IMPACT OF PERSISTENT ANTI-PHOSPHOLIPID ANTIBODIES ON RISK OF INCIDENT SYMPTOMATIC THROMBOEMBOLISM IN CHILDREN

Hale Ören

Dokuz Eylül University Faculty of Medicine, Department of Pediatric Hematology, İzmir, Turkey

The anti-phospholipid antibodies **(**aPLA) are immunglobulins (IgG, IgM, and IgA) directed against phospholipids and phospholipid binding proteins expressed on, or bound to, the surface of vascular endothelial cells or plateles. Lupus anticoagulants (LA), anti-cardiolipin (aCL) and anti-beta2glycoprotein I (aβ2GPI) antibodies are among subgroups of aPLAs. In the healthy child, the aPLAs are usually transient and present in low levels. A retrospective study in children (median age 5.3 years) found to have LA incidentally in preoperative screening showed that 84% were symptom free, 10% had bleeding symptoms, and 5% had thrombotic events. None of the children who were initially symptom-free developed thrombosis over a median follow-up of 2.9 years, nor did they develop autoimmune disease. aPLAs can be positive in otherwise healthy children secondary to vaccinations, drug use, or previous infections. In adults, aPLAs can be present in 8%-10% of the normal population and up to 40% of patients with SLE. The clinical significance of these antibodies is their association with thrombosis or recurrent fetal loss. This association constitutes the antiphospholipid syndrome (APS).

APS is an acquired autoimmune disease characterized by venous and/or arterial thrombosis in the presence of persistent production of circulating aPLAs. It can develop independently or associated with systemic diseases. The pediatric classification of APS is adapted from adult APS criteria. APS is diagnosed if a patient fulfills at least one clinical criteria and at least one of the laboratory criteria:

1. Clinical- one or more episodes of venous, arterial, or small-vessel thrombosis and/or pregnancy morbidity
   - Thrombosis is defined as unequivocal imaging or histologic evidence of thrombosis in any tissue or organ.
   - Pregnancy morbidity is defined as unexplained death at ≥10 weeks gestation of a morphologically normal fetus; or one or more premature births <34 weeks gestation due to placental insufficiency, preeclampsia, or eclampsia; or three or more pregnancy losses <10 week gestation unexplained by maternal or paternal chromosomal abnormalities or by maternal anatomic or hormonal causes.
2. Laboratory- the presence of aPLA on two or more occasions at least 12 weeks apart and no more than five years prior to clinical manifestations.
   - aPLA must be detected as IgG and/or IgM aCL in moderate or high titer (>40 units GPL or MPL or >99th percentile for the testing laboratory) or
   - Antibodies to ß2-GP-I of IgG or IgM isotype at a titer >99th percentile for the testing laboratory when tested according to recommended procedures or
   - LA activity detected according to published guidelines.

Primary APS, or that occurring in the absence of another underying disease is very rare in the pediatric population. In the largest published APS cohort, disease onset prior to age 15 years occurred in only 2.8% of patients (mean age was 10.7 years). Although thrombosis is one of the main complications of APS, children with aPLAs generally experience a lower rate of thrombotic events compared to adults with APS. The lower rate of thrombosis in

children may be related to higher levels of physiologic anticoagulants, lower levels of coagulation factors, and the absence of other thrombophilic risk factors such as smoking, atherosclerosis, oral contraseptive use, and pregnancy in this age range. Also, the healthier vascular endothelium in children may enhance the antithrombotic potential of the vessel wall.

In an Israeli study including 28 pediatric APS patients, it was shown that the thrombotic event may be spontaneous or due to predisposing factor, such as vascular stasis, trauma, surgery, use of oral contraceptives, and inherited thrombophilia. DVT of the lower limbs was the commonest thrombosis in pediatric APS patients in the Israeli cohort. A high rate of progression to lupus in girls with primary APS was found in that cohort. The study also found a high rate of inherited thrombophilias (45% of patients) and proposed that aPLAs may serve as a "second vascular hit" in children. Another pediatric APS registry reported earlier thrombotic manifestations in children with primary versus secondary APS. In this retrospective registry, 60% of the thromboembolic events reported were of venous thrombosis and thrombosis of arterial origin (32%) were mainly pediatric stroke.

According to guidelines, investigators are advised to classify APS patients in studies into one of the following categories: I. More than one laboratory criteria present (any combination); IIa. LA present alone; IIb. aCL antibody positive alone; IIc. aβ2GPI antibody positive alone. Patients with triple positive tests have a very significant association with thrombosis and high recurrence rate in the follow-up despite antithrombotic therapy. In patients with both aCL and aβ2GPI antibody positivity but negative for LA, thrombosis risk and recurrence rate for thrombosis is low. LA antibodies, specially those that target β2GPI have been shown to have the closest association with thrombosis in pediatric APS. Thus, the full laboratory profile of patients with suspected APS is essential.

Circulating persistant aPLA should be considered a thrombotic risk factor, with several other variables modulating the final clinical expression. Among these, the most important are the aPLA profile (type, level and persistence), the coexistence of other thrombotic risk factors, and the presence of an underlying autoimmune disease. Recently, Kenet et al reported the results of a systematic review and meta-analysis about persistent antiphospholipid antibodies and symptomatic thromboembolism in children. In total 1403 patients and 1667 population-based controls who were ≤18 years, a statistically significant association with a first thromboembolism was demonstrated for persistent aPLAs. This meta-analysis indicated that detection of persistent aPLAs is clinically meaningful in children with, or at risk for, thromboembolism.

In addition to thromboembolic events reported in childhood, rare cases of perinatal thrombosis in infants born to mothers with APS or aPLA have been reported. In this study, positive aPLA tests were detected in most infants and the clinical features demonstrated arterial and venous thromboses in multiple localizations being similar to adult APS patients. The contribution of aPLAs to the multifactorial nature of perinatal arterial stroke is not yet well known.

It should be in mind that pediatric thromboembolism is a multifactorial disorder and looking for underlying diseases and prothrombic risk factors are necessary. Apart from acquired thrombophilic risk factors such as aPLAs and LAs, inherited thrombophilic risk factors such as the mutations of the coagulation factor V and prothrombin II, protein C, protein S, or antithrombin deficiency have been established as additional risk factors for VTE events in children and adults. In three recent systemic reviews and meta-analysis including observational studies in pediatric patients with deep VTE and cerebrovascular occlusion, more than 70% of patients had at least one clinical risk factor. The pooled odds ratios showed statistically significant associations between factor V G1691A, factor II G20210A, protein C, protein S, or antithrombin deficiency, elevated lipoprotein(a), combined inherited thrombophilic and the presence of acquired LAs/aPLAs and VTE onset. The pooled odds ratio for persistants aPLAs/LAs was 6.6 for children with cerebrovascular occlusion and 4.9 for children with VTE. Thrombotic complications in APS patients are largely related with aPLA-mediated mechanisms (endothelial cell activation, inhibition of protein C and S activity, activation of platelets, increased tissue factor expression, and impairment of fibrinolytic activity).

There is no clear evidence to guide the optimal therapy for using primary prophylaxis in a patient who had persistently positive for aPLA testing, but had no thromboembolic event. Thromboprophylaxis is not recommended in asymptomatic aPLA positive children. Treatment in this group of

patient should focus on identification and removal of thrombophilic risk factors. Also, the presence of associated auto-immune diseases and other inherited and acquired risk factors for venous or arterial thrombosis should be carefully investigated and should be considered in therapeutic decisions in these patients. After the first event, long term anticoagulation is recommended in patients with APS. If pediatric patients additionally carrying genetic traits with chronic conditions associated with VTE, these children may require secondary anticoagulation in high risk situations, e.g. postoperatively, prolonged immobilization, or dehydration.

References

1. Kenet G, Aronis S, Berkun Y, et al. Impact of persistent antiphospholipid antibodies on risk of incident symptomatic thromboembolism in children: a systematic review and meta-analysis. Semin Thromb Hemost 2011;37:802-9.
2. Kenet G, Lütkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation 2010;121:1838-47.
3. Sen ES, Beresford MW, Avcin T, et al. How to use lupus anticoagulants. Arch Dis Child Educ Pract Ed 2012;0:1-6.
4. Nowak-Göttl U, JanssenV, Manner D, Kenet G. Venous thromboembolism in neonates and children-update 2013. Thrombosis Research 2013;131Suppl 1:S39–S41.
5. Tolbert J, Carpenter SL. Common acquired causes of thrombosis in children. Curr Probl Pediatr Adolesc Health Care 2013;43:169-77.
6. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med 2013;368:1033-44.
7. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295-306.
8. Pengo V, Ruffatti A, Legnani C, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011;118:4714-8.
9. Avcin T, Cimaz R, Rozman B. Ped-APS Registry Collaborative Group .The Ped-APS Registry: the antiphospholipid syndrome in childhood. Lupus 2009;18:894-9.
10. Kenet G, Lütkhoff L K, Albisetti M et al.. Impact of inherited thrombophilia on arterial ischemic stroke and cerebral sinovenous thrombosis in children: a systematic review and meta-analysis of observational studies. Circulation 2010;121:1838-47.
11. Gürgey A, Balta G, Gumruk F, Altay C. Analysis of some clinical and laboratory aspects of adolescent patients with thrombosis. Blood Coagul Fibrinolysis 2004;15:657-62.
12. Akar N. Factor V 1691 G-A mutation distribution in a healthy Turkish population. Turk J Hematol 2009;26: 9-11.
13. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. Pediatrics 2008;122:e1100-7.
14. Boffa M C, Lachassinne E. Infant perinatal thrombosis and antiphospholipid antibodies: a review. Lupus 2007;16:634-41.
15. Holzhauer S, Goldenberg NA, Junker R, et al. Inherited thrombophilia in children with venous thromboembolism and the familial risk of thromboembolism: an observational study. Blood. 2012;120:1510-5.
16. Lanzkowsky P. Manual of Pediatric Hematology and Oncology, fifth Ed. Elsevier, UK, 2011, pp 416-60.
17. Berkun Y, Padeh S, Barash J, et al. Antiphospholipid syndrome and recurrent thrombosis in children. Arthritis Rheum 2006;55:850-5.
18. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. Pediatrics 2008;122:e1100-7.
19. Boffa MCAM, Aurousseau MH, Lachassinne E, et al. European register of babies born to mothers with antiphospholipid syndrome. Lupus 2004;13:713-7.
20. Motta M, Boffa MC, Tincani A, et al. Follow-up of babies born to mothers with antiphospholipid syndrome: Preliminary data from the European neonatal registry. Lupus 2012;21:761-3.