Comparison Of Serum IgELevel Between Initial Attack And Relapse Cases Of Idiopathic Nephrotic Syndrome In Children

Abstract

Background: Nephrotic Syndrome (NS) is a common and recurrent glomerular disease in childhood. Although the exact etiology of NS is not fully known, it is believed that immune system plays a pivotal role in its pathogenesis. Studies have been reported a strong association between NS and increased level of serum immunoglobulin E (IgE). In addition, children with recurrent NS, the IgE level significantly increases, and there is a higher relapse rate. **Objective:** The aim of the study was to determine the difference of Serum IgE level between initial attack and relapse cases of idiopathic Nephrotic Syndrome in children. **Methodology:** A cross sectional analytical study has been conducted on 35 initial attack and 35 relapse cases of idiopathic Nephrotic Syndrome children admitted in the Department of paediatrics, Sir Salimullah Medical College Mitford Hospital (SSMCMH), Dhaka from May 2021 to April 2022. Study subjects were enrolled by purposive sampling after confirming the diagnosis and fulfilling the inclusion and exclusion criteria. Informed written consent was taken from each patient's legal guardian before enrollment. A detailed history and thorough physical examination was done in each patient on admission. With all aseptic precaution five ml of venous blood was collected and sent for serum albumin, serum cholesterol and serum IgE level measurement. Data were analyzed using the statistical package for social sciences (SPSS) version 23.0. Independent sample t test or Mann-whitney test was used to compare data between groups. P value of less than 0.05 was considered as significant. **Result:** The mean age of the studied samples was 3.86 (ranging from 2 to 6 years). Moreover, among the studied sample male was a little bit greater than female. A significant prevalence of relapse cases were found among the children with middle income family status ($P<0.05$).Spot urine protein and creatinine ratio and serum cholesterol level was significantly higher in patients experience relapse attack ($P<0.05$). However, serum albumin level was quite similar in both cases. The mean serum IgE of patients experiencing relapse attack was 985.11+433.65 which was significantly higher than patients experiencing initial attack 470.48+227.35 ($P<0.001$). **Conclusion:** This study showed that serum IgE levels are higher in relapse cases of Nephrotic Syndrome than that of initial attack. Further more serum IgE is more in frequent relapse as compared to infrequent relapse. Serum IgE levels have a positive correlation with disease activity and relapse of Nephrotic Syndrome.

Keywords: Idiopathic nephrotic syndrome, Initial attack, Relapse, Serum immunoglobulin E (IgE).

Introduction

Nephrotic Syndrome (NS) is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic range proteinuria is defined as proteinuria > 1 gm/m²/24 hr or a urine protein: creatinine ratio > 2. The triad of clinical findings associated with Nephrotic Syndrome arising from the large urinary losses of protein is hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol > 200 mg/dL).[1] The proteinuria in childhood Nephrotic Syndrome is relatively selective, constitute primarily by albumin.[2] Globally, the annual incidence of idiopathic Nephrotic Syndrome (NS) is 1.15-16.9 per 100, 000 children, varying by ethnicity and region.[3]Noone et al., prevalence is 12-16 per 100,000.[4] South Asians are reported to have a higher incidence of Nephrotic Syndrome ranging from 7.4 to 16.9 per 100,000 children.[5] The prevalence of minimal change Nephrotic Syndrome (MCNS) is also higher in Indian subcontinent with annual incidence of 9-16/100,000.[6] Approximately 90% of children with Nephrotic Syndrome have idiopathic Nephrotic Syndrome. Idiopathic Nephrotic Syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic Nephrotic Syndrome includes multiple histologic types: minimal change disease (MCD), mesangial proliferation, focal segmental glomerulosclerosis (FSGS), membranous nephropathy, membranoproliferative glomerulonephritis. Although relapse is common in Nephrotic Syndrome, about 90% children with MCNS responds promptly to corticosteroid therapy with complete clinical and biochemical remission, and have an excellent long term prognosis. Among who responds to prednisolone, 20-40% have infrequent relapse, 40% have frequent relapse and remainder are steroid dependent.[7] The pathogenesis of Nephrotic Syndrome (NS) in children is still not clearly understood. To date, no single theory can completely explain its entire pathophysiological process. At present, it is considered that NS is mainly correlated to immune dysfunction, especially T cell dysfunction, which leads to the abnormal secretion of osmotic factors, such as cytokines or specific antibodies, and attacks podocytes, resulting in glomerular filtration membrane damage.[8]Humoral immunity, namely, the immune response involved in B cells and their secreted immunoglobulins, may also be involved in the process of immune regulation in NS, and activated B cells are the main cells that produce antibodies.[9] Blood contains three types of globulins; alpha, beta and gamma, based on their electrophoretic migration rates. Antibodies are gamma globulins. There are five classes of

antibodies namely IgG, IgM, IgA, IgD and IgE.[10]An increase in the serum IgE may be a reflection of body immunoregulatory imbalance that play direct pathogenic role in the occurrence of NS and proteinuria. However, the time sequence of either increased serum IgE levels followed by NS development or NS development followed by increased serum IgE levels is still unknown.[11] Mean serum IgE at the time of relapse in frequent relapse (FR) was found to be more than 3 times higher than that in infrequent relapse (IR). Serum IgE level at the time of remission has decreased to almost normal in IR group but it was still found 5 times higher in FR group.[12]IgE is mostly known for its association with allergy. In addition, elevated serum IgE levels have been noted in glomerular diseases.[13] So higher levels of serum IgE in nephrotic children have been related to poor outcomes with frequent relapses.[14] Therefore, the study was conducted to compare the Serum IgE level between initial attack and relapse cases of idiopathic Nephrotic Syndrome.

Materials and Methods

Study design: Cross sectional analytical study.

Study period: The study was conducted over a period of one year from May 2021 to April 2022.

Place of study: Department of Paediatrics, Sir Salimullah Medical College Mitford Hospital (SSMCMH), Dhaka, Bangladesh.

Study population: Initial attack and relapse cases of Idiopathic Nephrotic Syndrome admitted in the Department of Paediatrics of SSMCMH, Dhaka, Bangladesh during the specified period of time.

Inclusion Criteria:

Children of both gender aged between 2 to 6 years diagnosed as Idiopathic Nephrotic Syndrome (Initial and relapse cases)

Exclusion Criteria:

1. Secondary Nephrotic Syndrome
2. Congenital Nephrotic Syndrome
3. Associated with other chronic diseases.

Sample size calculation:To conduct the study, the sample size was calculated by using the following statistical formula for hypothesis testing of the difference between two means.

$$N=\frac{(\sigma 12+\sigma 22)\,(Z\alpha+Z\beta)^2}{(\text{⍰}_1-\text{⍰}_2)^2}$$

(Ref.: ABC of research methodology & biostatistics, 3rd ed.)

= 35

Sample size, n = 35 initial cases and 35 relapse cases

Grouping of study population:

Group A: 35 cases of initial attack Idiopathic Nephrotic Syndrome

Group B: 35 cases of relapse Idiopathic Nephrotic Syndrome

Study procedure

All patients admitted in the Department of Paediatrics, SSMCMH, after confirming the diagnosis of Nephrotic Syndrome and fulfilling the inclusion and exclusion criteria and after proper counseling about the objectives and procedure of the study only positive respondents were enrolled. Informed written consent was taken from each patient's legal guardian before enrollment. The participants were allowed to withdraw themselves from the study even after participation in this study whenever they liked. After enrollment, detailed history was taken from parents/guardian/caretaker of each subject and thorough physical examinations were done. Demographic data included age; gender, parents' average monthly income and area of living were taken. Other necessary information relevant to the study like facial puffiness, swelling of the body and scanty micturation were taken according to the predesigned questionnaire. Bed side heat coagulation test was done in each study subjects. Then the study participants were divided into two groups, initial attack group (35 patients) and relapse group (35 patients). All the relevant investigations for the study were done in both the groups. With all aseptic precaution five ml venous blood was collected and sent for serum albumin, serum cholesterol and serum IgE. Urine was collected in a sterile test tube and sent for spot urine protein-creatinine ratio. Relevant data from history, physical examination and investigations were recorded in predesigned questionnaire.

Method of serum IgE estimation: Serum IgE level (IU/ml) was determined by Chemiluminescent Immunoassay using ADVIA Centaur, Siemens, Germany.

Data analysis: After collection, data were entered into a personal computer for analyzing, plotting and presented in suitable tables or graphs. Data were analyzed using the statistical package for social sciences (SPSS) version 23.0. Quantitative data were expressed as the mean standard deviation and categorical data as frequency and percentage. Continuous variables were compared through the Student's t-test categorical variables by applying the chi-square test. P value of 0.05 or less (at 95% CI) was considered as significant.

Ethical consideration

Data were collected after getting approval of the research proposal from the Ethics committee of SSMCMH to undertake the current study. The aims and objectives of the study along with its procedure, risk and benefits were explained to legal guardians of the patient in an easily understandable local language and then informed written consent was taken from each guardian. They were informed about the right to withdraw themselves from the research at any stage of study period. Assurance about the confidentiality concerning their information was ensured. The research was conducted in full accord with ethical principles.

Results

Table 1: Demography of the study subjects (n=70)

Parameters	**Frequency (%) (n=70)**
Age	
2-4 year	45 (64.3)
4-6 year	25 (35.7)
Age (Mean ± SD) in years	3.86± 1.15 (Range: 2-6)
Gender	
Male	38 (54.3)
Female	32 (45.7)
Area of Living	
Rural	17 (24.2)
Urban	44 (62.8)
Slum	9 (12.8)

It appears from table-1 that the mean age of the studied samples was 3.86 ± 1.15ranging from 2 to 6 years. Most of the children were in between 2 to 4 years of age. Moreover, male proportion among the studied sample was a bit greater. Apart from this, most of the samples were from urban population.

Table 2: Age distribution of the study subjects according to initial attack and relapse (n=70)

Age category	**Initial attack (n-35) (%)**	**Relapse (n=35) (%)**	**P value**
2-4 years	21 (60)	24 (68.6)	0.454*
4-6 years	14 (40)	11 (31.4)	
Mean ± SD (years)	4.00±1.29	3.71 ±0.994	0.304**

*P value obtained from chi square test, **P value obtained from Mann Whitney U test

Table-2 shows that the mean age of the initial attack and relapse cases are (4.00±1.29) and3.71±0.994 years respectively. No significant difference (P>0.05) was found between initial attack and relapse groups in terms of age.

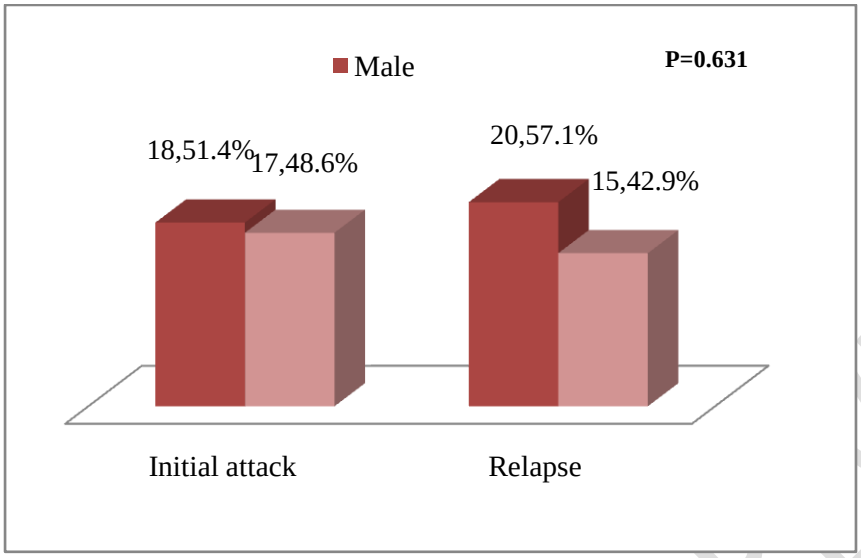

Figure 1: Gender distribution of the study subjects.

*P value obtained from chi square test

It appears from figure 1 that in both relapse and initial attack group a bit male dominance was found. Among relapse patients 57.1% were male and among initial attack patients 51.4% were male.

Table 3: Distribution of the study subjects according to socio-demographic parameters (N=70)

Parameters	**Initial (n=35) (%)**	**Relapse (n_2 -35) (%)**	**P value**
Monthly Income			
<15000	1 (2.9)	3 (8.6)	0.003
15000-25000	9 (25.7)	21 (60)	
>25000	25 (71.4	11 (31.4)	
Area of Living			
Rural	7 (20)	10 (28.6)	0.305
Urban	25 (71.4)	19 (54.3)	
Slum	3 (8.6)	6 (17.1)	

P value obtained from chi square test

Table-3 demonstrates the distribution of the study subjects according to the monthly income and area of living of their parents. A significant prevalence of relapse cases was found among the children with middle income family status (P<0.05). However, no significant association was found for relapse cases with the area of living.

Table 4: Comparison of clinical manifestation of the study subjects across initial attack and relapse groups (n=70)

Parameters		**Initial (n_1 =35) (%)**	**Relapse (n_2=35) (%)**	**P value**
Puffiness of eye		34 (97.1)	31 (88.6)	0.356**
Generalized swelling		32 (91.4)	27 (77.1)	0.101*
Decreased urination		32 (91.4)	30 (85.7)	0.710**
Bed side urine for albumin	+++	24 (68.6)	21 (60)	0.454*
	++++	11 (31.4)	14 (40)	

*P value obtained from chi square test, **P value obtained from Fisher's exact test

It appears from table 4 that the major clinical manifestation found among the study subjects were puffiness of eye, generalized swelling and decreased urination. However, no significant difference was found in those parameters between initial attack and relapse patients (P>0.05).

Table 5: Comparison of laboratory parameters of initial attack and relapse cases (n=70)

Parameters	**Initial Mean±SD (n1=35)**	**Relapse Mean±SD (n2=35)**	**P value**
Serum IgE level	470.48±227.35	985.11± 433.65	<0.001**
Spot urine protein: creatinine ratio	7.71±1.77	11.84 ±6.10	<0.001**
Serum albumin (mg/dl)	1.81±0.49	1.97±0.48	0.185*
Serum cholesterol (mg/dl)	288.14±50.39	343.03±51.61	<0.001*

*P value obtained from independent sample t test, **P value obtained from Mann Whitney U test

It appears from table 5 that Mann-whitney test was conducted to compare serum IgE level between initial and relapse attack patients. The mean serum IgE of patients experiencing relapse attack was 985.11±433.65 which was significantly higher than patients experiencing initial attack (P<0.001). Spot urine protein creatinine ratio and serum cholesterol level were

significantly higher (P<0.001) in patients experience relapse attack. However, serum albumin level was quite similar in both cases.

Table 6: Correlation among IgE and other laboratory parameters in both initial attack and relapse cases (n=70)

		Group-A Initial attack n=35		**Group-B Relapse cases n=35**	
		Correlation Coefficient (r)	**P value**	**Correlation Coefficient (r)**	**P value**
IgE	S. Albumin	0.04	0.819	0.023	0.896
	S. Cholesterol	0.499	0.002	0.483	0.003
	Spot urine protein-creatinine ratio	0.337	0.047	0.345	0.042

It appears from table 6 that a significant positive correlation was found between serum IgE level and Spot urine protein creatinine ratio in both initial attack (r=0.337; P<0.05) and relapse cases (r=345; P<0.05). Moreover, a significant positive correlation was found between serum IgE level and S, cholesterol in initial attack (r=0.499; P<0.01) and relapse cases (r=.483; P<0.01).

Table 7: Comparison of serum IgE level between different age group patients (n=70)

	2-4 years (n=45)	**4-6 years (n=25)**	**P value**
Serum IgE level	763.02±407.21	664.40±471.42	0.362

P value obtained from Mann-Whitney test

It appears from table 8 that Mann-Whitney test was conducted to compare serum IgE level between different age group of patients. The mean serum IgE of 2-4 years patients 763.02±407.21 which did not differ from patients of 4-6 years experiencing initial attack (p>0.05).

Table 8: Comparison of serum IgE level between frequent and infrequent relapse cases (n=35)

	Frequent (n=12)	**Infrequent (n=23)**	**P value**
Serum IgE level	1223.67±418.68	860.65±394.65	0.001

P value obtained from Mann-Whitney test

It appears from table 9 that Mann-whitney test was conducted to compare serum IgE level between frequent and infrequent relapse attack patients. The mean serum IgE of patients experiencing frequent relapse attack was 1223.67±418.68 which was significantly greater than patients experiencing infrequent relapse attack ($P<0.05$)

Discussion

Nephrotic Syndrome is a common chronic disorder. Patients with Nephrotic Syndrome are at risk for life threatening infections and thromboembolic episodes. Idiopathic Nephrotic Syndrome (INS), also known as nephrosis, is the most common cause of Nephrotic Syndrome in children.[15] Relapse NS carries a higher mortality and morbidity due to frequent association with severe complications.[16] The present study reported a distinct comparison of serum IgE level between initial attack and relapse cases of idiopathic Nephrotic Syndrome in children. The present study included a total of 70 children with idiopathic Nephrotic Syndrome ranging from 2 to 6 years of age. Among them 35 were of relapse cases and 35 of initial attack. The age and gender distribution of the two groups ideally matched since no significant difference was found. Hence, the major findings of the present study are not biased in term of age or gender. However, some studies found prevalence of relapse cases among the children aged under 5 or 6 years [17,18,19,20] but no significant results were found. The age predominance of < 6 years was also noticed in the study done by Andersen et al.[21] Moreover, gender was not found to be associated with frequent relapse in other studies.[17, 19, 22] The current study showed a significant prevalence of relapse cases among the children with middle income family status. In a study, poor class children were significantly prone to develop frequent relapse than the solvent children (middle and upper class).[19,23]Moreover, Minj et al.[18] also found prevalence of relapse cases among low income status group. Apart from this, no significant association was found in the present study for relapse cases with the area of residence. Nevertheless, Sarker et al [19] found a significantly higher incidence of relapse attack in rural children (72%) than that in urban children (24%).[19]In general, puffiness of eye, generalized swelling, decreased urination were the most common clinical manifestation associated with idiopathic Nephrotic Syndrome. However, no significant difference was found in those parameters between relapse and initial attack patients in the current study. Generalized edema was also found as a most common clinical manifestation associated with idiopathic Nephrotic Syndrome.[24] Mean serum total protein, and spot urinary protein: creatinine ratio was observed statistically non-significant ($p>0.05$) in initial attack and relapsing NS in some studies.[13,25]However, the present study found that spot urine

protein: creatinine ratio was significantly greater in children experience relapse attack. In the study of Sarker et al [19] serum albumin was significantly lower among relapse cases, but, the present study found no significant difference. Mean serum cholesterol level in relapsing NS was observed to be significantly higher than that in initial attack, which is coherent with other study outcomes.[13,19,25]Serum albumin was usually lower in patients with idiopathic Nephrotic Syndrome and urinary protein: creatinine ratio and serum cholesterol are usually higher in patients with idiopathic Nephrotic Syndrome.[26]IgE is mostly known for its association with allergy. In addition, elevated serum IgE levels have been noted in glomerular diseases. Higher levels of serum IgE in nephrotic children have been related to poor outcomes with frequent relapses or poor responses to steroid therapy.[27] In the present study, Serum IgE did not significantly differ with ages (Table 7), which was found otherwise in other study.[28] The present study showed mean serum IgE level of relapse cases was significantly ($p<0.05$) higher than that of initial attack cases. Hossain et al.[17] also found higher serum IgE level (1150.7 ±74.61) among patients experiencing relapse attack. The mean serum IgE levels were also found significantly elevated in the study of Mishra et al[29] in both infrequent and relapse attack than initial attack in patients. The raised IgE levels in patients of Nephrotic Syndrome, both in children as well as adults, have been previously reported by different authors[13,30]found significantly raised serum IgE levels in their frequent relapsers, steroid dependent/resistant cases in comparison with the infrequent and non- relapsers group ($p< 0.05$), emphasizing the variation in the levels in different subgroups of nephrotic patients. Mean serum IgE at the time of relapse in frequent relapse (1791±95 IU/mL) was found to be more than 3 times higher than that in infrequent relapse (560±50 IU/mL) ($p<0.001$) in the study of Jahan et al.[12] In the current study, it was about one and half times, which also supports previous literature.In the present study, as per Pearson's correlation co-efficient test (Table 6), it came to light that Serum IgE level have a significant positive correlation with spot urine protein: creatinine ratio ($r=0.337$), Serum cholesterol ($r=0.449$) in initial attack and moderately positive correlation with both spot urine protein: creatinine ratio ($r=0.345$), Serum cholesterol ($r=0.483$) in relapse cases. Patients with idiopathic Nephrotic Syndrome exhibit increased serum IgE levels with relapses. Further investigations are required to find out association of serum IgE level with relapse of steroid-sensitive Nephrotic Syndrome.

Conclusion

This study shown that serum IgE levels are higher in relapse cases of Nephrotic Syndrome than that of initial attack. Serum IgE is more in cases of frequent relapse as compared to

infrequent relapse. Furthermore, spot urine protein creatinine ratio and serum cholesterol are high in relapse cases in comparison to initial attack.

Limitation

1. This study may not reflect total community as it was conducted in admitted patients of single hospital.
2. Purposive sampling may cause biasness.

Recommendation

1. This finding suggests that level of the serum IgE can be used as a predictor indicator for relapse of Nephrotic Syndrome in children.
2. Further study including large sample size involving multiple center is recommended.

Conflict of Interest: None.

Source of fund: Nil.

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