

Immunoglobulin G and M levels in childhood nephrotic syndrome: two centers Egyptian studyGhada Mohamed El Mashad¹, Soha Abd El Hady Ibrahim², Sameh Abd Allah Abdelnaby³¹ Assistant Professor of Pediatrics, Faculty of Medicine, Menoufia University, Egypt² Assistant Professor of Pediatrics, Faculty of Medicine, Benha University, Egypt³ Lecturer of Pediatrics, Faculty of Medicine, Menoufia University, Egypt**Type of article:** Original**Abstract**

Introduction: Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in children. Immune cell subsets may play a role in pathogenesis of INS. We aimed to assess immunoglobulin G (IgG) and immunoglobulin M (IgM) levels in children with nephrotic syndrome (NS) to predict prognosis of the disease and response to treatment.

Methods: This prospective case control study was done in Pediatric Nephrology Units at Minoufia and Benha University Hospitals, during the period from 1st March 2014 to 30th June 2015. Seventy-five children in the active stage of INS and 75 apparently healthy children of matched age and sex were included in this study. Statistical evaluation was performed by SPSS version 18.0 using independent-samples t-test, Chi-square, and Pearson's correlation coefficient (r).

Results: Compared with healthy children, IgM level was high, IgG level and IgG/IgM ratio were low (p 0.05). The IgG level and IgG/IgM ratio decreased more in FRNS than in IFRNS group, and was the lowest in SRNS group. The IgM level increased more in FRNS than in IFRNS group, and was the highest in SRNS group (p<0.05, respectively).

Conclusions: Our findings support the idea that IgG level has a prognostic value in NS in children

Keywords: Nephrotic syndrome, Immunoglobulins, Children

1. Introduction

Nephrotic syndrome is a glomerular disease characterized by heavy proteinuria, hypoalbuminemia, edema and hyperlipidemia (1). INS is associated with changes in the immune response (2). Several studies have been performed in relation to NS and immunity and found abnormality of T-cell function in these patients. T-cell has an important role in the switch from IgM synthesis to IgG synthesis (switching defect), leading to reduced serum IgG and IgA levels and elevated serum IgM and IgE levels. Depression of IgG level is also due to its loss in the urine, and increase in its rate of catabolism (3, 4). Bacterial infection is a common and dangerous complication in children with NS. Reduced serum concentrations of IgG, due to its urinary loss and impaired ability to make specific antibodies, is a common cause of bacterial infection in NS. Decreased levels of the alternative complement pathway factors B and D, and immunosuppressive therapy are also contributing factors in these patients (5, 6). The purpose of this work was to study the IgG and IgM levels and IgG/IgM ratio in nephrotic children, to understand their level changes in these patients and predict response to treatment.

2. Material and Methods**2.1. Research design**

This prospective case control study was done in Pediatric Nephrology Units at Minoufia and Benha University Hospitals (Egypt), during the period from 1st March 2014 to 30th June 2015. 150 children were included in this study following approval of the Ethical Committee of Faculty of Medicine - Minoufia University, and a written consent

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was obtained from patients to participate in this study. Patients were divided into 2 groups of case (Group 1) and controls (Group 2).

2.2. Selection of cases (Group 1)

This group included 75 children with INS. All patients were in the active stage of the disease (heavy proteinuria >40 mg/m²/hr, hypoalbuminemia <2.5 g/dL, edema and hyperlipidemia) (7). Their ages ranged from 2-14 years. Of the groups (Mean=7.04±2.96 years), 45 (60%) were boys while 30 (40%) were girls. Patients fulfilled criteria of MCNS were included in this study. Patients were under full daily dose corticosteroid (CS) therapy, 60mg/m²/day (max 80mg/day) for 4 weeks with gradual withdrawal of steroid on alternate days. Children with INS were further classified into one of three groups, depending on their response to GC therapy: (1) steroid-sensitive NS (SSNS), (2) steroid-dependent NS (SDNS), or (3) steroid-resistant NS (SRNS). SSNS was further classified by: (a) an absence of relapses, (b) infrequent relapsers, or (c) frequent relapsers. Activity or relapse of NS were defined as increased urinary protein excretion > 40 mg/m² body surface area/h on 3 consecutive days after having been in remission. Remission was defined as proteinuria <4 mg/m²/h for 3 consecutive days. SSNS was defined as complete remission on corticosteroid therapy. SRNS was defined as failure to achieve remission after 4 weeks of prednisone therapy 60 mg/m² followed by 3 methylprednisolone pulses. Frequent relapse NS was defined as 2 or more relapses within 6 months of initial response, or 4 or more relapses within a period of 1 year. SDNS was defined as 2 consecutive relapses during corticosteroid therapy, or within 14 days after cessation of therapy (7, 8). Exclusion criteria were: 1) Children aged below one year or above 15 years, 2) Any patient who had infection or was receiving any medication that would be likely to affect the immune system, whether suppressors or stimulants, was excluded from study, 3) NS secondary to systemic disease like (systemic lupus erythematosus, hepatitis B, Henoch-Schönlein purpura, lymphoma, or amyloidosis) and children with severe protein energy malnutrition, and 4) Congenital NS.

2.3. Selection of controls (Group 2)

This group included 75 apparently healthy children of matched age and sex, and served as control group. There were 39 (52%) boys, while 36 (48%) were girls.

2.4. Data collection

All patients and controls were subjected to: Full history taking and thorough clinical examination. Dates and number of relapses were recorded. Laboratory investigations included serum albumin, serum cholesterol, 24 hour urinary protein levels, serum IgG and IgM. Urine samples were collected on admission, for routine microscopic and physical examination. An auto-analyzer (RA50 chemistry analyzer) was used to measure spot urinary protein creatinine ratio (Upr/Ucr ratio) or urinary total protein. Serum IgG and IgM levels were measured by liquid phase immunoprecipitation assay in all groups. Reference values of IgG and IgM were 700-1600 mg/dl and 40-150 mg/dl, respectively (9). Abdominal ultrasonography and plain X-ray chest were performed for all patients. Renal biopsy was done for atypical cases, of which there were 18 (24%). Follow up for one year to determine type of NS and response to therapy was carried out.

2.5. Statistical Analysis

Results were presented as Mean ± Standard Deviation. Chi-square test, independent-samples t-test, and Pearson's correlation coefficient ® were used to for data analysis. P-value below or equal to 0.05 was considered statically significant. All calculations were made with SPSS version 18 (SPSS Inc., Chicago, Illinois, USA).

3. Results

This study included 150 children, 84 were males and 66 females. There were 39 (52%) males and 36 (48%) females in the control group; 45 males (60%) and 30 (40%) in nephrotic group. Correlation of IgM, IgG and IgG / IgM ratio with clinical and laboratory data of patients is presented in Table 1 and correlation of IgM, IgG and IgG / IgM ratio with the pathological data of patients is shown in Table 2. There was no significant difference in sex distribution between both groups (p>0.05). The mean age of children in control group was (6.96±3.09 years) and in nephrotic group was (7.04±2.96 years) (p>0.05). In the 75 children with NS, 30 patients (40%) had SSNS, 15 (20%) had SRNS, 15 (20%) were FRNS and 15 (20%) were INFNS. Of the children in patient group, 15 (20%) were hypertensive. The number of attacks of NS in patients was 6 (±1.96). There were significantly more decreases in serum albumin levels in patients (2.22±0.48 gm/dl) than controls (3.53±0.41 gm/dl) and significantly more increases in serum cholesterol in patients (344±138.99 mg/dl) than controls (83.77±23.31 mg/dl). Upr/Ucr ratio was significantly higher in patients (2.1±0.8) than controls (0.18±0.15). The mean IgG levels in the patient group (759.84±373.18 mg/dl) were significantly lower than in controls (1187.54±299.34 mg/dl). The mean IgM levels in

the patient group (129.76±85.30 mg/dl) were higher than their levels in controls (102.15±24.26 mg/dl). The mean IgG/IgM ratio in the patient group was (15.9±9.5) which was lower than controls (20.1±28.3). The IgG level and IgG/IgM ratio decreased more in FRNS than in IFRNS group, and was the lowest in SRNS group. The IgM level increased more in FRNS than in IFRNS group, and was the highest in SRNS group (p<0.05, respectively) (Table 3). There was significant relationship (p 0.05) between serum albumin level with the mean concentration of IgG and IgM in sera of patients with NS. Decrease serum albumin is accompanied by reduction in mean concentration of serum IgG and increase IgM levels. There was significant relationship (p 0.05) between the degree of hypercholesteremia and the mean concentration of IgG and IgM. Increase in serum cholesterol level is associated with decrease in serum IgG and increase in IgM levels. There was significant relation between serum IgG level and Upr/Ucr ratio. There was no statistically significant difference between serum IgG, IgM and IgG/IgM ratio with pathological NS types, but significant difference with clinical types of nephrotic group was present. Cut-off value for low IgG was <700 mg/dl, high IgM >150 mg/dl.

Table 1. Correlation of IgM, IgG and IgG / IgM ratio with clinical and laboratory data of patients.

Variables	IgM		IgG		IgG / IgM ratio	
	r	p-value	R	p-value	R	p-value
Age (years)	0.259	0.025	- 0.548	0.001	- 0.405	0.001
Onset	0.385	0.001	- 0.488	0.001	- 0.388	0.001
No. of attacks	- 0.356	0.002	0.259	0.025	0.474	0.001
Serum Albumin (gm/dl)	-0.76	0.03	0.569	0.001	0.333	0.003
Serum cholesterol (mg/dl)	0.14	0.02	- 0.259	0.025	-0.05	0.04
Upr / Ucr ratio	0.063	0.594	- 0.245	0.034	0.049	0.674

Table 2. Correlation of IgM, IgG and IgG / IgM ratio with the pathological data of patients.

Pathology	IgM			IgG			IgG: IgM ratio		
	Mean	SD	p-value	Mean	SD	p-value	Mean	SD	p-value
Not done	88.6	63.2	0.2	980	404.5	0.5	18	27	0.6
FSGS	120.6	64.2		874	398		20.5	22.3	
MPGN	30			1400			46		

Table 3. Relation between serum IgG, IgM and IgG: IgM ratio with clinical types of nephrotic group.

Clinical type	IgM			IgG			IgG: IgM ratio		
	Mean	SD	p-value	Mean	SD	p-value	Mean	SD	p-value
IFRNS	108	46.6	0.03	715.2	270.6	0.00	6.6	5.8	0.05
SSNS	87.6	63.4		1165	303.7		13.2	4.8	
SRNS	193	99		632.4	487.6		3.3	4.9	
FRNS	113	73.3		686	470.5		6.1	6.4	

4. Discussion

Immunologic abnormalities have been demonstrated in SSNS, such as change of lymphocyte subsets, different cytokine profiles, and alterations of serum IGs (7, 10). In nephrotic patients, compared with healthy children, the serum level of IgG was low, IgM level was high, and IgG/IgM ratio was low (p<0.05). Our results are in agreement with a Nariman et al. study (9) which reported that changes in the serum IG levels can be attributed to either T cell dysfunction and/or increased urinary excretion of albumin. Also, Sahali et al., reported changes in serum IgG and IgM in children with NS which matches with our study (11). Ghazala et al. (2000), stated that the low level of serum IgG in NS may be due to any of the following: the increased IgG catabolism, decreased IgG synthesis, or altered distribution of IgG to the extra plasma compartments. Another mechanism which may explain IgG decrease in NS rather than IgM is the loss of IgG in urine because it has a lower molecular weight than IgM (12). Carlos et al. found that in MCNS, serum IgG levels are reduced, whereas serum IgM level is elevated. It was postulated that the primary defect in INS is the deficiency in the T-cell function that mediates the switch from IgM synthesis to IgG synthesis. Similar to albumin, IgG is lost in the urine, its serum concentration is decreased, and the fractional rate of its catabolism is increased, suggesting that the kidney contributes to IgG catabolism in conditions of proteinuria. IgG synthesis responds in a variable fashion in NS, and may be decreased, thus contributing to its reduced serum concentration. In contrast, the serum concentration of the high-molecular weight IgM is increased, similar to the

serum concentration of a variety of high-molecular weight liver-derived proteins (13). A generalized depression of serum IgG subclasses in relapse has been found not only for the INS, but also for other forms of NS. A previous study found that INS patients are capable of producing in vivo, active antibodies against viral or bacterial infections. IgG levels were decreased and IgM was increased in these patients during relapse of the disease. They also found that B lymphocytes number and distribution according to surface IGs were normal. IgG/IgM ratio was lower in NS patients than controls. From these results, they have shown that with higher IgG/IgM ratio, a favorable response to steroids is more predictable and with a lower ratio, a poorer response to steroids was predicted. These results agree with some other studies, who suggested a better response to treatment for patients with INS (including SSNS and FSGS with a high serum IgG/IgM ratio) (7). Ranjit et al. found lower IgG/IgM ratio (14). Our study revealed that increase in albuminuria is accompanied by a reduction in serum IgG level and these results were in accordance with that reported by Sibénil et al. who stated that in NS there is an increased urinary excretion of albumin and IgG accompanied by a decrease in their serum concentration (15). Patients with NS overproduce high molecular weight proteins, such as lipoproteins, which cause hyperlipidemia and are protected from urinary loss for maintaining the oncotic pressure. High molecular weight proteins such as lipoproteins are overproduced by patients with NS, which can cause hyperlipidemia, and are protected from urinary loss which maintains the oncotic pressure. Our study showed significant correlation between serum cholesterol and serum IgG level of the nephrotic group. These results were in accordance with that reported by other studies (15, 16). After one year of follow up, we found significant correlation between IgG and IgM serum levels at initial presentation with response to therapy and rate of relapse. The more the serum IgM and the lower the serum IgG levels at presentation, the more rate of relapse as reported by Ranjit et al. (14). Farid et al. (17) found that low serum IgG level at the onset of the disease, showed significant relation with the rate of relapse. Persistently low or low normal serum IgG level during the period of remission is an important predictor of frequent relapse in children with MCNS. Stachowski et al. found a lower serum IgG level in NS cases than in the control group and it was lower in activity than in remission. Comparing the level according to steroid response, it was lower in Group A (SRNS) either FRNS or SDNS compared with patients of Group B with SSNS. It was found that between the serum albumin values and serum IgG levels, there was a direct proportional correlation. A reference pool, consisted of only 76% of IgG values of SSNS patients in remission (mostly characterized as frequent relapsers), and the decrease in serum IgG during relapse may be responsible for some of the complications associated with NS (10). Regarding the study limitation, the limitation of our study is the economic problem in the cost of laboratory investigations.

5. Conclusions

In conclusion, in all patients with NS, in comparison to healthy children, the IgG serum level is decreased and the IgM serum level is increased. There is close relation between degree of albuminuria and serum IgG levels. Serum IgG levels have prognostic value in patients with NS and can be used as an important serological marker to predict responsiveness to treatment and frequency of recurrence of disease. Further studies are needed, to determine the exact ratio that would predict the type of steroid responsiveness.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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