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Original Article

Evaluation of Children with Nephrotic Syndrome: A Single Center Experience

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ABSTRACT

Aim: Nephrotic syndrome (NS) is the most common childhood glomerular disease manifested by proteinuria, edema and hypoalbuminemia. The aim of this study was to examine children with primary NS in terms of their clinical laboratory and histopathological features, and to evaluate their treatment responses.

Materials and Methods: Thirty-eight (21 boys/17 girls) patients followed up with primary NS were included in this study.

Results: The mean age at diagnosis was 6.4 years. The histopathological diagnoses were focal segmental glomerulosclerosis (FSGS) in 17 patients, minimal change disease (MCD) in 8, membranoproliferative glomerulonephritis (MPGN) in 3, and membranous glomerulonephritis in 1 patient. Those patients with MPGN were older than those with MCD and FSGS (p=0.035). Twenty-four patients were steroid sensitive. Steroid response rates were 88% in those patients with MCD, 41% in patients with FSGS and 33% in those with MPGN. At their last visit, three patients (7.9%) were diagnosed with chronic kidney disease.

Conclusion: NS is the most common glomerular disease of childhood. Early diagnosis and the histopathological features of this disease have an important place in its prognosis. Knowing the demographic, clinical and pathological features of the disease is helpful in monitoring its progress and its prognosis.

Keywords: Nephrotic syndrome, minimal change disease, focal segmental glomerulosclerosis

Introduction

Nephrotic syndrome (NS) is the most common childhood glomerular disease manifested by proteinuria, edema and hypoalbuminemia (1). The absence of concomitant diseases in patients diagnosed with NS is called primary NS. Idiopathic NS without signs of glomerular inflammation on kidney biopsy and primary glomerulonephritis, which is characterized by the presence of cells in the urinary sediment as well as signs of inflammation in biopsy, are classified as primary NS (2). The incidence of primary NS, which is one of the causes of chronic renal failure in childhood, has been reported as 1.5-2 per 100,000 individuals and its prevalence as 16 per 100,000 individuals per year (1,2). Due to hypercoagulability, infections, recurrent hospitalizations, the side effects of immunosuppressive treatments and the risk of progression to end-stage renal failure, NS is associated with high morbidity (3). The aim of this study was to examine those patients with primary NS in terms of their clinical laboratory and histopathological features, and to evaluate their treatment responses and also to contribute to the literature with our single center experience.

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Materials and Methods

Patients

The files of patients who were being followed up with a diagnosis of NS in Ege University Faculty of Medicine, Division of Pediatric Nephrology were retrospectively analyzed. Thirty-eight (21 boys/17 girls) patients with primary NS with a follow-up period of more than one year were included in this study. The patients were grouped according to their steroid responses and evaluated in terms of their admission and follow-up laboratory and clinical data and their histopathological diagnoses.

Definitions

NS: Protein excretion above 40 mg/m^2/h in collected urine or a protein/creatinine ratio above 2,000 mg/g in spot urine or >3+ protein in dipstick and concomitant hypoalbuminemia (<2.5 g/dL) and the presence of edema.

Remission: Protein less than 4 mg/m^2/h in collected urine or a protein/creatinine excretion rate below 200 mg/g in spot urine or <1+ protein on dipstick in the urine for 3 consecutive days.

Relapse: A protein/creatinine ratio above 2,000 mg/g in spot urine or >3+ protein on dipstick for 3 consecutive days.

Steroid sensitive NS: Complete remission after four weeks of steroid therapy.

Steroid resistant NS: Failure to achieve remission in the patient despite eight weeks of steroid therapy.

Steroid dependent NS: In patients who initially achieved remission with steroid therapy; two consecutive relapses during corticosteroid therapy or within 14 days after stopping treatment.

Frequent relapse NS: In those patients evaluated as steroid sensitive; two or more relapses within 6 months after their first response; or four or more relapses in any 12-month period (4).

Treatment and Follow-up

The patients were treated according to the Kidney Disease: Improving Global Outcomes clinical practice guidelines for glomerulonephritis and oral prednisolone was initiated as steroid therapy at the first step. In accordance with the protocol of our center, prednisolone was given as a single daily dose, at a dosage of 2 mg/kg per day [maximum (max): 60 mg]. After 4 weeks of treatment, the patient's response to steroid therapy was evaluated. In those patients with response (steroid sensitive NS), the treatment was switched to every other day (eod) and 2 mg/kg eod was continued for 2 months. Afterwards, the dosage was reduced by 0.5 mg/kg every 2 weeks and the total treatment was completed in 4.5 months. After one month of prednisolone treatment, those patients who could not achieve remission (steroid resistant NS) were treated with 3 days of pulse methylprednisolone (30 mg/kg per dose, max 1 gr) and the steroid was reduced to 2 mg/kg eod. These patients were re-evaluated at the 6th week of treatment.

In those patients who could not achieve remission, kidney biopsy was performed and immunosuppressive treatments other than steroids were started. As the first line therapy, prednisolone was used to achieve remission in those patients who were defined as steroid-dependent and frequent relapse. Later, immunosuppressive treatments other than steroids, called steroid sparing agents, were initiated. Renal biopsy was performed on those patients over 12 years of age at diagnosis with macroscopic hematuria lasting longer than 5 days, reduced Complement 3 (C3) levels, hypertension (HT), systemic disease and significant azotemia (2,4).

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (v.22.0, IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). The Gauss distributions for continuous variables were evaluated using the Shapiro-Wilk test; they were expressed as mean ± standard deviation and median [minimum (min)-max]. Categorical variables were defined as numbers and percentages. Chi-squared analysis and Fisher's exact test were used for categorical variables, and the Mann-Whitney U test was used for continuous variables. Continuous variables under nonparametric conditions were compared using Student's t-test. The significance level used for these tests was $p<0.05$.

Ethical Consideration

This study was approved by the Ethics Committee of Ege University (approval date: 23.02.2023, approval no: 23-2.1T/48).

Results

Patients Characteristics and Histopathological Diagnoses

The mean age at diagnosis was 6.4±4.0 years, and the mean follow-up time was 5.6±4.1 years. While the male/female ratio was 1.2/1 in the entire NS population, this rate was 0.6/1 in minimal change disease (MCD),

0.5/1 in membranoproliferative glomerulonephritis (MPGN) and 3.5/1 in focal segmental glomerulosclerosis (FSGS) (p=0.044). Two of the patients had consanguinity between their parents, and four patients had a family history of NS. At the time of diagnosis, 5 (13.2%) of the patients had HT and 3 (7.9%) had macroscopic hematuria. Protein excretions in the collected urine were 152±146 mg/m^2/h; serum total protein was 4.2±0.63 mg/dL; serum albumin was 1.68±0.59 g/dL; serum total cholesterol was 363±181 mg/dL; urea was 28±22 mg/dL; and creatinine was 0.35±0.31 mg/dL. Kidney biopsy was performed on 29 (76.3%) of the patients. The median biopsy time was 12 months (min: 0.2 - max: 80 months).

The histopathological diagnoses were FSGS in 17 (58.6%) patients, MCD in 8 (21.1%), MPGN in 3 (7.9%), and 1 patient (2.6%) had membranous glomerulonephritis (MN). The pathological diagnoses of those patients presenting with macroscopic hematuria were MPGN (two patients) and FSGS (one patient). The histopathological diagnoses of the patients presenting with a diagnosis of HT were FSGS (two patients), MPGN (two patients) and MCD (one patient). The mean age at diagnosis was 6.3±3.5 years in MCD; 5.8±4.0 years in FSGS and 12.4±2.9 years in MPGN. The mean MPGN diagnosis age was significantly higher than the mean MCD and FSGS diagnosis ages (p=0.035) (Figure 1). The laboratory analyses of the patients at the time of their diagnoses are shown in Table 1; The urea, creatinine, uric acid and neutrophil levels in the diagnoses of those patients with MPGN were found to be statistically significantly higher than in those with MCD and FSGS (p=0.015; p=0.005; p=0.001; p=0.018). The mean high-density lipoprotein (HDL) and C3 levels of those patients with MPGN at diagnosis were statistically significantly lower than for those patients with MCD and FSGS (p=0.011; p=0.001). In all three groups, serum total protein, albumin, total cholesterol, triglyceride, low-density lipoprotein, HDL, sedimentation, C4 levels, white blood cell count and protein excretions in the collected urine were similar (p>0.05) (Table 1).

Treatment

The patients were classified according to their steroid responses; 24 (63%) patients were steroid sensitive, and 14 (37%) were steroid resistant NS. Ten (42%) of the patients diagnosed with steroid sensitive NS were steroid dependent and 1 (4%) had frequent relapses. Steroid response rates were 88% in those patients with MCD, 41% in those with FSGS and 33% in those with MPGN. Those patients with steroid sensitive NS were treated with steroid therapy during their recurrent attacks. Other immunosuppressive treatments used were calcineurin inhibitors (CNI) in 22 (88%) patients (19 cyclosporine, 3 tacrolimus), cyclophosphamide (CyA) in 12 (48%), mycophenolate mofetil (MMF) in 6 (24%), rituximab (RTX) in 4 (16%), and eculizumab in 1 (4%) patient.

In those patients with steroid-resistant NS, the response rates to other immunosuppressive treatments were, 57% to CNI, 33% to MMF, 33% to RTX, and 20% to CyA. The steroid-dependent patients' response rates were 100% to RTX, 70% to CNI, and 67% to CyA. The response rates to CNI, CyA, MMF and RTX treatments were similar between the steroid resistant and dependent NS patients (p>0.05). The non-steroid immunosuppressive treatments and their response rates are shown in Table 2.

Last Visit

At their last recorded visits, 33 (86.8%) of the patients were in remission, 2 (5.3%) were in partial remission, and 3

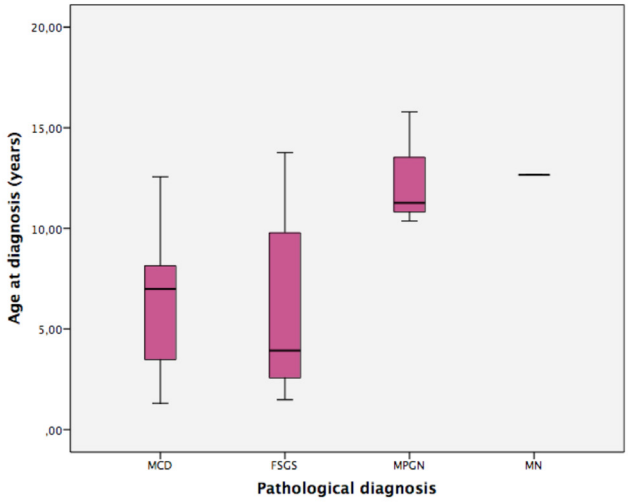

Figure 1. Age distribution of patients according to pathological diagnoses

(7.9%) were diagnosed as chronic kidney disease (CKD). The data of those patients followed up with CKD and those in partial remission are shown in Table 3.

The biochemical parameters of the patients such as urea, creatinine, uric acid values and neutrophil counts, which had been found to be significantly different among the groups according to their pathological diagnoses at the time of diagnosis, were similar in their last recorded visits (p>0.05). However, it was observed that HDL and C3 levels differed among the groups in their last recorded visits (Table 4).

Table I. Laboratory parameters at the time of diagnosis of patients according to pathological classification

	Minimal change disease		**Focal segmental glomerulosclerosis**		**Membranoproliferative glomerulonephritis**		
At the time of diagnosis	**Mean±SD**	**Median (Min.-Max.)**	**Mean±SD**	**Median (Min.-Max.)**	**Mean±SD**	**Median (Min.-Max.)**	**p-value**
Urea (mg/dL)	22±16	21 (4-45)	25±15	23 (16-62)	71±45	91 (31-120)	0.015*
Creatinine (mg/dL)	0.18±0.16	0.2 (0.1-0.4)	0.36±0.26	0.2 (0.1-1)	1.00±0.52	1.2 (0.6-1.6)	0.005*
Uric acid (mg/dL)	5.0±1.1	4.2 (3.9-6.5)	4.9±1.1	4.8 (3.0-7.6)	10.1±2.9	10 (8.0-12.2)	0.001*
Total protein (mg/dL)	4.0±0.6	4.1 (3.1-4-9)	4.2±0.6	4.5 (3.5-5.4)	4.3±0.7	4.7 (3.5-4.8)	0.868
Albumin (g/dL)	1.5±0.7	1.0 (0.6-2.4)	1.5±0.6	2.1 (0.6-2.5)	1.8±0.3	1.7 (1.6-2.2)	0.740
Total cholesterol (mg/dL)	452±177	514 (253-591)	380±211	312 (177-828)	229±180	196 (68-424)	0.517
Triglyceride (mg/dL)	168±107	170 (49-384)	198±139	102 (59-508)	245±136	249 (107-380)	0.804
LDL (mg/dL)	249±129	356 (75-402)	280±172	258 (61-651)	153±138	213 (33-304)	0.617
HDL (mg/dL)	49±13	51 (34-73)	65±17	62 (39-106)	27±15	34 (14-44)	0.011**
Sedimentation (mm/h)	59±32	60 (4-100)	57±43	58 (4-140)	37±29	28 (14-70)	0.863
WBC ($x10^3/mm^3$)	7.6±2.8	7.0 (4.4-13)	9.2±2.6	8.4 (6.0-15.4)	12.7±2.0	13.8 (10.3-14.1)	0.068
Neutrophil ($x10^3/mm^3$)	3.8±2.2	3.2 (1.5-8)	4.5±2.3	3.7 (1.3-9.5)	9.3±3.6	10.9 (5.3-12)	0.018*
Complement 3 (mg/dL)	107±13	112 (93-129)	137±20	127 (111-176)	45±27	45 (18-73)	0.001**
Complement 4 (mg/dL)	23±11	19 (12-36)	41±39	25 (12-61)	14±5	13 (8-19)	0.222
Urine protein ($mg/m^2/s$)	238±230	166 (63-642)	123±77	96 (41-291)	103±74	74 (56-182)	0.219

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, Min.-Max.: Minimum-Maximum

Table II. Non-steroid immunosuppressive treatments and distribution of treatment responses

	All patients N=25		**Steroid resistant NS N=14**		**Steroid dependent NS N=10**		**Frequent relapse NS N=1**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
CNI treatment	22	88	13	93	9	90	0	0
CNI responsive	15	68	8	57	7	70	-	-
CyA treatment	12	48	5	36	6	60	1	100
CyA responsive	6	50	1	20	4	67	1	100
MMF treatment	6	24	3	21	3	30	0	0
MMF responsive	1	17	1	33	0	0	-	-
RTX treatment	4	16	3	21	1	10	0	0
RTX responsive	2	50	1	33	1	100	-	-
ECU treatment	1	4	1	7	0	0%	-	0
ECU responsive	1	100	1	100	-	-	-	-

CNI: Calcineurin inhibitor, CyA: Cyclophosphamide, MMF: mycophenolate mofetil, RTX: Rituximab, ECU: Eculizumab

Table III. Data of patients followed up with partial remission and chronic kidney disease

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnose age (years)	4	11	9	10	10
Gender	Male	Male	Female	Male	Male
Creatinine level at diagnosis (mg/dL)	0.30	0.60	0.15	0.20	0.43
Histopathological classification	FSGS	FSGS	FSGS	FSGS	FSGS
Steroid response	Resistant	Resistant	Resistant	Resistant	Resistant
Genetic mutation	-	ADCK4	ADCK4	-	-
Follow-up (months)	35	43	142	42	13
Treatment	HD	PD	Coenzyme Q	Cyclosporine	Cyclosporine
Last visit	CKD Grade 5	CKD Grade 5	CKD Grade 4	Partial remission	Partial remission

FSGS: Focal segmental glomerulosclerosis, HD: Hemodialysis, PD: Peritoneal dialysis, CKD: Chronic kidney disease

Table IV. Laboratory parameters of the patients at last visit according to pathological classification

Last visit	Minimal change disease		Focal segmental glomerulosclerosis		Membranoproliferative glomerulonephritis		
	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)	p-value
Urea (mg/dL)	17±3	(13-22)	40±38	(15-137)	36±17	18-53	0.257
Creatinine (mg/dL)	0.53±0.10	(0.39-0.67)	1.37±2.2	(0.22-9.20)	0.77±0.21	(0.58-1.00)	0.532
Uric acid (mg/dL)	4.1±0.9	(2.6-5.7)	5.0±1.4	(3.1-8.3)	4.8±0.3	(4.5-5.1)	0.236
HDL (mg/dL)	52±15	(33-73)	70±45	(23-100)	122±94	(55-189)	0.019
Neutrophil (x10^3/mm^3)	3.7±1.1	(2.1-5.0)	4.4±2.1	(1.8-9.4)	3.6±1.9	(1.4-5.1)	0.643
Complement 3 (mg/dL)	94±8	(81-104)	133±27	(107-191)	92±11	(80-102)	0.002

HDL: High-density lipoprotein, SD: Standard deviation, Min.-Max.: Minimum-Maximum

Discussion

NS is the most common glomerular disease of childhood, and proteinuria, hypoalbuminemia and edema are its diagnostic criteria. Although the male/female gender ratio is variable, studies have reported male gender predominance at rates of 1.6-3.8 males to 1 female (1,4,5). In our study, although the male gender was more common, a much lower male predominance was found with a ratio of 1.2/1 compared to the literature. Looking at the gender distributions of NS subtypes, male dominance in minimal lesion disease (MLD) and FSGS has been reported in the literature at rates of 5-6/1, but this difference was found in our study only in the patient group diagnosed with FSGS (6).

Admission age has a prognostic importance on the histopathological diagnosis of this disease. The average age at diagnosis in idiopathic NS is 2-7 years; about 70% of patients with MCD are diagnosed under 5 years of age. The average age of FSGS at diagnosis is 6 years old (2,5,7). While MCD is the most common pathological diagnosis under 12 years of age, FSGS is common in the age group above 12 years of age (6). In our study group, the mean age of FSGS at diagnosis was found to be similar to MCD. We think that this difference in age and gender distribution is due to the fact that our study group consisted of a small patient population and our center is a reference center. MPGN, one of the primary glomerulonephritis group, is frequently diagnosed in late adolescence and adulthood (4). In our study, the mean age at diagnosis of MPGN was found to be 12.4 years, and this mean age was found to be significantly higher than the mean ages at diagnosis for MCD and FSGS.

HT suggest a diagnosis other than idiopathic NS (7). HT exists in one of every three patients in those individuals with MPGN, and the possibility of HT increases as the disease progresses (8). Macroscopic hematuria is a more common initial finding in patients with MPGN who were diagnosed in childhood compared to those diagnosed in their adulthood. The frequency of hematuria has been reported to be 20-30% in routine urine analysis in patients with MPGN (9). In our study, the prevalence of HT and macroscopic hematuria in patients with MPGN was 67%.

Histopathological features are of great importance in determining steroid sensitivity and the long-term prognosis in NS. Although indications for biopsy may differ between centers, the generally accepted indications are as follows; age of onset less than 1 year old or greater than 8 years old, steroid resistant NS unresponsive to 8-weeks prednisolone treatment, unusual clinical features such as HT and macroscopic hematuria and impairment in renal function. Depending on the patient population and the size of the centers, the biopsy and histopathological diagnosis frequencies vary in different studies, although FSGS and MLD are generally in the first two places (10-12). In this study, the frequency of biopsy was 76.3%, and similar to the literature, 17 (58.6%) of the patients were FSGS, 8 (21.1%) were MLD, 3 (7.9%) were MPGN and 1 (2.6%) was diagnosed with MN.

NS is also classified according to steroid sensitivity in addition to its histopathological classification, and this classification and the treatment responses of the patients also guide the prognosis. Steroid sensitivity rates were seen to vary between 80-90% in recent studies; and steroid dependence has been reported with a rate of up to 50% in steroid sensitive groups (13-15). In our patients, while the rate of steroid sensitive NS was 63%, 42% of these patients were steroid dependent.

In those patients with steroid-resistant NS, FSGS is the histopathological diagnosis with the highest rate of steroid resistance and the highest rate of CKD (16). The pathological diagnosis of 54% (8/14 patients) of the patients with steroid-resistant NS in our study was FSGS. The steroid response rate was 88% in those patients with MCD, 41% in those with FSGS; and 33% in those with MPGN. All of the patients who progressed to CKD were steroid-resistant NS and their histopathological diagnosis was FSGS. Table 3 shows the data of those patients followed up with partial remission and CKD.

Study Limitations

The retrospective nature and limited number of patients are the limitations of this study.

Conclusion

NS is the most common glomerular disease of childhood. Early diagnosis and the histopathological features of this disease have an important place in its prognosis. Knowing the demographic, clinical and pathological features of this disease is helpful in monitoring its progress and for its prognosis.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Ege University (approval date: 23.02.2023, approval no: 23-2.1T/48).

Informed Consent: Written informed consent was obtained from all the patients or their parents/guardians.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.K.B., C.K, A.K., Design: S.T., Data Collection or Processing: S.T., N.E.K., Analysis or Interpretation: S.T., İ.K.B., Literature Search: S.T., N.E.K., Writing: S.T.

Conflict of Interest: None of authors have any conflicts of interest to report.

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