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Original article

Serum IgE Level in Children with Idiopathic Nephrotic Syndrome

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Abstract:

Background: Nephrotic syndrome (NS) is one of the most common chronic renal diseases in children, characterized by selective proteinuria, hypoalbuminemia, hyperlipidemia, and edema. This study aimed to assess the level of serum immune globulin E (IgE) in children with idiopathic nephrotic syndrome (INS) as a marker for response to therapy. **Methods:** This prospective study was conducted in the Pediatric Department, Benha University Hospital. The study consisted of two groups: Group I: Fifty children suffering from idiopathic nephrotic syndrome treated with corticosteroid. Group II: Fifteen healthy children as a control group. All included children were subjected to full history taking, complete clinical examination, and laboratory assessment as complete blood count (CBC), absolute eosinophilic count, serum urea & creatinine, serum level of IgE, serum electrolytes, and 24 h's protein in urine. **Results:** About three-quarters of group I were steroid sensitive (72.0%), and one-quarter were steroid-resistant (28.0%), median serum IgE was significantly higher (p= 0.001) in group I (275.55) than group II (100.5). Median serum IgE was significantly higher (p= 0.001) in the steroid-resistant group (911.85) than the steroid-sensitive (164.5). ROC analysis was done for differentiating between nephrotic patients and controls. For IgE, it revealed a significant area under curve (AUC) of 0.788. **Conclusion:** Significantly higher serum IgE levels were associated with nephrotic syndrome and more prominently in patients with steroid-resistant nephrotic syndrome (SRNS).

Keywords: Children; INS; IgE; Eosinophilic count.

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Introduction

Nephrotic syndrome is an immune mediated kidney disease characterized by massive proteinuria (urinary total protein > l g/m^2) per day or urinary spot (protein/creatinine ratio >200 mg/mmol), hypoalbuminemia (serum albumin < 2.5 g/dl), edema and hypercholesterolemia (serum cholesterol > 200 mg/dl) [(1)].

The most common cause of nephrotic syndrome in children is idiopathic nephrotic syndrome (INS), also called nephrosis, which is defined by the combination of nephrotic syndrome and nonspecific histological abnormalities of the glomeruli including minimal changes, focal segmental glomerular sclerosis (FSGS) and diffuse mesangial proliferation [(2)].

Many agents or conditions have been reported to be associated with INS such as infectious diseases, drugs, allergy, vaccinations and malignancies. The question remains whether these agents or conditions are real causes, or simple coincidences or precipitating factors [(3)].

Allergy is associated with up to 30% of cases. The allergens reported include fungi, pollens, house dust, jellyfish stings, bee stings and cat fur. [(2)]. Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin (IgE) antibodies to the antigens that trigger their illness that manifests as hyper-responsiveness in target organs such as the lung, skin, gastrointestinal tract and nose [(4)].

There has not been an easily available and affordable marker that can be used to predict initially the responsiveness of the patients to corticosteroid therapy. So, measuring the level of serum immunoglobulin IgE in patients with nephrotic syndrome and studying the relationship between its level and the steroid responsiveness of the disease may implicate the effectiveness of serum immunoglobulin E in predicting steroid responsiveness in nephrotic syndrome patients [(5)].

The study aimed to assess the level of serum immunoglobulin (E) in children with idiopathic nephrotic syndrome as a marker for response to therapy.

Patients and Methods

This prospective study was conducted in the Pediatric Department, Benha University Hospital. During the period from October 2019 to October 2020.

The study was approved by the local ethics committee of faculty of medicine, Benha University (approval number=MS-28-10-2019). Oral and written consents were taken from the patients' parents that participated in this study.

The study consisted of two groups: Group I: Fifty children suffering from idiopathic nephrotic syndrome treated with corticosteroid and Group II: Fifteen healthy children as a control group.

Inclusion criteria

- Age: from 1 to 12 years old.
- Sex: both sexes.
- Idiopathic nephrotic syndrome.

Exclusion criteria

- Nephrotic syndrome with infection.
- Gross hematuria.
- Secondary nephrotic syndrome.

All included children were subjected to full history taking, complete clinical examination, and laboratory assessment as complete blood count (CBC), absolute eosinophilic count, serum urea & creatinine, serum IgE, serum electrolytes, and 24 h's protein in urine.

Statistical methods

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United States). Data normality was assessed using the Shapiro-Wilk test and direct data visualization methods. According to normality testing, numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Comparisons

between both groups were done using independent t-test or Mann-Whitney U test for normally and non-normally distributed numerical data, respectively. Categorical data were compared using the Chi-square test. Correlation analyses were done between IgE or AEC and other parameters using Spearman's correlation. "r" is the correlation coefficient. It ranges from -1 to +1. Minus one indicates a strong negative correlation, +1 indicates a strong positive correlation, and zero indicates no correlation. ROC analyses were done for IgE and AEC for differentiation between nephrotic patients and controls, and between steroid-resistant and sensitive patients. Area Under Curve (AUC) with 95% confidence interval, best cutoff point, and diagnostic indices were calculated. All *p* values were two-sided. *p* values less than 0.05 were considered significant.

Results

This prospective study was conducted in the Pediatric Department, Benha University Hospital. The study consisted of two groups: Group I: Fifty children suffering from idiopathic nephrotic syndrome treated with corticosteroid. Group II**:** Fifteen healthy children as a control group.

The body weight was significantly higher (p>0.001) in group I (21.4 ±5.4 kg) than in group II (17.5 ±2.4 kg). Age, gender and height showed no significant difference (p>0.05) between both groups (Table, 1).

The mean hemoglobin and hematocrit were significantly lower (p>0.001) in group I (9.9 g/dl & 28.6%) than group II (11.4 g/dl & 33%). The mean total leucocytic count (TLC) was significantly higher (p>0.001) in group I ($8.1x10^3$/mm3) than group II ($6.8x10^3$/mm3). The median absolute eosinophil count (AEC) was significantly higher (p>0.001) in group I (0.52 $x10^3$/mm3) than in group II (0.3 $x10^3$/mm3). The mean platelet count was significantly lower (p>0.001) in group I (273 $x10^3$/mm3) than in group II (294 $x10^3$/mm3) (Table, 2).

The median serum IgE was significantly higher (p>0.001) in group I (275.55 IU/mL) than group II (100.5 IU/mL). (Figure, 1). There was no significant difference (p=0.566) between both groups regarding the presence of atopic diseases.

About three-quarters of group I were steroid sensitive (72.0%), and about one-quarter was steroid-resistant (28.0%) (Figure, 2).

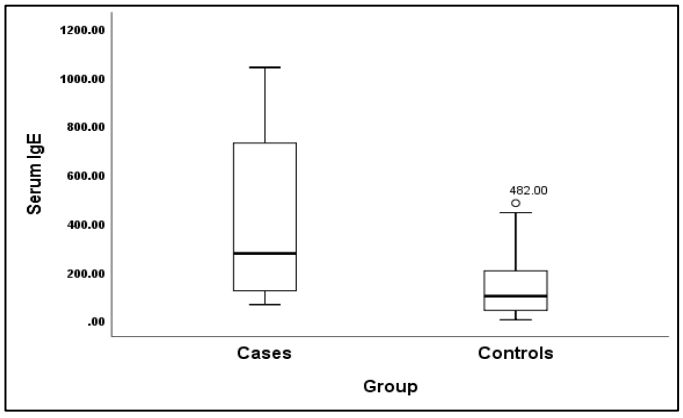

Figure (1) Serum IgE (IU/ml) in both groups.

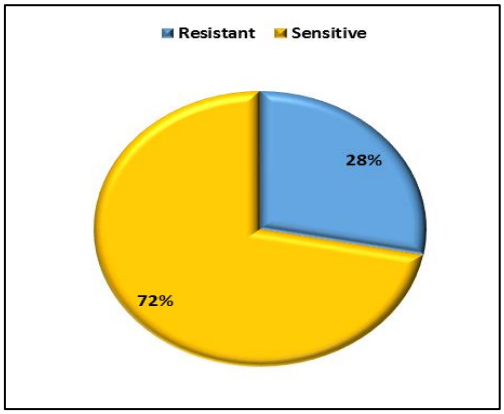

Figure (2) Steroid response in the cases group

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Table (1) General characteristics in both groups.

Characteristics		Group I (n = 50)	Group II (n = 15)	*p* value
Age (years)	Mean ±SD	4.8 ±2	4.7 ±1.2	0.856
Gender	Males: n (%)	33 (66.0)	8 (53.3)	0.373
	Females: n (%)	17 (34.0)	7 (46.7)	
Weight (kg)	Mean ±SD	21.4 ±5.4	17.5 ±2.4	<0.001
Height (cm)	Mean ±SD	106 ±13.9	106.3 ±8.2	0.927

Independent t-test was used for age; chi-square test was used for categorical variables; non-significant= $p>0.05$; highly significant= $p<0.001$; SD= standard deviation.

Table (2) Complete blood count (CBC) in both groups.

CBC		Group I (n = 50)	Group II (n = 15)	*p* value
Hemoglobin (g/dl)	Mean ±SD	9.9 ±1.1	11.4 ±0.7	<0.001
Hematocrit (%)	Mean ±SD	28.6 ±3.2	33.3 ±1.7	<0.001
TLC (10^3/mm3)	Mean ±SD	8.1 ±1.3	6.8 ±1.3	0.001
AEC (10^3/mm3)	Median (range)	0.52 (0.07- 0.96)	0.3 (0.03- 0.92)	0.041
Platelets (10^3/mm3)	Mean ±SD	273 ±49	294 ±27	0.042

Independent t-test was used for all parameters except AEC, in which Mann Whitney U test was used; CBC= Complete blood picture; TLC = Total leucocytic count; AEC = Absolute eosinophil count; non-significant= $p>0.05$; highly significant= $p<0.001$; SD= Standard deviation.

The median AEC was significantly higher ($p>0.001$) in the steroid-resistant patients (0.64 x10^3/mm3) compared to steroid-sensitive ones (0.43 x10^3/mm3). No significant differences ($p<0.05$) were observed between the two groups regarding hemoglobin, hematocrit, TLC, and platelets count (Table, 3).

Median serum IgE was significantly higher ($p>0.001$) in the steroid-resistant group (911.85 IU/ml) than in the steroid-sensitive one (164.5 IU/ml). No significant difference ($p=0.089$) was noted regarding atopic diseases (Figure, 3).

ROC analysis was done for IgE and AEC for differentiating between nephrotic patients and controls. For IgE, it revealed a significant area under curve (AUC) of 0.788 with a 95% confidence interval ranging from 0.657 to 0.919. The best cutoff point was >113.4, at which sensitivity and specificity were 84% and 66.7%, respectively. For AEC, ROC analysis showed a significant area under curve of 0.675 with a 95% confidence interval ranging from 0.5 to 0.851. The best cutoff point was > 0.3, at which sensitivity and specificity were 82.0% and 53.3%, respectively. (Figure, 4).

ROC analysis was done for IgE and AEC for differentiating between steroid-resistant and steroid-sensitive patients. For IgE, it revealed a significant area under curve (AUC) of 0.998 with a 95% confidence interval ranging from 0.992 to 1. The best cutoff point was > 600.6, at which sensitivity and specificity were 100% and 97.2%, respectively. For AEC, ROC analysis also showed a significant area under curve of 0.804 with a 95% confidence interval ranging from 0.681 to 0.927. The best cutoff point was > 0.5, at which sensitivity and specificity were 92.9% and 63.9%, respectively. (Figure, 5).

Serum IgE showed a significant negative correlation with K (r = -0.327 & p value = 0.021). No other significant correlations were shown between serum IgE and other parameters. (Table, 4).

Table (3) Complete blood count (CBC) according to steroid response in nephrotic patients.

CBC		Sensitive (n = 36)	Resistant (n = 14)	*p* value
Hemoglobin (g/dl)	Mean ±SD	10 ±1.2	9.7 ±1	0.467
Hematocrit (%)	Mean ±SD	28.8 ±3.3	28 ±3.1	0.439
TLC (10^3/mm3)	Mean ±SD	8 ±1.4	8.4 ±0.9	0.311
AEC (10^3/mm3)	Median (range)	0.43 (0.07 - 0.96)	0.64 (0.38 - 0.86)	0.001
Platelets (10^3/mm3)	Mean ±SD	267 ±46	289 ±56	0.163

Independent t-test was used for all parameters except for AEC; Mann Whitney U test was used; CBC= Complete blood picture; TLC = Total leucocytic count; AEC = Absolute eosinophil count; non-significant= $p>0.05$; highly significant= $p<0.001$; SD= standard deviation.

Table (4) Correlation between serum IgE and other parameters in nephrotic patients.

Parameters	Serum IgE	
	r	*p*-value
Age (years)	0.036	0.802
weight (kg)	0.031	0.829
Height (cm)	0.003	0.981
Hemoglobin (g/dl)	-0.082	0.571
Hematocrit %	-0.066	0.65
TLC (10^3/mm3)	0.076	0.599
Platelets (10^3/mm3)	0.163	0.259
Urea (mg/dl)	-0.18	0.21
Creatinine (mg/dl)	0.064	0.659
Na (mEq/L)	0.041	0.779
K^+ (mEq/L)	-.327*	0.021
Ca^{++} (mg/dl)	0.143	0.323
Serum albumin (g/dl)	0.21	0.142
24h Urine protein (g)	-0.109	0.451

Spearman's correlation was used, r = Correlation coefficient; *Significant=$p<0.05$; TLC = Total leucocytic count; Na= Sodium; K= Potassium; Ca= Calcium.

Figure (3) Serum IgE (IU/ml) according to steroid response in nephrotic patients.

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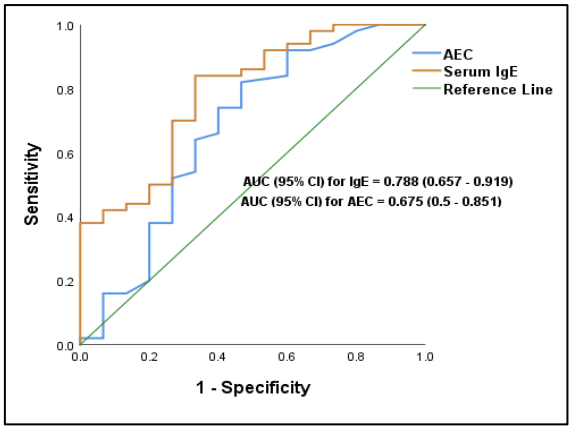

Figure (4) ROC analysis for IgE and AEC for differentiating between nephrotic patients and controls.

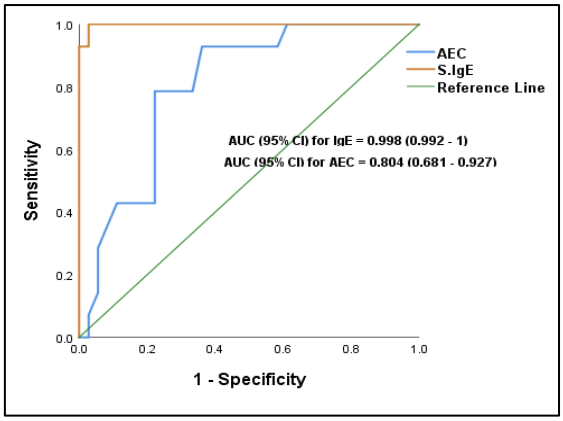

Figure (5) ROC analysis for IgE and AEC for differentiating between steroid-sensitive and steroid-r.

Discussion

In our study, the median serum IgE was significantly higher in group I (275.55IU/ml) than group II (100.5IU/ml). Our results were matched with Ni et al. [6], who reported that analysis of IgE concentration indicated significantly greater levels in the active phase (first-onset) group with atopic constitution (1350.67 ± 837.39 IU/mL, $p < 0.05$) and the active phase group with non-atopic constitution (441.01 ± 357.45 IU/mL, $p < 0.05$) than in the control group (57.76 ± 48.25 IU/mL). Also, Hossain [7], reported that the mean serum IgE level of nephrotic syndrome in children was (537.98±52.56IU/ml) which was higher than controls (38 ± 18 kU/L), p (<0.05). Liu et al., [8], reported that serum total IgE concentrations were significantly higher in total NS patients (median, 711.57 IU/mL; range, 53.96–3000.00 IU/mL) than in normal controls (median, 37.92 IU/mL; range, 1.84–141.30 IU/mL; $p < 0.001$). Our results agreed with Mishra et al., [9], who reported that serum immunoglobulin E (IgE) was assayed in 48 children with idiopathic nephrotic syndrome and 20 controls. The mean serum IgE was significantly raised in active nephrotic syndrome compared with controls ($p < 0.001$). The mean value of IgE in nephrotic patients was 228.6 per cent of the normal mean. Similarly, Tain et al., [10], reported that 69% (60/87) of nephrotic children had elevated serum IgE levels (>150 kU/l). Serum IgE levels were significantly higher in NS patients than in allergic asthmatics and normal controls. It became evident that the underlying immune dysfunction in these patients predisposes them to

developing both nephrotic syndrome and increased serum IgE levels [11,12].

In our study, ROC analysis was done for IgE and AEC for differentiating between nephrotic patients and controls. For IgE, it revealed a significant area under curve (AUC) of 0.788 with a 95% confidence interval ranging from 0.657 to 0.919. The best cutoff point was > 113.4, at which sensitivity and specificity were 84% and 66.7%, respectively. For AEC, ROC analysis showed a significant area under curve of 0.675 with a 95% confidence interval ranging from 0.5 to 0.851. The best cutoff point was > 0.3, at which sensitivity and specificity were 82.0% and 53.3%, respectively.

Our results were in agreement with Hsaio et al, [11], who reported that IgE exhibited a satisfactory discriminating power in predicting the diagnosis of nephrotic syndrome, with AUROCs of 0.781. A cutoff value of 110 mg/dl, as determined by the Youden index, exhibited the best sensitivity of 92% and specificity of 56%.

Nephrotic syndrome is frequently associated with allergic symptoms and an elevated serum IgE level. High serum IgE levels can be associated with poor outcome with frequent relapses or poor response to corticosteroids of INS in children [13]. There are data showing that, in atopic children with INS, serum IgE levels were higher when they were in remission of the atopic disease than in non-atopic patients with INS. Both atopic and non-atopic nephrotic children develop high levels of IgE during relapses of NS compared to those with remission [14].

In our study, median serum IgE was significantly higher in the steroid-resistant group (911.85) than in the steroid-sensitive one (164.5).

Similarly, Tain et al, [10], reported that patients with steroid-resistant nephrotic syndrome (SRNS) had higher serum IgE levels than patients with steroid-sensitive nephrotic syndrome (SSNS), both pre and post treatment. Elevated initial serum IgE levels appeared to be associated with poor outcome.

This was matched with Youn et al, [15], who reported that, in a comparison of the clinical characteristics of NS patients with normal IgE and those with high IgE, the high-IgE group required a significantly longer time to reach their initial remission, with more susceptibility to frequent relapse and comorbid allergic diseases, thus required longer steroid therapy to recover from the nephrotic phase than the normal-IgE group. However, it should be noted that some of the nephrotic children had persistently normal serum IgE levels, indicating different etiologies in the pathogenesis of NS.

In the study of Salsano et al, [16], pretreatment serum IgE levels in both SS and SR children were significantly higher than in normal controls. However, patients with SR tended to have higher serum IgE after steroid treatment, while patients with SS tended to have lower IgE after treatment. In the study done by Cheung et al, [17], serum IgE levels were elevated in nephrotic patients in relapse (median 500 IU/ml) compared with those in remission (median 129 IU/ml) and non-atopic controls (median 177 IU/ml;) (p <0.001). However, there was no significant difference in serum IgE levels between nephrotic children in remission and non-atopic controls.

ROC analysis was done for IgE and AEC for differentiating between steroid-resistant and steroid-sensitive patients. For IgE, it revealed a significant area under curve (AUC) of 0.998 with a 95% confidence interval ranging from 0.992 to 1. The best cutoff point was > 600.6 at which sensitivity and specificity were 100% and 97.2%, respectively. For AEC, ROC analysis also showed a significant area under curve of 0.804 with a 95% confidence interval ranging from 0.681 to 0.927. The best cutoff point was > 0.5, at which sensitivity and specificity were 92.9% and 63.9%, respectively.

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This matched with Chen et al, [18], who reported that ROC curve analysis showed that the cut-off value of IgE in the diagnosis of SSNS was 174.3 IU/ml (AUC=0.828, 95% CI 0.751-0.905, $p < 0.001$). The area under the ROC curve for IgG < 2.57 g/L in combination with IgE >174.3 IU/ml in the diagnosis of SSNS was 0.904 (95%CI 0.834-0.953, $p < 0.001$). Logistic regression showed that children who met both IgG < 2.57 g/L and IgE >174.3 IU/ml were 51 times more likely to have SSNS than those who did not ($p < 0.001$).

In our study, serum IgE showed a significant negative correlation with K (r = -0.327 & p= 0.021). No other significant correlations were shown between serum IgE and (age, weight, height, hemoglobin, hematocrit, TLC, platelets count, blood urea, serum creatinine, serum Na, serum Ca, serum albumin or 24 hr urine protein.

However, Hossain [7] reported that serum IgE is increased with age. Mean serum IgE level in age group 7-10 years, both patients and controls, was significantly higher than that in age group 2 to 6 years.

Conclusion

Our results showed that significantly higher serum IgE levels were associated with nephrotic syndrome and more prominently in patients with steroid-resistant nephrotic syndrome (SRNS).

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This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Author contribution

Authors contributed equally in the study.

Conflicts of interest

No conflicts of interest.

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