Managing antiphospholipid antibodies and antiphospholipid syndrome in children

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Antiphospholipid antibodies (aPL) and antiphospholipid syndrome (APS) are increasingly being recognized in children. Transient non-pathogenic aPL are often seen after childhood infections, while thrombotic events seem rare in those with *true* aPL. We discuss the main scenarios faced when dealing with children with aPL – asymtomatic aPL, primary APS and secondary APS. Children with thrombotic events present difficult management problems, as there is little evidence-based medicine in this area. We discuss the manifestations and management of childhood aPL – asymptomatic aPL, primary and secondary APS elucidated with case histories. Insufficient safety data on anticoagulation and limited information on the effects of warfarin, use of aspirin, duration and intensity of anticoagulation are some of the unresolved issues in managing aPL and APS in children. Multicenter randomized controlled trials may provide answers to some of these issues.

Key words: antiphospholipid antibodies, chidren, thrombosis.

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The incidence of thrombosis in children is very low compared to than in adults, reflecting the less prothrombotic hemostatic profile of children due to increased levels of physiological anticoagulants and lower levels of coagulation factors. In hospital populations, however, the incidence of thrombosis in children appears to be increasing. In the Canadian Registry of 137 children identified prospectively, the incidence of venous thromboembolism was 5.3/10,000 hospital admissions or 0.07/10,000 children.[1] An incidence of 1.2/10,000 admissions for thrombosis was seen at the Children's Hospital of Denver between 1952 and 1972.[2] A prospective study in Germany (ESPED) reported an incidence of thrombosis in children to be 5.1/100,000 live births.[3] Most of these hospital thromboses were provoked by the use of an invasive vascular intervention in sick children. This study excluded newborns and children with thrombosis in the central nervous system, portal system, renal veins or other non-limb venous systems. The incidence of ischemic stroke in children younger than 15 years has been reported to be about 1.2/100,000 per year[4] but ischemic stroke in children has diverse etiologies such as congenital malformation, cardio-embolic disease, sickle cell disease, moyamoya syndrome, arterial dissection and occasionally thrombophilia.[5] Apart from the predominance of upper venous system venous thrombosis due to central lines in sick children, other features differentiating venous thromboembolism in childhood from that in adults are unusual locations and prothrombotic congenital rarities such as homozygous deficiencies of proteins C and S. Poor venous access and thus difficulty with phlebotomy further compound thrombotic issues in children The antiphospholipid syndrome (APS) is an autoimmune condition characterized by the persisting presence of antiphospholipid antibodies (aPL), in association with thrombosis (which can be arterial, microvascular or venous) and/or pregnancy morbidity.[6-9] APS can occur alone when it is known as primary APS or associated with another auto-immune disease, most commonly systemic lupus erythematosus, when it is known as secondary APS. Unlike the congenital thrombophilias, which mainly predispose to venous thrombosis, APS can produce thrombosis in any part of the vasculature - artery, vein or microvasculature - and so it can present with a variety of clinical manifestations with brain, heart, skin and other organ involvements secondary to thrombosis. Very rarely it is associated with bleeding. In this review we describe the varied manifestations of aPL – asymptomatic, primary and secondary APS- with case histories to illustrate the diversity and difficulty in managing these children. We strongly suspect that outside of our tertiary referral center, which attracts difficult management problems, the incidence of thrombosis is much lower in children with aPL.

Detecting antiphospholipid antibodies

Antiphospholipid antibodies are a family of antibodies reactive with proteins that are

themselves complexed with negatively charged phospholipid. For example, aPL may require β2-glycoprotein I (β2GPI), a phospholipid-binding plasma protein with weak anticoagulant activity, for binding to acidic phospholipids such as phosphatidyl serine and cardiolipin. Because aPL are so heterogeneous among individuals, it is essential to perform both the anticardiolipin assay and lupus anticoagulant (LA), for many patients are only positive for one of these assays. The LA assay is a double misnomer for it is neither a test of lupus nor one for an *in vivo* anticoagulant. *In vitro* LA slow down the assembly of the components of prothrombinase on phospholipid due to interference by the antibody. The tests most frequently employed in LA testing are the activated partial thromboplastin time (APTT), the dilute Russell's viper venom time (DRVVT) and the kaolin clotting time (KCT). The most important part of these assays is the correction time - repeated testing using a large amount of phospholipid which will remove the aPL and thus allow for coagulation to occur in the normal way.

The anticardiolipin (aCL) assay is performed using an enzyme-linked immunosorbent assay (ELISA)

Persistent positivity of laboratory tests is important. LA, IgG and/or IgM aCL present at high titers (>40 GPL or MPLβ or above the 99th percentile) and/or anti-β2 GPI antibody of IgG and/or IgM isotype (above the 99th percentile) should be present on two or more occasions, at least 12 weeks apart as per the revised classification criteria for APS.[10]

Antiphospholipd antibodies in pediatrics asymptomatic antiphospholipid antibodies

Acquired infections in children can be responsible for transient and asymptomatic aPL. These antibodies in children may or may not be associated with another autoimmune disease. Case 1 is an example of asymptomatic aPL. *Case 1*. A 14-year-old African girl with sickle cell disease had an abnormally prolonged APTT at 2.68 (normal value, 0.8-1.20). Further investigations during a chest crisis were consistent with the presence of lupus anticoagulant according to the KCT and DRVVT. The KCT was prolonged at 1.60 (normal value, 0.80 – 1.20); KCT 1+ 4 mix 1.18 (normal value, 0.80–1.20); DRVVT 1.60 (normal value 0.90–1.09); DRVVT correction 1.13 (normal value, 0.90–1.09); DRVVT 50:50 mix 1.45 (normal value, 0.90-1.09). The APTT was also prolonged. Anticardiolipin antibodies were not detected - aCL IgG level 5.5 (normal value, <9 GPL U/mL); IgM level 3.5 (normal value, <11 MPL U/mL). Free protein S was mildly reduced, 65.8 u/dL (normal value, 66.0–150.0) but a congenital thrombophilia screening was otherwise normal. There was no evidence of pulmonary embolism on ventilation – perfusion scanning. At 18 months follow-up, despite normalization of the aPTT, the lupus anticoagulant remained detectable by DRVVT and dilute aPTT but the child was clinically well.

This case illustrates the difficulty in managing patients with aPL. Once detected, clinical problems are suspected of being related to thrombosis. In case 1 there was concern that the chest sickle cell crisis was precipitated or associated with pulmonary emboli. However a V/Q scan was negative. It is difficult to be sure whether a transient aPL had been pathogenic or not.

Review of the literature shows a high incidence of transient aPL in children following viral infections.[11-13] These aPL are not thought to be pathogenic in that they do not cause thrombosis. In one study of 88 children with upper airway infections, positive aCL was detected in 30%.[14] Since post-infectious aPL tend to be transient, aPL positivity should be confirmed on at least two occasions. Rarely aPL are associated with varicella infection with co-infection with streptococcus in which case multiple thrombotic events can occur; however this is usually related to profound protein S deficiency due to a direct anti-protein S antibody, not the associated LA.[13] Reduced levels of free protein S are a common accompaniment of aPL, as described in case 1, and may be due to acute phase-induced high levels of C4bBP, the binding protein of protein S.[14]

The prevalence of aCL in healthy children has been reported in various studies to range from 2% to an extraordinary 82%.[14-20] Lupus anticoagulant in healthy children has also been reported in a few studies.[21-24] Most of these children present with a prolonged aPTT that corrects spontaneously to the normal range.[21-23]

The management of healthy children with persisting aPL is uncertain as this case illustates. We advocate careful review, with minimal intervention. Prophylactic treatment with low-dose aspirin is not advocated for asymptomatic children with aPL.[25,26] Subcutaneous low molecular weight heparin may be used for thromboprophylaxis in periods of stress such as prolonged immobilization or after surgery. Adult patients with APS are advised to avoid prothrombotic risk factors such as combined oral contraception and smoking. Similar advice is logical for adolescents with aPL.

Primary antiphospholipid syndrome (PAPS) in children

The prevalence of PAPS in children is not known. Several studies have reported APS in children with arterial and/or venous thrombosis.[25-27] In 1995, Manco-Johnson *et al.* identified LA in 25% of 78 consecutive children admitted with thrombosis.[28] Children with *catastrophic APS* with widespread vascular occlusions have also been reported.[29] We strongly suggest that PAPS is rare in children but being a tertiary referral center, our experience is biased, and we do see a steady trickle of cases. Clinical features occurring in adults are also seen in children but very little is known abot the pediatric aspects of aPL and APS due to the rarity of the clinical problems. Pregnancy morbidity, which is an important

Table 1. Case summary.

Patient no.	Age (years)	Sex	aCL IgG	aCL IgM	APTT	Lupus anticoagulant	Presenting thrombus	Diagnosis	SLE/related complications	Other	Treatment problems	Outcome
1.*	14	F	Normal	Normal	Prolonged 2.68#	Present	None	HbSS/antiphospholipid antibodies	No	None	None	Asymtomatic
2.+	6	M	Normal	Normal	Mildly prolonged 1.18/(normal initially)	Present	R putamen infarct (Pos. thrombosis of small branch of R MCA)	Primary antiphospholipid syndrome	No	Recurrent episode of left sided parasthesia/ weakness (TIA)	Aspirin (stopped after 14 months). Tinzaparin/Warfarin INR 2-3 now INR 3-4	Mild left hemeparesis otherwise good recovery
3. *	13	F	59.1	329.6	Normal	Present	Recurrent left leg DVT	SLE with secondary antiphospholipid syndrome	Generalised arthralgia, dry eyes	Bacterial meningitis, bilateral deafness	Heparin, warfarin INR 3-4, Hydroxychloroquine, Cochlear implant	Controlled

**Normal aCL values: IgG <9.0 GPL U/mL; IgM <11.0 MPL U/mL; + Normal aCL values: IgG <20.1 GPL U/mL; IgM <11.0 MPL U/mL; #normal aPTT value: 0.8-1.2/normal aPTT value: 0.85-1.1.*

clinical criterion in women, is a rarity in the pediatric population, while risk factors such as underlying atherosclerosis, cigarette smoking and contraceptive medication are again not relevant in children.[30] It has been noted that associated clinical features seen more commonly in children include migraine, chorea, epilepsy,[31,32] thrombocytopenia,[33-34] and hemolytic anemia.[33,35]

Case 2. PAPS with multiple cerebral thromboses. A 6-year old boy had suffered a stroke affecting the right basal ganglia whilst on holiday. He had previously been fit and healthy. While camping with his father and sister on holiday in the USA he felt tired and began to have difficulty walking. A gradually increasing weakness of the left side of body led to a dense left hemiplegia and mild weakness on the left side of the face. Computed tomography (CT) scanning at the local hospital showed a focal non-enhancing low attenuation lesion in the basal ganglia (putamen) suggestive of a small infarct. Clinical examination showed mild palsy of cranial nerve VII and a dense left hemiplegia. His initial laboratory investigations, including a full blood count and congenital thrombophilia testing, were all normal. He was started on aspirin 81 mg daily and received physiotherapy and a foot splint for left foot drop. Magnetic resonance imaging (MRI) findings were consistent with the CT results and an MR angiogram showed normal vessels without any visible occlusions 48 hours after the episode. An echocardiogram and electrocardiogram were both also normal. On his return to the UK, the boy was further investigated and this time his coagulation screen showed a normal PT, a mildly elevated aPTT 1.18 (normal value, 0.85-1.16), with a lupus anticoagulant with dilute aPTT 1.66 (normal value, 0.81-1.23), confirmatory dilute aPTT 1.19 (normal value, 0.81-1.13), dilute aPTT with equal volume mixing 1.19 (normal value, 0.86-1.15) without anticardiolipin antibodies. An autoimmune screen was negative. A diagnosis of PAPS was made. His subsequent duplex scanning demonstrated normal flow velocities bilaterally in the internal carotid and basal cerebral arteries. Vertebral velocities were also within normal limits.

His aspirin dosage was reduced to 37.5 mg once daily, but 14 months after his initial presentation, he was readmitted with paresthesia and mild weakness on his left side and had a persisting lupus anticoagulant. MR imaging scanning revealed a new small cerebral lesion in the deep white matter lateral to the trigone of the right lateral ventricle in addition to the old established infarct in the posterior right basal ganglia. Aspirin was stopped and he was started on a low molecular weight heparin, tinzaparin, at 175 U/kg subcutaneously daily with formal anticoagulation with warfarin aiming for a target International Normalized Ratio (INR) of 2-3. His parasthesia settled and he was discharged on warfarin. He had a further cerebral event after 4 months when his target INR was increased from 2-3 to 3-4. He continues to have mild weakness on the left side but otherwise has resumed full normal activities.

Systemic lupus erythematosus and secondary APS

Several studies have reported varying prevalences of aCL and LA in children with systemic lupus erythematosus (SLE). The range varies from 19–87 % for aCL and 6-62 % for LA.18, 34-41 Some children with APS may progress to develop overt SLE 18,42 and hence, children with aPL-related features such as thrombocytopenia and hemolytic anemia should have a prolonged follow-up.[43] The prevalence of aCL in juvenile idiopathic arthritis varies from 7-53%[16-18,20,36,41,44] However, thrombotic complications in juvenile idiopathic arthritis with aCL are uncommon suggesting a poor association between aCL in this form of arthritis and a thrombotic event.

Of the many studies in children with SLE and/or juvenile idiopathic arthritis, some have shown a higher incidence of thrombotic events in the presence of aPL while others differ in their conclusion. Seaman *et al*. found a significant association of aPL, specifically aCL with thrombotic events.[35] Similarly, Berube *et al*. found a significant relationship between the presence of LA and thrombotic events.[40] On the other hand, Ravelli *et al*. found aCL to have a low predictive value for the development of vascular thrombosis.[34] Massengill *et al*. did not find aCL or LA to be predictive of thrombotic complications.[39] The following case shows the difficulty in managing the complex set of problems SLE and APS can raise.

Case 3. A 13-year old girl presented with recurrent left ilio-femoral vein thrombosis. She had been diagnosed a year previously with a left leg deep vein thrombosis whilst on holiday abroad, one month after starting a continuous oral contraceptive pill regime to regulate her menstruation. She had received anticoagulation for 6 months and had developed the second episode just 2 months after stopping warfarin. She also complained of generalized joint pains with occasional dry and itchy eyes and a dry mouth from time to time. Her baseline laboratory investigations showed an aCL IgG level of 59.1 (normal value, <9.0 GPL U/mL); IgM level of 329.6 (normal value, <11 MPL U/mL); DRVVT 1.7 (normal value, <1.2) normalizing on correction and a positive anti nuclear antibody with anti-double stranded DNA level of 127 (normal value, 0-3- IU/ml). A congenital thrombophilia screen showed no abnormality.

The girl was treated with intravenous heparin and then switched to warfarin with a target INR range of 3-4. Hydroxychloroquine was started to control her arthralgia. At the age of 14 she had *N. meningitides* meningitis and septicemia and developed bilateral sensorineural deafness. This has responded well to cochlear implants. Now aged 17 she continues on warfarin. Her latest blood tests showed persistence of antiphospholipid antibodies with aCL IgG 41.5 (normal value, <20.1 GPL U/mL); IgM 24.5 (normal value, <11 MPL U/mL) and β2GPI antibody 27 (normal value, 0.0-15.0 IU/mL) and persisting positive lupus serology. Her mild symptoms are controlled with hydroxychloroquine.

This case shows how complex the management of SLE/APS can become in children. In 1998 Berube *et al.* discussed the relationship of aPL to thromboembolic events in 59 pediatric patients with SLE. Of the ten patients with a thrombotic event and positive for LA, eight were persistently positive for LA. The relationships between thrombotic events and persistent as well as transient presence of LA were both found to be highly significant, as seen in our patients. The relationship between thrombotic events and a persistent presence of aCL was not significant. Higher mean levels of IgG and IgM aCL were seen in patients with thrombosis compared to in those without thrombosis, but this was not statistically significant. The persistent presence of both LA and aCL did not strengthen the relationship between patients with thrombotic events and an aPL.[40]

Male *et al*. showed that acquired activated protein C resistance (defined as activated protein C resistance not associated with factor V Leiden) in association with aPL was associated with a higher risk of thrombosis in children than aPL alone, thus raising the suggestion that acquired activated protein C resistance may serve as a marker to identify LA-positive patients at high risk of a thrombotic event.[45] There is a case report of an 8-year old girl with SLE and secondary APS who developed a fatal myocardial infarction.[46] A high suspicion should be maintained to look for valvular lesions and evidence of sterile endocarditis in children with SLE and/or APS.

Discussion points

Cerebral APS

Cerebral ischemia in association with aPL has been reported by several investigators with a prevalence ranging from 16–76%.[47-52] Only factor V Leiden and aPL have been found to be significant risk factors for ischemic stroke in children.[51] In one study, aCL was found to be the most common prothrombotic factor in children with cerebral sino-venous thrombosis.[53]

Other neurological manifestations have been reported in children with APL or SLE with aPL, including chorea,[32,54-57] migraine,[31] spinal cord ischemia,[58] optic neuropathy,[59] retinal ischemia with visual impairment,[60] sudden onset profound deafness,[61] moyamoya disease 62 and partial seizures.[32]

A high prevalence of aPL has been reported in children with epilepsy. A study of 50 children with epilepsy showed a prevalence of aPL of 44% and these antibodies were more common in children with multiple seizure types often associated with symptomatic etiology, early onset and high frequency of seizures.[63] The significance of these autoantibodies is not clear. May microthrombotic events have led to an epileptic tendency in some ?

Hematologic manifestations

Hematologic manifestations in children with aPL or SLE with aPL include thrombocytopenia, autoimmune haemolytic anemia (Evans' syndrome in the presence of thrombocytopenia) and bleeding problems 64 which may be transient due to hypoprothrombinemia with the presence of antiprothrombin antibodies.[11,65,66] Thrombocytopenia in SLE may be APS-related or due to SLE itself.

Other diseases

The presence of aPL has also been reported in various diseases both autoimmune and non-autoimmune such as insulin-dependent diabetes mellitus, rheumatic fever, hemolytic-uremic syndrome, non-lupus nephropathy,[67-68] Perthes' disease,[25] complicated Henoch-Schonlein purpura,[69] purpura of ears in children with nephrotic syndrome on long term levamisole treatment[70] and atopic dermatitis.[43] Many children with aPL also have chronically cold hands and livedo reticularis.[43]

Management

Short term management

In the three cases presented, heparin/low molecular weight heparin and warfarin was used in two children (case 2 and 3) while the other child (case 1) was asymptomatic.

The INR range in the children receiving warfarin was 2-3 and 3-4 in case 2, who developed recurrent events on treatment and it is interesting to note that this latter child had cerebral APS and his target INR was initially <3, but like many adults he required an INR of 3-4 to prevent recurrent events.[71] There is paucity of information on the management of thrombotic events in children. Often, management decisions for children are extrapolated from recommendations for adults. Therapeutic interventions in children with deep vein thrombosis have included anticoagulation with heparin, thrombolytic therapy, oral anticoagulation therapy and other treatment modalities such as surgical removal of thrombi and removal of indwelling central venous lines.[1]

Likewise, there are few data on the safety of anticoagulation in children. We experienced no bleeding problems, and in the analysis of the Canadian registry there were no children who had any evidence of serious hemorrhagic complications secondary to therapy such as central nervous system bleeding or a requirement for hemorrhage or blood transfusion because of excessive bleeding.[1] Due to the association between aspirin use in children and Reye's syndrome, there has been a general reluctance to do randomized, controlled trials with this drug in children with thrombosis. Aspirin at low dose is used as prophylaxis in children with autoimmune diseases such as SLE along with aPL. Aspirin has also been used in the presence of mild hemolytic anemia and thrombocytopenia[43] in this group of patients. No studies have been reported on the use of other antiplatelet drugs, such as clopidogrel, in children.

Both unfractionated and low molecular weight heparins (LMWH) have been used in the acute management of thrombotic event in children.[1] The more recently introduced LMWH, with their ease of administration, reduced number of laboratory assays, nursing hours and reduced phlebotomy time, compare favorably with unfractionated heparin. In an earlier dose-finding trial,[72] larger doses of LMWH were required in neonates. A retrospective study reviewed the use of LMWH in children with acute, ischemic, non-hemorrhagic strokes.[73] Eight children who had experienced an ischemic stroke between 1991 and 2001 were treated with enoxaparin at a dose of either 1 mg/kg every 12 hours or, if they weighed more than 60 kg, 60 mg every 12 hours. The aim was to achieve the therapeutic adult level of 0.5 to 1.2 anti-Xa U/mL in children older than 2 months although anti-Xa levels were not monitored in the patients in this study. No major bleeding complications were observed and no new thrombi or extensions of thrombi occurred.

A study of 146 courses of treatment and 31 courses of prophylaxis for thromboembolic events in pediatric patients revealed efficacy and safety similar to that in adults with 17% of patients experiencing minor bleeding and 5% experiencing major bleeding.[74] Another study of 14 patients treated for active thrombosis and five treated prophylactically revealed that LMWH were at least as effective and safe as unfractionated heparin in pediatric patients immediately after a thrombotic event.[75] A review by Albisetti *et al.* concluded that LMWH seem to be an efficient and safe alternative to standard anticoagulation therapy with unfractionated heparin and oral anticoagulants for both treatment and prevention of thromboembolic events in children of varying ages and with different underlying disorders.[76]

Long term management

Oral anticoagulation

Due to its infrequent use, there is limited information on the effects of warfarin in children. Warfarin has been used in children with prosthetic cardiac valves, as thromboprophylaxis in autoimmune disorders and protein C or protein S deficiency, as treatment for deep vein thrombosis and to prevent clots in central venous catheters. Dosing should be adjusted to achieve a target INR, although the target range in children is not well established. INR values of 2-3 are recommended for most patients. Higher values have been used in children with prosthetic cardiac valves and hereditary thrombophilia. In a comprehensive review of warfarin use in infants and children,[77] an initial dosage of 0.1 mg/kg/day was suggested but another study on the effect of a loading regimen in children,[78] the authors concluded that it is impossible to predict the INR accurately after a given loading dose of warfarin and recommended a loading dose of 0.2 mg/kg/day for 2 days, provided that the prothrombin time after the first day is <14.0 seconds. Anticoagulation with heparin followed by oral anticoagulation is the standard treatment for an acute venous

or arterial thrombosis. The duration and intensity of anticoagulation in children with APS is debatable in the absence of evidence. An intermediate intensity anticoagulation treatment with a target INR of 2.0-2.5 has been suggested in children with APS.[27,28] In adults there is still debate about the appropriate INR targets for APS patients. Crowther *et al*. and the European WAPS (Warfarin in Antiphopspholipid Syndrome) suggested that target INR of 2-3 is satisfactory for adult patients.[79] However a critique of these studies was that they had few patients with arterial thrombosis and exclusion included those with recurrent events on warfarin. We recommend that those with previous venous disease should run a target INR of 2-3 but those with recurrent events on warfarin and/or arterial events should run a target INR of 3-4.[71]

In summary, there are many unresolved issues in managing aPL and APS in children. An improved understanding of the pathogenetic mechanisms as well as multicenter randomized controlled trials may provide answers to some of these issues.

A registry to enroll children with APL with and without clinical manifestations of the syndrome should also be considered due to the rarity of the condition and thus the difficulty in running clinical trials in this group of subjects.

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