20 Antiphospholipid Syndrome in Children

Lori B. Tucker and Rolando Cimaz

Introduction

The scientific and clinical understanding of the phenomenon of antiphospholipid antibodies (aPL) has grown enormously since the first descriptions of an inhibitor of in vitro clotting tests in the serum of some patients with systemic lupus erythematosus (SLE) by Conley and Hartman [1], and the subsequent connection of these inhibitors to the occurrence of thromboses [2]. The lupus anticoagulant (LA) described in these early studies was found to be an antibody directed against phospholipids [3]. Extensive studies of adult populations have further identified the primary clinical associations of aPL: recurrent venous and arterial thromboses, thrombocytopenia, and recurrent fetal losses. Other less common or minor clinical findings described in adults with aPL include valvular heart disease, early myocardial infarction, pulmonary hypertension, renovascular microthrombotic disease, hemolytic anemia, transverse myelitis, chorea, and livedo reticularis [4].

In comparison to the enormous amount of information concerning aPL in adults, there has been relatively less research in the area of aPL in pediatrics [5–10]. aPL and their associated clinical features are now recognized to occur in children, although not commonly. Pathogenic mechanisms involved in pediatric antiphospholipid syndrome (APS) appear to be the same as in adults. However, because pediatric patients generally do not have many of the prothrombotic risk factors that can be present in adults, there are clearly differences in the spectrum of clinical findings. The presence of aPL and associated clinical events have been well-described in some children with SLE but occurs in those without SLE as well. In children, one of the most common reported clinical problems associated with aPL is that of cerebral ischemic stroke, in general a relatively rare occurrence in childhood. The less common thrombotic events in children found to have aPL have mainly been the subject of individual case reports.

This chapter will review the current state of knowledge of aPL in pediatrics. The focus of the chapter will be clinical; to date, there is no information to suggest that aPL in children are immunochemically different from those found in adults.

aPL in Healthy Children

aPL can be found in children without any discernible disease. Such naturally occurring aPL are usually present in low titer and could be the result of previous

infections and/or vaccinations, common events in the pediatric populations [11–13]. A number of studies have addressed the of aPL in healthy children. Findings have been variable, with results ranging from 2% to 82% of healthy children having measurable aPL [12, 14–19]. This wide range may be related to methodological issues such as inappropriate study groups, different definitions of cut-off values, and lack of uniformity in assay methods. Kontiainen et al looked for anticardiolipin antibodies (aCL) in 173 children who had minor surgical or psychosomatic problems and found a surprisingly high frequency of positive aCL (82%). However, a much lower percentage of these children (5%) had aCL of a moderate-high titer [45 G phospholipid units (GPL) or higher] [17]. The significance of such a high percentage of well children testing positive for low titer aCL is unknown. A similar study looking at children with functional disorders was performed by Rapizzi et al, who found positive aCL in 26% of the children in the study group [12]. In contrast, the other smaller previously mentioned studies have reported quite low frequencies of aCL (under 5%) in healthy children. Avèin et al have examined aPL in a group of 61 apparently healthy children at regular preventive visits and found aCL positivity in 11% and anti–β_2-glycoprotein I (β_2-GPI) in 7%, respectively [13]. In addition, mean values of IgG and IgM aCL were comparable between different age groups, while the mean value of IgA aCL was significantly higher in adult blood donors than in preschool children and adolescents. Moreover, it was found that the mean value of IgG anti–β_2-GPI was highest in preschool children and in this group it was significantly higher than in adolescents and blood donors. This novel finding was attributed by the authors to a possible faulty immune response to nutritional exposure to β_2-GPI in infancy. In particular, because β_2-GPI molecule has been remarkably conserved during the evolution of animal species [20], it is possible that ingestion of bovine β_2-GPI found in different milk or meat products could act as an oral immunization agent and induce transitory production of anti–β_2-GPI in infants, in whom the intestinal mucosa is more permissive for large molecules [21].

LA have also been described in healthy children [11, 22, 23]. They are usually discovered incidentally in pre-operative evaluations of children scheduled for surgeries such as tonsillectomy, who present with prolonged activated partial thromboplastin time (aPTT). In many cases no definite diagnosis is established, and the aPTT spontaneously corrects to the normal range. In one series, positive LA were identified in 7% of 61 apparently healthy children (Avèin et al, unpublished data), and, similarly to previous studies [11, 22, 23], no correlations between LA and aCL/anti–β_2-GPI were observed.

The clinical significance of positive aPL or LA discovered incidentally in children is unknown. In the study by Male et al [11], 95 children identified in a single pediatric tertiary care center and who were found to have a positive LA were followed over a 27-year time period. Eighty-four percent of these children had a LA diagnosed incidentally, in most cases during pre-operative screening tests, when routinely coagulation profiles are performed. One of these patients was found to have SLE. However, in follow up, none of these asymptomatic children developed bleeding, thrombosis, or autoimmune disease. This study suggests that most children with a LA discovered incidentally during laboratory screening will not have any clinical manifestations of APS, both at the time of diagnosis and in further follow up.

Studies of children with aPL that have included healthy controls are summarized in Table 20.1.