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Assessment of Immunoglobulin M in Children with Steroid Resistant Nephrotic Syndrome

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ABSTRACT

Background: Nephrotic syndrome (NS), which accounts for 40% of renal morbidities in Egypt, is thought to be the most common kidney illness in Africa.

Objective: This study aimed to evaluate the role of IgM in early diagnosis of nephrotic syndrome of steroid resistant in children.

Patients and methods: This cohort study included 48 children with NS. It was conducted in the Pediatrics Nephrology Unit, Faculty of Medicine at Zagazig University Pediatric Hospitals. Patients were divided into Group (A) 24 children: new cases of nephrotic syndrome with steroid resistance. All patients were in the active stage of the disease (heavy proteinuria >40 mg/m^2/hour, hypoalbuminemia <2.5 g/dL, edema and hyperlipidemia) and Group (B): included 24 children with steroid sensitive nephrotic syndrome.

Results: There was a significant higher percent of infection of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. There was a significant higher percent of albuminuria and lower 24 hours protein in urine of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. There was a significant lower serum total protein of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. There was a significant lower serum IgG and IgM of steroid resistant nephrotic group compared to steroid sensitive nephrotic group.

Conclusion: Serum IgM and IgG levels have prognostic value in patients with nephrotic syndrome and can predict the outcome and the frequency of recurrence of the disease.

Keywords: Steroid Resistant Nephrotic Syndrome, Immunoglobulin M, Children.

INTRODUCTION

Patients who experience a syndrome complex of low levels of serum albumin, high levels of blood lipid, lipids in the urine, and edema are said to have nephrotic syndrome (NS), which is caused by a growing loss of albumin, proteins, and other plasma components with similar mass [(1)].

Idiopathic nephrotic syndrome (INS) is divided into steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) taking in account that response to steroid therapies is highly correlated with tissue subtype and disease progression prognosis, the International Study of Kidney Disease in Children (ISKDC), revealed that the great portion of children with INS had minimal change nephrotic syndrome (MCNS) in their renal biopsies [(2)].

According to the International Study of Kidney Disease in Children (ISKDC), SRNS is defined as a non-response to an 8-week exposure (at a minimum) of 60 mg/m^2 prednisone per day, or 2 mg/kg prednisone per day for 4 weeks followed by 40 mg/m^2 per day on alternate days for 4 weeks [(2)].

Different diseases are observed between steroid-sensitive NS (SSNS) and SRNS. Most children with SSNS have minimal change disease (MCD), whereas children with SRNS have focal segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis (MesPGN), or MCD [(3)].

Previously, various studies have been conducted on NS and immunity. It was postulated that MCNS could be caused by a systemic dysfunction of T-cells [(4)]. Serum concentrations of the high–molecular weight IgM increase, like the serum concentration of many other high–molecular weight liver-derived proteins [(5)]. Atypical IgM on the surface of T cells predisposed patients to the onset of severe childhood INS. However, few studies have evaluated the difference in serum IgM between SSNS and SRNS. Conversely, the total serum protein–albumin ratio (TA ratio) would directly reflect protein excretion in the urine [(6)].

Therefore, this study aimed to evaluate the role of IgM in early diagnosis nephrotic syndrome of steroid resistant.

PATIENTS AND METHODS

This cohort study included 48 children with nephrotic syndrome, which was conducted in the Pediatrics Nephrology Unit, Faculty of Medicine at Zagazig University Pediatric Hospitals.

Inclusion criteria: Children aged from 2 to 14 years of both gender with NS. Patients who fulfilled the criteria of minimal change NS (MCNS) were included in this study. Patients had uncomplicated NS at initial onset and were treated at one of the hospitals. Patients were under treatment with 1-2 mg/kg corticosteroid (CS) therapy.

Exclusion criteria: Children aged below one year or above 15 years. Children with severe protein energy malnutrition, congenital or infantile NS, hereditary or secondary forms of NS, low complement components and known active chronic infection (hepatitis B virus, hepatitis C virus, HIV, syphilis). Any patient who had

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an infection or was receiving any medication that would be likely to affect the immune system, whether suppressors or stimulants were excluded from the study.

Ethical consideration:

Written informed consent was obtained from all the guardians of the participants and the study was approved by the Research Ethical Committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients were divided into two groups:

Group (A): included 24 children: new cases of nephrotic syndrome with steroid resistance. All patients were in the active stage of the disease (heavy proteinuria >40 mg/m^2/hour, hypoalbuminemia <2.5 g/dL, edema and hyperlipidemia).

Group (B): included 24 children with steroid sensitive nephrotic syndrome.

All patients in this study were subjected to full history taking including age, sex, education status, age at onset of INS, and duration of disease. Thorough clinical examination: with special emphasis on vital data, and all body systems examination. Assessment of the anthropometric measurements to calculate body weight, height, and body mass index (BMI = weight in kg/height^2 in meters) of all enrolled children and adolescents. Details of medical therapy (type, dose, and frequency) and disease presentation and complications were record.

Steroid resistance is often diagnosed as a failure to induce complete remission after 4 weeks of standard steroid therapy with 60 mg/m^2 intravenous or oral prednisolone per day. In accordance with the guidelines of the International Study of Kidney Disease in Children, complete remission is defined as a reduction in proteinuria to < 0.2 mg/mg protein-creatinine ratio in the first-morning urine void, or negative dipstick test results for three consecutive days [(2)].

All of the biomarkers were measured only once upon patient admission to the hospital including **c**omplete blood count (CBC)**,** total serum protein, serum albumin, total cholesterol, total urinary protein level, TA ratio, (total serum protein-albumin ratio), eGFR, serum IgM level and IgG.

Venous blood sample of 5 ml was collected for the determination of serum albumin, total protein, cholesterol, creatinine, and blood urea. Serum Ig (IgG, IgM) levels were measured using a liquid-phase immunoprecipitation assay in all groups. Reference values of IgG and IgM were 7-16 and 0.4-1.5 g/l, respectively. The cut-off value for low IgG was less than 7 g/l, high IgM more than 1.5 g/l, and IgG : IgM more than 5. Chest radiography and ultrasonography of the kidneys, ureter, and bladder were performed for all the patients. Renal biopsy was performed for steroid-resistant nephrotic syndrome (SRNS) patients.

Urine analysis (Urine samples were collected on admission, and routine microscopic and physical examination. Spot UPCR or urinary total protein was measured using an autoanalyzer (RA50 chemistry analyzer, India)).

Renal biopsy:

Renal biopsy is an important diagnostic tool in the hands of a pediatric nephrologist. While the first biopsy was done more than 100 years ago in United States, its utility in diagnostics has increased in the last few decades. Since its regular introduction in 1951 by Iverson and Brun, renal biopsy has made a revolution in the study of renal diseases. Renal pathology can be better delineated with the advent of newer stains, immunofluorescence and electron microscopy. While a renal biopsy is more useful in diagnosing glomerular diseases, it often provides information on tubular conditions as well [(7)].

Statistical analysis

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative were represented as number and percentage and were compared by chi square test and Fisher's exact test. Quantitative continuous group were represented by mean ± standard deviation (SD), and were compared by independent t-test and Mann-Whitney test. P value was set at <0.05 for significant results and <0.001 for high significant result.

RESULTS

The current study showed that there was no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding sex and age **(Table 1)**.

Table (1): Demographic characteristics of steroid resistant and steroid sensitive nephrotic children

Variables	Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	p
Sex n. (%) **i. Females** **ii. Males**	**9(37.5%)** **15(62.5%)**	**5(20.8%)** **19(79.2%)**	**0.204**
Age per year **1. Mean± SD** **2. Median (range)**	**3.94±1.97** **3.5 (1-7)**	**5.3±2.8** **5 (1.3-12)**	**0.124**

SD= standard deviation

There was no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding anthropometric measures **(Table 2)**.

Table (2): Anthropometric measures of steroid resistant and steroid sensitive nephrotic children

Variables	Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	p
Weight (Kg) Mean± SD	**17.69±4.47**	**20.3±4.99**	**0.449**
Height (cm) Mean± SD	**115.79±27.8**	**123.67±30.11**	**0.351**
BMI (kg/m^2) Mean± SD	**14.39±3.48**	**14.18±3.45**	**0.563**

SD=standard deviation

There was a significant higher percent of infection in the steroid resistant nephrotic group compared to steroid sensitive nephrotic group **(Table 3)**.

Table (3): Associated diseases of studied children

Variables			Studied groups		p-value
			Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	
Hypertension (HTN)	**yes**	**N**	**6**	**1**	**0.097**
		%	**25.0%**	**4.2%**	
	no	**N**	**18**	**23**	
		%	**75.0%**	**95.8%**	
Infection	**yes**	**N**	**20**	**1**	**0.0001**
		%	**83.3%**	**4.2%**	
	no	**N**	**4**	**23**	
		%	**16.7%**	**95.8%**	
Diabetes mellitus (DM)	**yes**	**N**	**23**	**24**	**1**
		%	**95.8%**	**100.0%**	
	no	**N**	**1**	**0**	
		%	**4.2%**	**0.0%**	
Cataract	**no**	**N**	**24**	**24**	**1**
		%	**100%**	**100%**	
Chronic kidney disease (CKD)	**no**	**N**	**24**	**24**	**1**
		%	**100%**	**100%**	

There was a significant higher percent of albuminuria (++) and higher 24 hours protein in urine of steroid resistant nephrotic group compared to steroid sensitive nephrotic group **(Table 4)**.

Table (4): Urine analysis of steroid resistant and steroid sensitive nephrotic children

Variables			Studied groups		p-value
			Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	
Hematuria	No	N	24	24	1
		%	100%	100.0%	
Albuminuria	+	N	6	19	0.001
		%	25.0%	79.2%	
	++	N	16	5	
		%	66.7%	20.8%	
	+++	N	2	0	
		%	8.3%	0.0%	
24 hours protein in urine	Mean± SD		9556.1±2100.36	2395.77±425.29	0.001
GFR	Mean± SD		343.72±74.33	357.6±79.3	0.66

There was a significant lower serum total protein of steroid resistant nephrotic group compared to steroid sensitive nephrotic group **(Table 5)**.

Table (5): CBC and serum analysis of steroid resistant and steroid sensitive nephrotic children

Variables	Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	p
WBCs N (4--11×10^3/mm^3)	12.33±1.77	12.47±1.07	0.75
Hg N (12-18 g/dl)	12.19±3.01	10.15±2.3	0.173
Platelet N (150-400×10^3/mm^3)	397.91±7.7	390.33±7.38	0.773
Serum albumin (g/L)	1.68±0.3	1.92±0.44	0.056
Total protein (g/L)	3.66±0.76	4.24±0.76	0.01
Total protein albumin ratio	1.92±0.4	1.98±0.3	0.73
Cholesterol (mg/dL)	416.97±80.03	395.78±8.4	0.43

WBCs: White blood cells **Hg:** Hemoglobin, **SD=**standard deviation, **N:** Normal

There was a significant higher percent of abnormal ultrasound finding in steroid resistant nephrotic group compared to steroid sensitive nephrotic group **(Table 6)**.

Table (6): Ultrasound finding of steroid resistant and steroid sensitive nephrotic children

Variables			Studied groups		p-value
			Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	
US finding	normal	N	3	17	0.00004
		%	12.5%	70.8%	
	abnormal	N	21	7	
		%	87.5%	29.2%	
b.p.e in s	N		1	0	1
	%		4.2%	0.0%	
Increase kidney echo	N		2	3	1
	%		8.3%	12.5%	
Increase size of both kidney	N		7	3	0.16
	%		29.2%	12.5%	
Increase size of left kidney	N		3	0	0.23
	%		12.5%	0.0%	
Left pleural effusion with minimal ascites	N		0	1	1
	%		0.0%	4.2%	
Both size pleural effusion minimal ascites	N		2	0	0.49
	%		8.3%	0.0%	
Increase size of kidney with minimal ascites	N		1	0	1
	%		4.2%	0.0%	
M.F.F.	N		2	0	0.49
	%		8.3%	0.0%	
Minimal pleural effusion minimal ascites	N		2	0	0.49
	%		8.3%	0.0%	
Minimal ascites with increase kidney size	N		1	0	1
	%		4.2%	0.0%	

There was a significant lower serum IgG and IgM value of steroid resistant nephrotic group compared to steroid sensitive nephrotic group **(Table 7)**.

Table (7): Immunology of steroid resistant and steroid sensitive nephrotic children

Variables	Steroid resistant nephrotic group n.24	Steroid sensitive nephrotic group n.24	p
IgG (g/L) Mean ±SD	276.92±6.84	859.88±11.6	0.016
IgA (g/L) Mean ±SD	75.54±15.8	156.83±30.6	0.934
IgM (g/L) Mean ±SD	1216.67±268.9	2132.5±519.8	0.0001
C3 Mean ±SD	3.79±0.6	1.38±0.28	0.764

SD=standard deviation

DISCUSSION

Serum IgM might relate to the severity or pathogenic factors in idiopathic nephrotic syndrome. Low serum IgG and IgA, and high serum IgM are observed in MCD patients, which is common among SSNS children [2]. **Colucci *et al.*** [6] demonstrated that atypical IgM on the surface of T cells predisposed patients to the onset of severe childhood idiopathic nephrotic syndrome. However, few studies have evaluated the difference in serum IgM between SSNS and SRNS.

This cohort study was conducted in the Pediatrics Nephrology Unit, Faculty of Medicine at Zagazig University Pediatric Hospital on 48 children with nephrotic syndrome to assessment of immunoglobulin m in children with steroid resistant nephrotic syndrome.

The current study showed that there was no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding sex and age. Which is in agreement with the study of **Youssef *et al.*** [8] who reported that steroid-resistant nephrotic group included 16 patients (10 males and 6 females) with a mean age of 12.3±1.4 years, while steroid sensitive nephrotic group included 11 patients (5 males, 6 females) with a mean age of 11.6±2.1 years with no significant difference between both groups regarding sex and age. **Guimarães *et al.*** [9] found that no significant differences were observed in the comparison between SS and SR groups regarding age and gender distribution.

Akbar *et al.* [10] showed that the distribution of male children was highest in the SRNS group of 18 (72%) and the distribution of many female children in the SSNS group was 17 (68%). From these data there was a meaningful difference with p = 0.005. Median age in the SRNS group was 10 years and in the SSNS group was 12.5 years with a minimum age of almost the same in both groups

Also, **Mortazavi and Khiavi** [11] showed that there is no statistically difference between steroid resistant and steroid sensitive nephrotic children regarding to sex and age. In contrast **Udagawa *et al.*** [2] showed that among 80 patients with idiopathic nephrotic syndrome, 13 patients (M:F = 5:8) with mean age 3.87 ± 3.27 were steroid-resistant and 67 patients (M:F = 47:20) were steroid-sensitive with mean age = 4.88 ± 3.98 years, with a statistical difference between steroid resistant and steroid sensitive nephrotic children regarding to sex and age ($p< 0.05$).

The current study showed that there was no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding to anthropometric measures, which is in agreement with the study of **Akbar *et al.*** [10], which showed that there was no statistical difference between steroid resistant and steroid sensitive nephrotic children regarding weight (32.92 ± 16.12) versus 40.9 (39.30 ±16.81) and height (131.40 ±28.35) versus (136.76 ±22.19) respectively. Also, **Khurana *et al.*** [12] who found no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding weight 47.2 (25.2–93.8) versus 40.9 (20.4–151.1) and height 144.8 (125.6–153.8) versus 129.6 (104.4–177.6) respectively. **Souto *et al.*** [13] reported that there was no statistically significant difference between steroid resistant and steroid sensitive nephrotic children regarding to anthropometric measures ($p>0.05$). **Mohammed *et al.*** [14] showed that there were no statistically significant differences between the groups studied in demographic data and anthropometric measurements. Thus, the effect of age and sex can be excluded as a factor explaining the difference in their medical and biochemical characteristics.

The current study showed that there was a significant higher percent of infection of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. **Kim *et al.*** [15] found high significant difference regarding hypertension between steroid sensitive nephrotic group compared to steroid resistant nephrotic group (P= 0.009)**. Le Viet *et al.*** [16] found no significant difference in steroid sensitive nephrotic group compared to steroid resistant nephrotic group regarding hypertension (18.2% versus 21.1%, P= 0.817) and anemia (22.7% versus 26.3%, P = 0.79). Also, **Mortazavi and Khiavi** [11] found that there was no statistically significant difference in steroid resistant nephrotic group compared to steroid sensitive nephrotic group regarding hypertension 6 (14.6%) versus 13 (10.5%) P = 0.3.

The current study showed that there was a significant higher percent of albuminuria (++) and higher 24 hours protein in urine of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. **Le Viet *et al.*** [16] found a higher 24 hours protein in urine of steroid resistant nephrotic group compared to steroid sensitive nephrotic group (P = 0.007). **Guimarães *et al.*** [9] reported that 24-hours urinary protein excretion and protein/creatinine ratio were significantly higher in SR then in SS patients.

Kim *et al.* [15] found no significant difference regarding hematuria and GFR between steroid sensitive nephrotic group compared to steroid resistantnephrotic group (P= 0.009). **Mortazavi and Khiavi** [11] showed that there is a highly significant difference in steroid resistant nephrotic group compared to steroid sensitive nephrotic group regarding hematuria; 21 patients (51.2%) versus 19 patients (17.3%) P = 0.001, but 24 hours protein in urine was higher in steroid resistant nephrotic group compared to steroid sensitive nephrotic group (4157.78 ± 448.86 versus 3190.3 ± 322.34).

Al-Assadi *et al.* [17] found that there was a highly significant relationship ($P< 0.01$) between the serum

albumin concentration and mean levels of serum IgG and IgM of children with NS. Reduced albumin levels were accompanied by lowering in mean levels of serum IgG and elevate IgM levels. There was highly significant relationship (P<0.01) between the degree of hypercholesterolemia and the mean level of IgG and IgM. Rise in concentration of serum cholesterol was associated with reduction in serum IgG and elevation in IgM levels. There was a highly significant (P<0.01) correlation between protein in urine and mean concentration of IgG and IgM. Increase albumin in urine was associated with decrease of IgG and increase IgM concentration.

Our results were in identity with that reported **El Mashad *et al.*** [18] who pronounced that in NS there is an elevated albumin urinary excretion and IgG accompanied by a reduction in their serum level. Proteins with large molecular weight such as lipoproteins are overproduced by children with NS, which can lead to hyperlipidemia, and are conserved from urinary loss which maintains the oncotic pressure.

The current study showed that there was a significant lower serum total protein of steroid resistant nephrotic group compared to steroid sensitive nephrotic group p=0.01. But there was no significant difference between the two groups regarding serum albumin, total protein albumin ratio and cholesterol. While **Le Viet *et al.*** [16] found a significant difference between steroid resistant nephrotic group and steroid sensitive nephrotic group regarding serum total protein, serum albumin, total protein albumin ratio and cholesterol. In contrast **Udagawa *et al.*** [2] showed that there was no significant difference between steroid resistant nephrotic group compared to steroid sensitive group regarding serum total protein (4.31±0.66 versus 4.2 ± 0.53, P = 0.47), serum albumin (1.59 ±0.61 versus 1.33 ± 0.52, P = 0.12), total cholesterol (437.36± 95.74 versus 396.34 ±105.41, P = 0.23)

The current study showed that there was a significant higher percent of abnormal ultrasound finding in steroid resistant nephrotic group compared to steroid sensitive nephrotic group, which is in agreement with the study of **Shah *et al.*** [19] who found that there was a significant higher percent of abnormal ultrasound finding in steroid resistant nephrotic group compared to steroid sensitive nephrotic group. Also results of **Seif *et al.*** [20] supported the current results.

The current study showed that there was a significant lower serum IgG and IgM value of steroid resistant nephrotic group compared to steroid sensitive nephrotic group. There was statistically insignificant difference of IGA and C3 between both groups, which is in agreement with the study of **Al-Assadi *et al.*** [17] who found that the serum IgG means level in patients with NS (464.72 ± 50.34 mg/dl) was significantly lower than healthy control children (1209.34 ± 75.51 mg/dl). The serum IgM mean level in patients with NS (201.37 ± 10.12 mg/dl) was significantly higher than healthy control children (113.08 ± 8.42 mg/dl). The serum IgA mean level in patients with NS (175.47 ± 12.93 mg/dl) showed no significant difference compared with healthy control children (193.57 ± 20.30 mg/dl).

Le Viet *et al.* [16] found that the median level of serum IgA and IgG, and IgG/IgM ratio were significantly lower in the SRNS group than the SSNS (P = 0.04, < 0.001, and < 0.001, respectively). **Youssef *et al.*** [8] reported that there is a significant lower serum IgG of steroid resistant nephrotic group compared to steroid sensitive nephrotic group (2.29±1.13 versus 6.2±1.2, p < 0.01), but in contrast to current results there was no significant differences between both group regarding IGA and IGM.

Mohammed *et al.* [14] showed that there was a highly statistically significant difference between steroid resistant nephrotic group compared to steroid sensitive nephrotic group as regard IgG (g/L). But in contrast to current results there was no significant differences between both group as regard IgM (g/L). In contrast **Udagawa *et al.*** [2] showed that there was no significant difference between steroid resistant nephrotic group compared to steroid sensitive nephrotic group regarding serum IgG, serum IgM, serum IgA and complement C3.

We recommend doing studies with large number of patients with long period of follow up in multicenter studies to confirm our finding.

CONCLUSION

Low levels of serum IgM at initial diagnosis might predict steroid resistance among children with idiopathic nephrotic syndrome. Serum IgM and IgG levels have prognostic value in patients with nephrotic syndrome and can predict the outcome and the frequency of recurrence of the disease. There is a close relationship between the degree of albuminuria and the levels of serum IgG and M.

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