

# Antiphospholipid Syndrome and Antiphospholipid Antibodies in Children: The Two Sides of the Coin

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The antiphospholipid syndrome is considered the most common acquired hypercoagulation state of autoimmune etiology, being clinical hallmarks in adult arterial and/or venous thrombosis and recurrent pregnancy loss [1]. APS may also affect younger patients, as estimated in a large cohort of 1000 European patients in 2.8% of whom the disease onset occurred before age 15 [2]. There are actually two different modalities: APS presenting in children as a passively acquired autoimmunity from the mother or as a de novo synthesis of antiphospholipid antibodies that leads to clinical manifestations.

Neonatal APS is a rare clinical entity characterized by passively acquired maternal antiphospholipid antibodies and thrombosis. Sixteen cases of perinatal thrombosis have been described so far [3]; in most of them additional risk factors were present (asphyxia, sepsis, arterial or venous catheter, congenital thrombophilia), modulating the thrombophilic action of aPL. Therefore, although maternal aPL do not seem sufficient to determine thrombosis in the neonate, it is recommended that aPL be checked in children born to mothers with these auto-

antibodies, especially in the presence of concomitant risk factors. With this aim, the need for a neonate-specific cutoff for aPL was addressed, and evaluation of anticardiolipin and anti- $\beta$ 2 glycoprotein I was performed in a large group of healthy newborn cord sera [4].

On the other hand, older children with a mature immune system may produce aPL and develop clinical manifestations resembling those of adult patients [5]. However, there are many differences between pediatric and adult APS, such as the absence of traditional acquired risk factors for thrombosis (smoking, obesity, use of contraceptives, etc.) and the absence of pregnancy-related morbidity. The APS in children should still be placed in the frame of systemic autoimmunity, with careful evaluation of other concomitant diseases, mostly systemic lupus erythematosus, where the presence of aPL may be associated with significant organ damage and, consequently, poorer outcome [6]. In fact, primary APS in a pediatric population may be as frequent as APS associated with SLE (Ped-APS Registry, a collaborative project of the European aPL Forum) [7], but, even if no signs or symptoms of SLE are present at disease onset, APS may be a forerunner of SLE and therefore children should be closely monitored [7].

In this issue of *IMAJ*, Zamora-Ustaran and colleagues [8] report their experience with pediatric APS in 32 Mexican children [8]. Supporting the hypothesis of an intimate connection between APS and SLE in children, the authors did not find any significant difference in clinical

manifestations between primary APS and SLE with APS. Hematological (Evans syndrome, thrombocytopenia and hemolytic anemia), neurological (epilepsy, migraine) and skin disorders (Raynaud's phenomenon and skin ulcers) were the most common non-thrombotic clinical manifestations, in agreement with the finding of the Ped-APS Registry. Interestingly, the prevalence of these manifestations is higher in the pediatric population as compared to adult APS. For instance, frequency of small vessel thrombosis is much higher in APS children than in adult APS patients [2]. Interestingly, this frequency is higher in Mexican children (44%) than in the European Ped-APS Registry (6%).

The interpretation of aPL in children becomes more difficult when there is no clinical event, such as thrombosis or other typical manifestations, or no previous diagnosis of a systemic autoimmune disease. In fact, it is well established how aPL may arise as a consequence of infections. Several studies demonstrated that viral and bacterial infections are able to induce the synthesis of aPL [9,10]. Infection-related aPL is usually transient and disappears within 2 or 3 months, otherwise these antibodies may become persistent, raising the question whether infections may be the major trigger for the development of aPL in autoimmune diseases [10]. In some cases, post-infectious aPL may become truly pathogenic and contribute to thrombotic events [9,10]. Interestingly, a remarkable similarity of aPL specificity was demonstrated in patients with parvovirus B19 infection and in patients with SLE [11].

If we consider that childhood is the period when the immune system is mostly

aPL = antiphospholipid antibodies

SLE = systemic lupus erythematosus

challenged by infections, we would expect a greater predisposition of children to produce aPL. Therefore, a critical issue is to identify cutoff values for aPL tests that are specific for the pediatric population. A Mexican study calculated pediatric cutoffs for aCL and anti-β2GPI as the 95th and 99th percentile in a cohort of 360 healthy children [12]. An Italian group addressed this problem by studying immunoglobulin G, M and A aCL levels in healthy children, the elderly and adults, demonstrating that there was a significant increase of IgG aCL and a decrease of IgA aCL in children [13]. Using adult cutoffs, 26% of children tested positive for IgG aCL. A similar finding was present in 61 apparently healthy children at school visits (11% IgG aCL and 7% IgG/IgA anti-β2GPI, mostly high titer) [14]. Our group showed that 55% of 1 year old healthy children born to mothers with systemic autoimmune diseases had positive anti-β2GPI [15].

The presence of aPL in apparently healthy children, without any sign or symptom suggestive of APS or other systemic autoimmune disease, may raise the hypothesis that these antibodies carry a different pathogenic potential from those aPL of patients with definite APS. The dissection of the fine specificity of anti-β2GPI has indeed brought many interesting considerations. β2GPI is a single-chain protein composed of five repeated sequences (domains). Domain 5 (D5) is critical for binding to anionic phospholipid membranes, while domain 1 (D1) projects into the extracellular space and can interact with other proteins/antibodies. Anti-D1 antibodies seem to be associated with thrombotic events and therefore to be more specific for APS [16]; on the other hand, anti-domain 4/5 has been detected in non-thrombotic conditions, like atherosclerosis [17], leprosy [18] and in children with atopic dermatitis [19]. Our group reported that 1 year old children born to mothers with systemic autoimmune diseases produce anti-β2GPI with preferential recognition for D4/5, dif-

ferently from APS patients who generally carry anti-D1 [20].

A de novo synthesis of anti-β2GPI in healthy children seems to be a common event, probably due to the exposure to infections, vaccines or nutritional exposure to β2GPI after weaning. The fine specificity of these antibodies, preferentially directed to domain 4/5 and different from that of APS patients, could account for their “not pathological” profile from the clinical point of view.

In conclusion, the interpretation of aPL antibodies in children has multiple faces. In the presence of a clinical event such as thrombosis, the presence of aPL may be indicative of an autoimmune disorder, and the performance of an extended panel of autoantibodies may be recommended for better classification and stratification of the patient’s prognosis. In fact, testing for all the aPL tests included in the classification criteria (lupus anticoagulant, aCL, anti-β2GPI) may be strongly suggested in children as in adult patients [21]. The search for other autoantibodies (antinuclear, anti-DNA, etc.) and specific clinical manifestations may switch the diagnosis toward SLE, bearing in mind that APS may be the forerunner in 30% of the cases [7]. The other side of the coin is the interpretation of aPL in apparently healthy children. These antibodies are generally ‘non-pathogenic’ and transient, as a consequence of environmental factors. Novel diagnostic tools that are able to identify the fine specificity of anti-β2GPI may be valuable in confirming the ‘not pathological’ nature of the antibodies or to shift the attention toward an ‘autoimmune’ setting.

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anti-β2GPI = anti-beta2 glycoprotein I antibodies

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