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ORIGINAL RESEARCH ARTICLE

# The impact of antiphospholipid antibodies in children with lupus nephritis

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**Abstract** *Background and objectives:* To evaluate the frequency of antiphospholipid antibodies (APLa) among patients with childhood lupus nephritis (cLN) and to assess their impact on long-term renal outcomes.
*Design and setting:* This is an observational hospital based study.
*Patients and methods:* Patients with cLN diagnosed by renal biopsy seen between January 2002 and June 2014 were included. APLa positivity was defined if detection was positive on 2 occasions 6—12 weeks apart during their follow up. Demographic features, age at disease onset, disease duration, follow-up duration and clinical and laboratory variables at the time of renal biopsy were collected. The renal biopsy was reviewed for the nephritis class, microthrombi, activity and chronicity indices. Renal outcome measures included the serum creatinine levels, protein/creatinine ratio and end stage renal disease (ESRD).
*Results:* Fifty-nine, (49 female) patients with a mean age of 19.8 years and mean disease duration of 6.8 years were involved. APLa were detected in 46 (78%) patients. Twenty-two patients had class IV nephritis, which was more prevalent in APLa positive patients. The frequencies of class III and V nephritis was similar in 10 patients in each class (7 patients in each class with APLa). The presence of APLa did not correlate with nephritis activity or the chronicity indices. Microthrombosis was found in 10 patients, and 8 of them had APLa. Patients with APLa had a higher frequency of elevated serum creatinine and hypertension, 9 developed ESRD, and 7 had APLa. There was no statistically significant association between the presence of APLa and the accrual damage index and clinical manifestations. Furthermore, there was no association between APLa and other autoantibodies.

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*Conclusion:* The frequency of APLa in cLN was high. While the association is not statistically significant, APLa positive patients tend to develop renal microthrombi and are probably at higher risk of ESRD.


## 1. Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease, and while it is predominantly a disease of young women, childhood SLE represents approximately 20% of all SLE cases [1,2]. The onset and clinical manifestations of childhood SLE are often aggressive, with widespread organ involvement [3,4]. Childhood lupus nephritis (cLN) occurs in almost 30–60% of cases, and it may present with proteinuria, haematuria, hypertension, and occasionally, renal impairment. Furthermore, the renal outcomes reported by several studies suggest that it is more frequent and aggressive compared to the adult disease [5,6].

In general, cLN remains indicative of poor outcomes, which is especially true of diffuse proliferative glomerulonephritis, the most severe type, which is most frequently associated with the development of end stage renal disease (ESRD) or death [7,8].

Like other autoimmune diseases, the aetiology of SLE remains unknown. However, the primary pathology results from massive autoantibody production followed by immune complex deposition. Among these autoantibodies, antiphospholipid antibodies (APLa), which are a heterogeneous group of pathogenic autoantibodies, are directed against negatively phospholipid-binding proteins. APLa, including lupus anticoagulant (LAC), anticardiolipin antibody (aCL), and anti-β2 glycoprotein I (β2GPI) antibody, are frequently observed in SLE patients and are associated with the increased risk and frequency of thrombosis at different sites [9,10]. A variety of renal manifestations, including intra-glomerular capillary thrombosis and nephropathy, have been reported in APLa positive SLE patients. However, the true significance of APLa on the progression of lupus nephritis is still controversial [11–14].

In this study, we evaluated the frequency of APLa among patients with cLN and assessed the impact of APLa on long-term renal outcomes. To the best of our knowledge, there is no available published data from the Middle East about the impact of APLa in cLN.

## 2. Patients and methods

This observational study was composed of all of the patients with childhood onset SLE with biopsy-proven nephritis who were followed at the lupus clinic at the King Faisal Specialist Hospital and Research Centre (KFSHRC)-Riyadh, Saudi Arabia, between January 2002 and June 2014. All included patients fulfilled the definition of SLE using the Systemic Lupus International Collaborating Clinic classification criteria for systemic lupus erythematosus [15].

The patients were classified APLa positive if they had at least one of APLa (aCL IgG >15 GPL/mL, IgM >7 MPL/mL, β2GPI IgA >3 SA U/mL, β2GPI IgG >10 SG U/mL, or β2GPI IgM >12 SM U/mL) detected on 2 occasions 6–12 weeks apart during their follow up. The measurement of APLa was performed by Automated ELISA (ETI -Max 3000) using commercial kits (Diasorin kit, Saluggia, Italy).

A renal histopathologist reviewed all of the renal biopsies independently without knowledge of the APLa status. The histopathology assessment included a classification of the nephritis class according to the lupus nephritis classification system of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) and the activity and chronicity of nephritis and the presence of microthrombosis [16].

Demographic data, age at disease onset, disease duration, and follow up duration data were extracted from patients' medical records. Clinical and laboratory data, including serum urea and creatinine, urinalysis, protein/creatinine ratio, antinuclear antibody (ANA), anti-double stranded DNA antibody (ds-DNA), and serum complement ($C_3$, $C_4$) levels, were collected at the time of the renal biopsy.

The renal outcomes were assessed according to the serum creatinine level, the protein/creatinine ratio, and the ESRD. The previous items are indicated in the pediatric adaptation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index score (pSDI) [7].

All of the collected data were analyzed confidentially, and no identifying data were needed. All of the clinical and laboratory assessments were a result of routine medical care, and informed consent was obtained at the time of the renal biopsy. The proposal was approved by the Research Affairs Council at KFSHRC.

## 3. Statistical methods

To determine the impact of APLa on nephritis, we compared APLa positive cLN patients with APLa negative cLN patients. SAS 9.2 (SAS Institute Inc., Cary, NC, USA) software was used for the statistical analyses. The variables were compared using 2-sample *t*-tests, chi-square tests and Fisher's exact tests. The results are expressed as the mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Regression analysis was carried out to examine the impact of APLa on long-term renal outcomes. *P* values $< .05$ were considered significant.

## 4. Results

A total of 59 (49 females) patients with biopsy-proven nephritis were included, with a mean age of 19.8 years