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ORIGINAL ARTICLE

Serum immunoglobulin E level in children with nephrotic syndrome

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ABSTRACT

Background and objective: The most supported theory for Nephrotic Syndrome (NS) etiology is that it is immune-mediated. This study aims to assess the level of serum IgE in children with Steroid Sensitive NS (SSNS) at relapse and remission, and its correlation with the presence of atopy.

Methods: This cross-sectional study was approved by the Department of Pediatrics, College of Medicine, Al-Nahrain University (Baghdad, Iraq) and conducted at Al-Imamain Al-Kadhimain Medical City (Baghdad, Iraq), and Child Central Teaching Hospital (Baghdad, Iraq), and included 31 children SSNS. The data collected was: age, sex, residency, onset of NS, response to steroid, frequency of relapses, and the history of atopy of the patient and his relatives. Serum IgE level was measured during relapse for all patients and for 9 patients while in remission.

Results: Atopy was present in 18 (58.06%) of patients. The median serum IgE level was 295.5 IU/mL (range 54-2864 IU/mL) in relapse, which is significantly higher (P-value =0.006) than in remission 228.5 IU/mL (range 62-2069 IU/mL). Median serum level of IgE in patients with atopy was 290.5 IU/mL (range 24-2864 IU/mL) which was higher than that of patients without atopy (median 231 IU/mL, range 23-1314 IU/m) (*P*-value = 0.029). Patients required longer period to respond to steroid therapy (>10 days) had a significantly higher median of IgE (341 IU/mL) than those who required <10 days to respond (161 IU/mL) (*P*-value =0.045).

Conclusions: Increased IgE level is documented during relapse and in atopic children with SSNS. Longer duration to respond to steroid therapy is associated significantly with higher serum IgE during relapse.

Keywords atopy, children, IgE, nephrotic syndrome, relapse

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INTRODUCTION

Nephrotic syndrome (NS) is the commonest glomerular disease affecting children. The characteristic features of this syndrome include massive proteinuria, hyperlipidemia,

hypoalbuminemia and peripheral edema.[1,2] According to several studies carried out worldwide, the incidence and prevalence of NS was 1.5 to 16.9% and 16 cases per 100,000 children, respectively.[1,2]

Three types of NS have been identified: primary or minimal change NS (MCNS), secondary NS and congenital NS. The first type is the most common one accounting for about 80% of all NS cases and occurs at any age. It commonly affects males more than females. More than 90% of children with MCNS respond to treatment with oral corticosteroids, and accordingly, known to have steroid-sensitive NS.[2,3] Pathologically, MCNS considered as a T cell-mediated disorder that associated with podocyte dysfunction and proteinuria.[1]

About 30% of the SSNS cases are presented with allergic symptoms such as asthma, atopic dermatitis, allergic rhinitis, and urticaria. In this regard, NS can be activated by several inhaled allergens like dust, mold and pollens.[3] The term "atopy" is used to define these reactions which are mediated by immunoglobulin E (IgE) from activated B cells. Activated T helper 2 (Th2) cells produce two main cytokines, IL-4 and IL-13, that induce class switching from IgG to IgE production.[4] Indeed, some studies have revealed a strong relationship between SSNS and atopy accompanied by high serum levels of IgE antibodies.[5] Furthermore, IL-13 was found to induce proteinuria in MCNS patients through direct upregulation of CD80 expression on the podocyte.[6–8]

This study aims to assess the level of serum IgE in children with SSNS at relapse and remission, and its correlation with demographic, clinical factors and presence of atopy in those children.

MATERIALS AND METHODS

Study design and patients

A cross-sectional study was conducted at the Department of Pediatrics (College of Medicine, Al-Nahrain University), Al-Imamain Al-Kadhimain Medical City, and Child Central Teaching Hospital (Baghdad, Iraq). The study started on October 1, 2019 until April 30, 2020. It included children of both genders with age range of 1-15 years, who were diagnosed as SSNS and were admitted to Pediatrics Ward or visiting the Pediatric Nephrology Consultation Clinic for follow up.

The following definitions were applied in this study: NS when proteinuria greater than 40 mg/h/m^2 or greater than 50 mg/kg/day, and hypoalbuminemia greater than 25 g/l with or without edema. The SSNS when steroid therapy achieved complete remission. The relapse is when Albustix reveal +++ result for three consecutive days after remission. And, the remission is when Albustix result is zero or trace for three consecutive days. Frequent relapses: when two or more relapses occur within six months of initial response or four or more relapses within one year period. Finally, infrequent relapsing was defined as less than two relapses during 6 months of the initial response or less than four relapses for any year thereafter.[9–11]

A well-formed questionnaire was prepared by the researchers to fill with the following data: Age, sex, residency, onset of NS, response to steroid, frequency of relapses, history of atopy in the patient and his relatives. Atopy was regarded as positive if one or more than one of the following diseases were present in the patient himself or one or more than one of his relatives: asthma, allergic rhinitis, eczema. Patients with relapse were involved in the study, given follow up appointment to confirm remission. Verbal consent from patients and their parents was collected to participate in this work. Patients less than one year of age, those with secondary and congenital NS were excluded from the study.

Laboratory work

In relapse, before starting steroid therapy, an extra 2 mL of blood was aspirated from each patient along with that required for his/her routine investigations. The second sample, in remission, was taken only from 9 patients. Unfortunately, the others were not strict to their follow up visits when got remitted. Estimation of serum IgE level was done in an External Private Laboratory using TOSOH device (Japan) which works on the basis of immune-enzymometric assay. The kit designed for IgE quantification using TOSOH device was used and the manfacturer's instructions were followed. Briefly, 10 μl of serum is used to estimate the IgE level by end points method. Reference values for IgE level were 1.5 – 144 IU/mL.[12]

Statistical analysis

All statistical analyses were performed using SPSS v19.0 (IBM, NY, USA). Quantitative variables were expressed as mean and standard deviation as well as range, while discrete variables were expressed as number and percentages. Due to small sample size, data regarding IgE levels were subjected to normality Shapiro Wilk test and were found to be non-normally distributed. Therefore, Wilcoxon matched-pair signed-rank was used to compare the median between relapse and remission statuses, while Mann Whitney U test was used to examine the association of different factors with IgE level. The correlation between IgE level and other quantitative variables was explored using Pearson's correlation test. A p-value of $\leq$0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the patients

The total number of patients enrolled in this study was 31 children with SSNS. Mean age of them was 8.52$\pm$3.46 years (range 3-15 years). The vast majority of patients (i.e. 28 or 90.32%) were males and the male:female ratio was 9:1. Mean age at diagnosis of NS

was 4.56±2.28 years. Frequent relapses were reported in 13 patients (41.94%) while the other 18 children (58.06%) had infrequent relapses. More than half of patients (58.06%) were suffering from atopy, while family history of this disorder was reported in 14 cases (45.16%). Patients, overall, required 1-3 weeks in order to respond to steroid therapy with an average of 1.74±0.73 weeks (Table 1).

Table 1 **Patients' characteristics and demographic data (n=31).**

Variables	Values
Age (years)[a]	8.52±3.46 (3.0-15.0)
Gender	
Male	28(90.32%)
Female	3(9.68%)
Age at diagnosis (year)[a]	4.56±2.28 (1.0-11.0)
Relapse	
Frequent	13(41.94%)
Infrequent	18(58.06%)
Personal a topy	
Yes	18(58.06%)
No	13(41.94%)
Family history of atopy	
Yes	14(45.16%)
No	17(54.84%)
Response to steroid[a] **(weeks)**	1.74±0.73 (1.0-3.0)

[a] mean±SD (range)

As shown in Table 2, atopy was reported in 18 out of the 31 patients. The atopy distribution was as follow: asthma presents in 2(11.10%) of patients, eczema in 4(22.20%) of patients and allergic rhinitis in 12(66.70%) of patients. None of the patients showed two types of atopy at the same time. Distribution of atopy among 14 family members was as following: asthma presents in 2 persons (14.29%), eczema in 3(21.43%) and allergic rhinitis in 9 persons (64.28%) of the family members. No family members showed combined types of atopy.

Serum level of IgE

Data regarding serum level of IgE were found to be non-normally distributed. Accordingly, Wilcoxon matched-pair signed-rank was used to compare the median between relapse and remission statuses. The results are depicted in Figure 1. Median serum level of IgE at relapse was 295.5 IU/mL (range 54-2864 IU/mL) which was higher than that at remission (median 228.5 IU/mL, range 62-2069 IU/mL) with highly significant difference (p-value = 0.006).

Table 2 Presence of atopy among patients and family members.

	Patients	
Atopy	**No.**	**%**
Asthma	2	11.10
Eczema	4	22.20
Allergic rhinitis	12	66.70
Total	18	100%
	Family members	
Atopy	**N o.**	**%**
Asthma	2	14.29
Eczema	3	21.43
Allergic rhinitis	9	64.28
Total	14	100

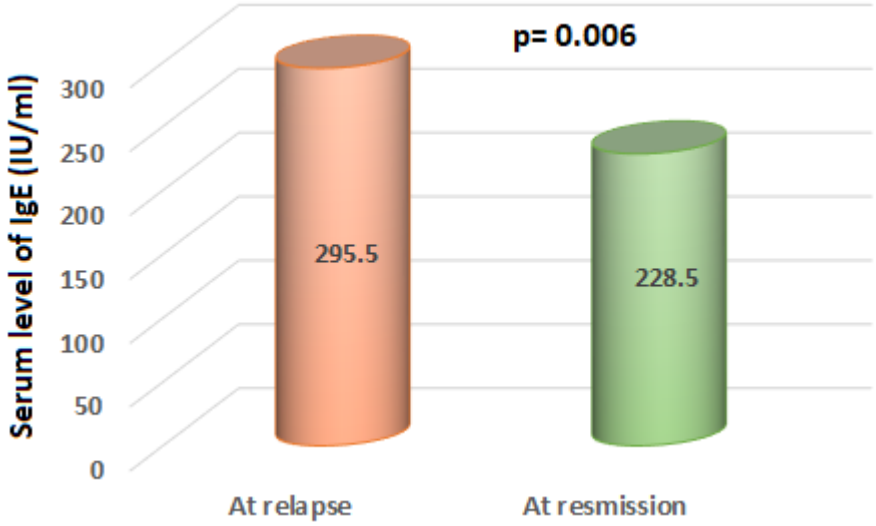

Figure 1 Median serum level of IgE at relapse and remission.

The association between IgE serum level and demographic-clinical characteristics

For this analysis, each continuous variable was categorized into two categories using appropriate cut-off value. Median serum level of IgE at relapse was higher in patients with older age (>8 years), male gender, frequent relapse, longer onset (> 4.5 years) and negative family history of atopy than patients with younger age ($\leq$ 8 years), female gender, infrequent relapse, shorter onset ($\leq$ 4.5 years) and positive family history of atopy. However, the differences were no significant.

In contrast, patients required longer period to respond to steroid therapy (>10 days) had significantly higher median of IgE (341 IU/mL) than those who required <10 days to

respond to steroid therapy (161 IU/mL) (p-value =0.045) as shown in Table 3.

Table 3 **The association between IgE serum level and clinico-demographic characteristics of patients.**

Variables	At relapse	*P*-value
Age (years)		
≤8	260(51-2864)	0.984
>8	277.5(23-2108)	
Gender		
Male	272(23-2864)	0.545
Female	231(24-1112)	
Relapse		
Infrequent Frequent	258(23-2864)	0.352
	278.5(54-2108)	
Onset (years)		
≤4.5	257.5(23-2864)	0.828
>4.5	260(54-2108)	
Family history of atopy		
No	284(23-1787)	0.799
Yes	244.5(24-110)	
Response to steroid (days)		
≤10	161(51-2108)	0.045
>10	341(23-2864)	

The association of IgE serum level and Atopy

Median serum level of IgE in patients with atopy was 290.5 IU/mL (range 24-2864 IU/mL) which was higher than that of patients without atopy (median 231 IU/mL, range 23-1314 IU/m) with a significant difference (p-value = 0.029) (Figure 2).

Correlation between IgE and other variables

Pearson's correlation was used to explore the possible correlation between serum concentration of IgE at relapse with age, onset and time required to response to steroid. There was a positive significant correlation between serum IgE and response to steroid (r= 0.427, p= 0.017) as shown in Figure 3 and Table 4.

DISCUSSION

The present study aimed to evaluate the association of serum IgE at relapse and remission with demographic and clinical features in children with SSNS. One interesting finding in the present study was the presence of atopy in 18(58%) of the patients. The prevalence of atopy among patients with NS ranges between 10% and 50% in different studies, while most

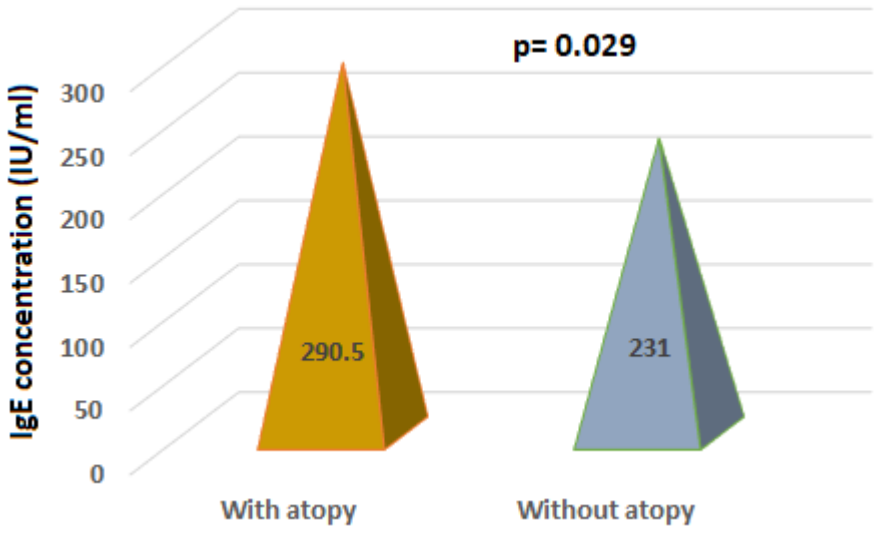

Figure 2 Median serum level ofIgE in patients with and without atopy

Table 4 **Pearson's correlation between IgE at relapse with age, onset and response to steroid variables in NS patients.**

	At relapse	
Variables	**r**	***P* -value**
Age	-0.057	0.761
Onset	-0.124	0.508
Response to steroid	0.427	0.017

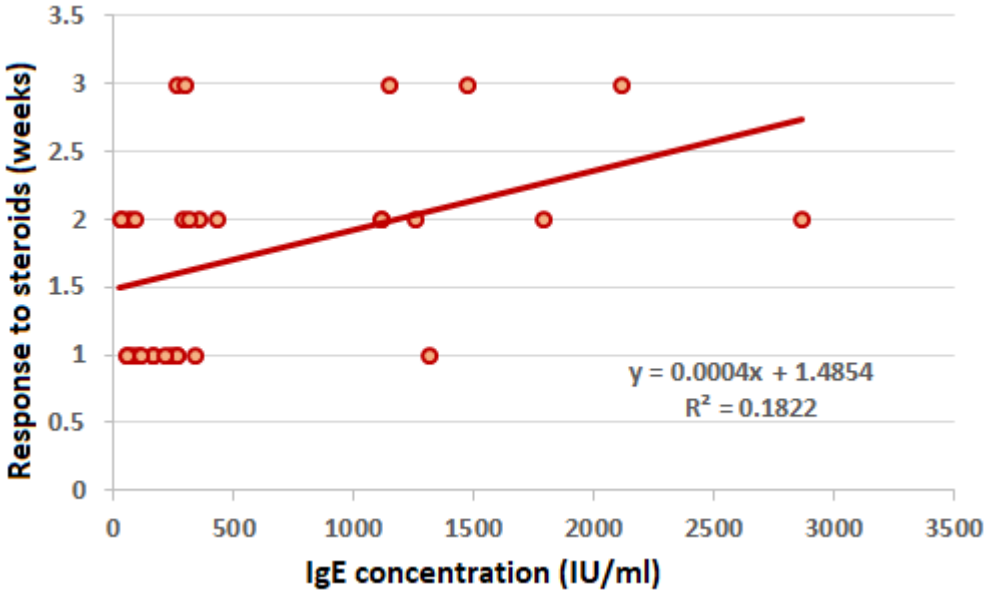

Figure 3 **Regression line between IgE concentration at relapse and response to steroids.**

studies reported a range of 30% to 40%.[13,14] The different rates related to patients' histories of atopy seem to be resulting from the use of different criteria in defining the condition. In a previous Iraqi study, the relatively high level of atopy was attributed to several factors, the most important of which are the high levels of pollutants and predisposing genetic factors.[6] However, these factors were not studied in this work.

The other finding in the present study was that serum level of IgE at relapse was significantly higher than that at remission. This result is in accordance with almost all studies in this regard. In a Turkish study, Yilmaz et al.[13] investigated the serum IgE in 30 children with SSNS. They demonstrated that the median IgE level at relapse was 342.5 IU/mL (range 60.3-495 IU/mL) compared with 62.5 IU/mL (range 34.8-210 IU/mL) in remission with a significant difference. In another study, Mishra et al.[14] estimated IgE and IL-13 levels of 40 Indian patients with SSNS and 16 healthy controls. Mean serum IgE was 86.1±31.9 IU/mL, 154.1±10.3 IU/mL and 55.9±24.7 IU/mL in controls, relapse and remission, respectively. In China, Tan et al.[15] reported a median of 709 IU/mL (range 516-1230 IU/mL) of IgE at relapse compared to 164 IU/mL (range 39-526 IU/mL) in remission among patients with SSNS. Almost similar results were obtained by Salsano et al.[16] In another study included 53 Iraqi children with NS, found that median serum IgE was 110.43 IU/mL during relapse compared to 45.12 IU/mL during remission (p-value was 0.003).[17] Conversely, Youn et al.[18] showed that raised serum IgE persisted during remission, and the authors concluded that it reflected abnormal immune status even in the disease free state.

The explanation for this elevation in serum IgE during relapse is mainly refers to the role of immune response in the pathogenesis of NS. The possible link between aberrant T cell response and glomerular dysfunction was proposed before more than 30 years ago. Asmaningsih et al.[19] demonstrated that infusion of T lymphocytes obtained from patients with MCNS relapse caused proteinuria in rats. Such findings indicate that a circulating factor is produced by activated immune cells which interferes with the glomerular filtration.[20]

Another interesting finding in the present study was the positive association of IgE level with delayed response to steroid. Some studies indicated the refractory for steroid response in NS patients with high level of IgE.[13,15] The production of IgE by activated B cells needs two signals: the releasing of IL-4 and IL-13 from Th2 cells, and the interaction of the B-cell surface antigen CD40 with its CD40 ligand on T cells.[21] On the other hand, prolonged treatment with steroids has an impact on the IgE level and that hydrocortisone increases the production of IgE in mature B-cells in non-atopic individuals through the mediation of IL-4.[14]

According to the results of the present study, median serum level of IgE in patients with atopy was significantly higher than that of patients without atopy. This association between atopy and serum IgE in NS was a debatable issue. Several studies reported that serum IgE levels were higher in atopic than non-atopic SSNS children, which is in accordance with the present study.[17,19] However, in other studies, no significant difference was found between those with and without atopy in terms of their IgE levels.[15,16] This disparity between different studies can be related to the factors that may associate with IgE production. The most important of these are the type of atopy (asthma, eczema, atopic dermatitis or others),

demographic characteristics of the patients (such as age, gender, family history). Ethnicity and the presence of coinfection like parasitic diseases. The association of serum IgE with atopy in SSNS patients during nephrotic relapse implies that it not just perturbation in the humoral immune response in this phase of the disease. Rather, the presence of atopy with an elevated IgE has a direct role in the pathogenesis of the disease.[17]

Study limitation was small sample size, however; it highlighted the importance of atopy, and serum IgE level relation with NS. This will guide future studies in this field.[5]

CONCLUSIONS

The increased IgE level is documented during relapse and atopic children with SSNS. Longer duration to respond to steroid therapy is associated significantly with higher serum IgE during relapse.

ABBREVIATIONS

IgE, immunoglobulin E; MCNS, minimal change nephrotic syndrome; NS, nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome.

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DECLARATIONS

Authors' contributions

Conceptualization, data curation, formal analysis, project administration, investigation, methodology, resources, and software: ShHA, SHA, LQH. Funding acquisition: N/A. Supervision: SHA. Validation, visualization, writing-original draft, review, and editing: ShHA, SHA, LQH. All authors reviewed and approved the final version of the manuscript before publishing.

Conflict of interest

The authors declare that there are no conflicts of interest.

Ethical approvals

This study was approved by the Instiutional Review Board of the College of Medicine, Al-Nahrain University. In addition, it has been conducted in accordance to the terms of the Code of Ethics in Research of Ministry of Health in Iraq and the Iraqi Board of Medical Specializations Ethics Committee. No.: 3014 on 29-12-2020.

Data availability

The data that support the findings of this study is available from the corresponding author, upon reasonable request.

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