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Evaluation of Response to Treatment in Children with Nephrotic Syndrome over a 10-Year Period: A Retrospective Study

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Abstract

Background

Nephrotic syndrome (NS), defined as massive loss of urinary protein results in a triad of hypoalbuminemia, hyperlipidemia and edema. We aimed to determine the frequency of clinical symptoms, laboratory findings and treatment response in children with Nephrotic Syndrome.

Materials and Methods: We conducted a longitudinal retrospective study from 2009 to 2019 at a single regional pediatric center, Zahedan, Iran, on 206 children (up to 14 years) with NS that were selected from all clinical records files. Parameters extracted included age, sex, presenting symptoms, blood pressure. Laboratory information included complete blood count, urine analysis, 24-hour urinary protein excretion, creatinine clearance, serum electrolytes, serum urea and creatinine levels, total protein and albumin, triglyceride and cholesterol, acute phase reactant, treatment and outcome. All the data extracted were recorded in pre-prepared forms.

Results: A total of 107 men (52%) and 99 women (49%) participated in the study. Edema was most commonly found in 197 (95.6%), respiratory distress in 2 (0.9%), abdominal pain in 45 (21.8%), nausea and vomiting in 28 (13.5%), and gross hematuria in 6 (2.9%). Leukopenia was seen in 0.5% followed by 42.4% of normal white blood cells (WBCs) and 57.1% leukocytosis. 74.4% of all patients had anemia in their laboratory tests in spite of thrombocytopenia only seen in 1.7%. 49% had pyuria and hematuria was seen in 41%. The mean level of serum albumin was 2.5 g/l, cholesterol was 381 mg/dl, triglyceride was 287 mg/dl and the mean level of 24-hour urinary protein excretion was 2084 mg/dl.

Conclusion

The most common clinical symptom in nephrotic syndrome was edema followed by nausea and vomiting and abdominal pain.

Key Words: Pediatrics, Nephrotic syndrome, Therapeutics.

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1- INTRODUCTION

Nephrotic syndrome (NS) defined as massive loss of urinary protein (proteinuria, mostly albuminuria greater than 40 mg/m2 per hour (>3.5 g/24 hr or a urine protein: creatinine ratio >2), results in a triad of hypoalbuminemia (less than 30 g/L), hyperlipidemia (cholesterol > 300 mg/dl) and edema (most common presenting symptom) (1, 2). Since 24-hour urine collection in children, especially young children, is difficult and unreliable, many pediatric nephrologists prefer to use morning urine samples to determine the protein: creatinine ratio. Although rare presentations of NS as part of the syndrome, hypertension, hematuria, and azotemia may occur (3). In healthy individuals most of the filtered albumin infiltrated to the tubules by glomerular filtration barrier (involved fenestrated endothelium, glomerular basement membrane, and glomerular epithelium) is reabsorbed and less than 0.1% of plasma albumin may traverse (4, 5). In NS patients due to increased permeability through the damaged basement membrane in the renal glomerulus especially infectious or thrombo-embolic conditions, glomerular urinary space albumin concentration is 3.5 mg/L (5, 6). Estimated annual incidence of NS is believed to affect 1-3 per 100,000 children < 16 years of age. More common in boys, once adolescence is reached there is no significant difference between genders. According to steroid response, NS is divided into steroid-responsible and steroid-resistant groups (2). Steroid-responsible NS, in spite of generally having a good prognosis, may have periodic recurrences and complications because of long term use of corticosteroids. However, steroid-resistant patients are at risk for chronic kidney failure and account for 10-20% of the causes of advanced kidney failure in children. FSGS (Focal segmental glomerulosclerosis) is the most common glomerular disease leading to chronic kidney failure in children (7, 8). Data on differences in racial predispose to NS in children are lacking. In the United States (9), the annual incidence of Nephrotic Syndrome is 2-7 cases per 100,000 children under 16, and the cumulative incidence is 16 cases per 100,000. In a study in New Zealand, the incidence of Nephrotic Syndrome was 20 cases per 1 million children under 15 years of age (9). NS is categorized as Primary NS (PNS or Idiopathic Nephrotic Syndrome) and Secondary NS (SNS). PNS Glomerular lesions include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (1, 2, 4). Secondary causes include systemic lupus erythematosus, Henoch Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria), (2, 6). Congenital and hereditary proteinuria syndromes may result from mutations of genes that code for podocyte proteins, including nephrin, podocin, or the cation channel 6 protein (6).

2- MATERIALS AND METHODS

Nephrotic syndrome (NS) defined as massive loss of urinary protein (proteinuria, mostly albuminuria greater than 40 mg/m2 per hour (>3.5 g/24 hr or a urine protein: creatinine ratio >2), results in a triad of hypoalbuminemia (less than 30 g/L), hyperlipidemia (cholesterol > 300 mg/dl) and edema (most common presenting symptom) (1, 2). Since 24-hour urine collection in children, especially young children, is difficult and unreliable, many pediatric nephrologists prefer to use morning urine samples to determine the protein: creatinine ratio. Although rare presentations of NS as part of the syndrome, hypertension, hematuria, and azotemia may occur (3). In healthy individuals most of the filtered albumin infiltrated to the tubules by glomerular

filtration barrier (involved fenestrated endothelium, glomerular basement membrane, and glomerular epithelium) is reabsorbed and less than 0.1% of plasma albumin may traverse (4, 5). In NS patients due to increased permeability through the damaged basement membrane in the renal glomerulus especially infectious or thrombo-embolic conditions, glomerular urinary space albumin concentration is 3.5 mg/L (5, 6). Estimated annual incidence of NS is believed to affect 1-3 per 100,000 children < 16 years of age. More common in boys, once adolescence is reached there is no significant difference between genders. According to steroid response, NS is divided into steroid-responsible and steroid-resistant groups (2). Steroid-responsible NS, in spite of generally having a good prognosis, may have periodic recurrences and complications because of long term use of corticosteroids. However, steroid-resistant patients are at risk for chronic kidney failure and account for 10-20% of the causes of advanced kidney failure in children. FSGS (Focal segmental glomerulosclerosis) is the most common glomerular disease leading to chronic kidney failure in children (7, 8). Data on differences in racial predispose to NS in children are lacking. In the United States (9), the annual incidence of Nephrotic Syndrome is 2-7 cases per 100,000 children under 16, and the cumulative incidence is 16 cases per 100,000. In a study in New Zealand, the incidence of Nephrotic Syndrome was 20 cases per 1 million children under 15 years of age (9). NS is categorized as Primary NS (PNS or Idiopathic Nephrotic Syndrome) and Secondary NS (SNS). PNS Glomerular lesions include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (1, 2, 4). Secondary causes include systemic lupus erythematosus, Henoch Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria), (2, 6). Congenital and hereditary proteinuria syndromes may result from mutations of genes that code for podocyte proteins, including nephrin, podocin, or the cation channel 6 protein (6).

Table-1: Age distribution of the studied children.

Age group (Year)	Number	Percentage
Less than 1 year	6	3
1 – 5 years	99	48
More than 5 years	101	49

Table-2: Abundance of laboratory findings**.**

WBC	Leukopenia	0.5%
	Normal	42.4%
	Leukocytosis	% ۵۷/۱
HB	Anemia	% ۷۴/۴
	Normal	% ۲۵/۶
PLT	Thrombocytopenia	% ۱/۷
	Normal	% ۵۸/۹
	Thrombocytosis	% ۳۹/۴
Pyuria	Yes	% ۴۹
	No	% ۶۰
Hematuria	Yes	% ۴۱
	No	% ۵۹

WBC: White Blood Cell, HB: Hemoglobin, PLT: Platelet.

Table-3: Laboratory findings in patients with nephrotic syndrome.

Variables	Number	Minimum	Maximum	Mean	Std. Deviation
WBC (*1000/mm^3)	198	3.7	30.6	11.4	4.0
HB (gm/dl)	199	6.2	16.8	11.8	1.9
PLT (*1000/mm^3)	180	104	935	417	146
BUN (mg/dl)	197	5	90	18.3	14.0
Creatinine (mg/dl)	193	.30	7.8	.63	.65
Na (mEq/L)	185	120	173	139	5.19
Triglyceride (mg/dl)	163	34	851	287	178
Cholesterol (mg/dl)	163	61	900	381	145
Total protein (mg/dl)	178	2.8	8.7	4.7	1.07
Alb (g/dl)	179	1.2	5.3	2.5	0.7
Pro24h (gr)	104	408	8150	2084	1475
Urine Pr/Cr	104	.3	49	9.6	10.7

WBC: White Blood Cell, HB: Hemoglobin, PLT: Platelet.

Table-4: Comparison of children based on treatment response, age and gender**.**

Treatment response	Number (%)	Age distribution (p-value = 0.892)			Phenotype (P-value = 0.316)	
		<1 year (%)	1-5 year (%)	>5 year (%)	Male	Female
Steroid sensitive	140 (69%)	66.7	68.8	69.3	73.6	63.9
Frequent relapsers	19 (9.4%)	0	10.4	8.9	8.5	10.3
Steroid resistance	44 (21.7%)	33.3	20.8	21.8	17.9	25.8

4- DISCUSSION

The aim of this study was to evaluate the frequency of clinical symptoms, laboratory findings and response to treatment of children with Nephrotic Syndrome referred to Ali-Ibn-Abitaleb hospital. The records of 206 children with nephrotic syndrome who were admitted to hospital during the years 2009 to 2019 were evaluated. In our study the male to female ratio was 1.08/1 (52% male vs. 49% female). According to studies in Iran, Sorkhi in Babol hospital, showed male to female ratio was 1.6/1 (11), Mortazavi in Tabriz, showed male to female ratio was 2:1 (12), and Madani et al. in Center for Medical Pediatrics showed male to female ratio as 1.75:1 (13). In a study in Turkey, the male to female ratio was estimated as 1.6/1 (14). Kumar et al. in India showed this ratio as 2.76/1. (15). According to the findings of our study and studies in different geographical locations, nephrotic syndrome occurs more frequently in male gender. In this study, edema was the most common clinical manifestation in children with Nephrotic Syndrome (95.6%). 40% of children had pyuria and 41% had microscopic hematuria. In Safaei et al.'s study conducted in 2010, facial edema was present in 95%, microscopic hematuria in 23%, Gross hematuria in 5% and hypertension in 11% of children. At the time of referral, 11% of children had peritonitis, 18% had pneumonia and upper respiratory infection, and 4% had cellulitis (3). In Kumar et al.'s study in India in

2003, facial edema was present in 98.6% of children, microscopic hematuria in 41%, and Gross hematuria in 2.5% and hypertension in 27% of children (15). In other studies done all over the world, the incidence of edema as initial presentation of NS was higher and was in line with our findings (11, 12, 14). In our study, 57% of children had leukocytosis, 74% Anemia and 39% were diagnosed with thrombocytosis. The mean level of serum triglyceride was 287±178 mg/dl (range of 34-851), mean serum cholesterol was 386±141 mg/dl (range of 61-900), mean serum albumin was 2.5±0.7 g/l (range of 1.2-5.3) and mean 24-hour urinary protein was 2084±1475 mg/dl (range of 408-8150). In Safaei and Maleknezhad's study, the mean level of serum albumin was 1.75±0.45 g/l, the mean level of 24-hour urinary protein excretion was 3344.84±2344.38 mg/dl, mean level of serum cholesterol was 473±160 mg/dl and mean level of serum of triglyceride was 335.4±113.8 mg/dl (3).

In Safaei and Maleknezhad's study, the mean level of albumin was lower than ours and was much nearer to international range of albumin in NS and it was perhaps because of the much higher level of 24-hour protein excretion than our study detected. In another study by Esfahani et al. done in Tehran in 2008, proteinuria in children with Nephrotic Syndrome ranged from 300 to 16450 mg in 24-hour urinary (mean: 2915±2244 mg). Mean serum albumin, triglyceride and cholesterol levels were 2.2±0.7 g/dL, 340±214 mg/dl, and 415±139 mg/dl, respectively (16). This study was closer to our findings. In Banh et al.'s study which evaluated the ethical and laboratory findings in children diagnosed with NS between ages 1 and 18 years old in Toronto, Canada, the children were divided to three ethnic groups of Europeans, South Asians, and East/Southeast Asians. The mean levels of serum albumin in Europeans, South Asians and East/Southeast Asians were 2.02±0.53 g/dl, 1.76±0.48 g/dl and 1.97±0.55 g/dl respectively. Mean level of serum cholesterol was 383±114 mg/dl, 449±125 mg/dl and 422±100 mg/dl respectively (17). The findings of study was in line with our study. In our study, 69% of children diagnosed with NS were steroid sensitive and remission was achieved after treatment. 21.7% of them were steroid resistant and 9.4% of all patients had frequent relapse after treatment. In Seyedzadeh et al.'s study conducted in Kermanshah, from 104 children diagnosed as NS, 26 (25%) of them were steroid resistant, 78 (75%) were steroid sensitive and from these, 39 cases had frequent relapses (18). These findings were close to ours. In Safaei's study, 66% of patients were steroid sensitive, 20% were steroid resistant and 14% were steroid dependent.

Among steroid-sensitive patients, 37% had no recurrence, 39% had frequent recurrence, and 26% had infrequent recurrence (3). These findings were close to ours. In Mortazavi et al.'s study, from 103 NS children, 77% were steroid sensitive and 23% were steroid resistant (12), which was in line with other previous studies done in this region and ours as well. In Banh et al.'s study findings of treatment response in Europeans, South Asians and East/Southeast Asians were reported. Complete remission was seen in 26 (15%), 52 (21.9%), and 19 (27.5%) cases, respectively. Initial steroid resistance seen in 13 (7.5%), 6 (2.5%), 5 (7.2%) cases, respectively as well (17).

The complete remission was lower in Europeans group by higher incidence of steroid resistance in the same group. This differences may be because of differences in ethical situation and should further evaluated in future investigations. Other numerical findings in two remaining groups were in line with our findings. In Obiagwu et al.'s study conducted in Nigeria, in 2013, that investigated the

treatment response in 20 Nephrotic Syndrome pediatric patients, 55% were steroid resistant, and 15% of them experienced frequent relapses (19). This higher level of resistance to steroid may initially be again, because of the ethical situation.

4-1. Limitations of the study

The incompleteness of the files extracted from the hospital's database limited the number of patients.

5- CONCLUSION

Our study showed that the most common clinical symptom in nephrotic syndrome was edema, which has been achieved in all studies. There have been some differences in treatment response in these patients around the world, which may be due to differences in race and genetics, which is suggested to be examined more closely in future studies.

6- AUTHORS' CONTRIBUTION

Simin Sadeghi-Bojd developed the protocol and revised the manuscript, Seyed Hosein Soleimanzadeh Mousavi wrote the abstract, performed data analysis and interpretation, wrote and prepared the manuscript, and was the corresponding author; Zeinab Tavakolikia performed the laboratory studies; Somaie Naderijo collected the data.

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8- CONFLICT OF INTEREST: None.

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