-ß$_2$ GPI antibodies in response to such nutritional antigens as bovine ß$_2$ GPI from milk and/or beef products [38–39]. It appears that the risk of thrombosis in these otherwise healthy children incidentally found to have aPL (e.g. during a work-up for prolonged aPTT) is exceedingly low, given the low titres, non-pathogenic subtypes, and transient nature of the aPL in these cases.

4. Additional clinical and laboratory features

Although not part of the formal classification criteria, there are several additional 'characteristic' clinical and laboratory features of APS. Clinical features include, but are not limited to, livedo reticularis, Raynaud's phenomenon, transient cerebral ischemia, transverse myelitis, chorea, migraine, and cardiac valve abnormalities. A non-exhaustive list of laboratory features includes hemolytic anemia, thrombocytopenia, and some research-identified antibodies. In children with APS, there is a high prevalence of Evans Syndrome, livedo reticularis, Raynaud's phenomenon, migraines, and chorea [4]. Neurologic involvement in the form of attention or memory difficulties in pediatric patients can be difficult to differentiate from other more common developmental issues, such as learning disabilities or attention deficit

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