ORIGINAL RESEARCH PAPER
Volume-6 | Issue-12 | December-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 93.98
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF NEPHROTIC SYNDROME IN CHILDREN

Pediatrics

Vishruti Gandhi	Associate Professor, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India.
Dr. Hemal Dave*	Assistant Professor, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India. *Corresponding Author
Dr. Varun Paliwal	Resident, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India.
Dr. Shivangi Tetarbe	Resident, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India.
Dr. Manish Rasania	Professor, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India.
Dr. Rahul Gupta	Resident, Department Of Pediatrics, S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth, Waghodiya, Vadodara, Gujarat, India.

ABSTRACT

Objectives: To study the clinical and biochemical profile and response to Prednisolone in Nephrotic Syndrome patients presenting typically and atypically.

Method: A Prospective observational study was done in 40 cases of nephrotic syndrome. Detailed history of presenting symptoms, age of onset of disease, sex of child and family history was taken.

Result: Mean age was 6.28±3.82 years. Male to female ratio was 1.35:1. 19 (47.5%) patients had atypical and 21 (52.5%) patients had typical presentation. Biochemical profile was similar except for S. creatinine levels which was significantly higher in atypical type (0.001) as compared to typical type (p=0.001). A total of 36 (90%) patients had infection during proteinuria out of which UTI was most common infection (27.5%). During remission, 18 (45%) patients had infection out of which URTI was most common (25%) and no infection was seen in 55% cases. All the patients received Tab. Prednisolone 6 week daily then on every alternate day for 6 weeks. In present study 52.5% showed no relapse during follow up, 37.5% had infrequent relapse, 10% had frequent relapse.

Conclusion: The present study showed male predominance with variable clinical presentation and biochemical findings during hospitalization in both typical and atypical cases of nephrotic syndrome. Also rate of infection was higher during proteinuria phase while during remission infection rate was low. Study showed no difference in outcome of steroid therapy in atypical and typical cases of nephrotic syndrome. Frequent relapse was more common in patients with atypical presentation.

KEYWORDS

Nephrotic syndrome, atypical, typical, prednisolone.

INTRODUCTION

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy protenuria. Nephrotic range protenuria is defined as protenuria >3.5g/24hrs or a urine protein creatinine ratio >2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (</= 2.5g/ dl), edema and hyperlipidemia (cholesterol >200 mg/dl).[1]

Nephrotic syndrome has an incidence of 2 to 7 per 100,000 children and a prevalence of about 16 cases per 100,000 children per year.[2] Epidemiological studies indicate a relatively higher incidence of nephrotic syndrome in children from south Asia.[3] Nephrotic syndrome is seen to affect adults as well as children in all the ethnicities and in both the genders. It can present in typical form, or in association with nephritic syndrome, *viz.* presence of glomerular inflammation, hematuria and impaired kidney function. It can be idiopathic as well as non-idiopathic in nature. However, idiopathic nephrotic syndrome is more common, affecting nearly 95% of children.[3] There may be some underlying disorder in remaining 5 per cent cases. These disorders include systemic lupus erythematosus, Henoch Schonlein purpura, amyloidosis and infection with HIV, parvovirus B19 and hepatitis B and C viruses.[4]

Irrespective of nature of type, it is responsible for a number of complications including infection, cardiovascular disease, bone mineral loss, acute renal failure, and thromboembolism[2]. Nephrotic syndrome in children has a long-term effect on the health of children. The majority of nephrotic children have minimal change lesions, and these will either remit spontaneously within three years (two-thirds of the cases) or have earlier remission without complications following treatment with corticosteroids (CS) or cytotoxic agents (95%).5 However, the minority of children who have lesions of focal segmental glomerulosclerosis and severe and prolonged proteinuria are at high risk for complications. In these children, full nephrotic syndrome may progress to renal failure and even to dialysis, ultimately requiring renal transplantation.[6] Adequate oral corticosteroid therapy is recommen ded at the initial episode of nephrotic syndrome in children.[7] The commonly used preparations are prednisone (USA) or prednisolone (most other countries including India)[3]. Around 80% of children with nephrotic syndrome show remission of proteinuria after corticosteroid therapy and are termed as "steroid sensitive". However, most of the patients have multiple relapses which place them at risk for steroid toxicity, systemic infections and other complications. Nearly 20% of remaining children do not respond to steroid therapy are termed as "steroid resistant" and are also at risk for complications including renal insufficiency.[7]

Frequently relapsing and steroid-dependent NS is associated with long-term complications of steroids, including dyslipidemia, cataracts, osteoporosis and fractures, obesity, impaired growth, and infertility.[8] Risk factors for frequent relapses include an early age of onset, short initial therapy, delayed time to remission and brief duration of the first remission. The management of patients with frequent relapses, steroid dependence and late resistance is difficult and requires the use of alternative agents.[9] Minimal change Nephrotic syndrome (MCNS) has been documented to be the most common histopathological lesion in children, especially in temperate regions, and it generally has a favorable response to glucocorticoid therapy in over 80% of patients.[10,11] Children having steroid-resistant Nephrotic syndrome (SRNS) with Focal and Segmental Glomerular sclerosis (FSGS) or MCNS run a high risk of resistance to immunosuppressive therapy.[12]

The present study was carried out with the aim to study the clinical and biochemical profile, treatment response to prednisolone therapy and infection rate in children presenting in classical way and those who present in atypical way and comparison between them.

METHODS

Study Design: Prospective observational study.

Settings: Dhiraj General Hospital, affiliated to Smt. B.K. Shah Medical Institute and Research Centre, Vadodara, is a tertiary care teaching hospital catering to a diverse demography of patients in and around Vadodara.

Participants:

- All cases of Nephrotic syndrome full filling diagnostic criteria – including relapse cases.
- **Exclusion criteria:** Cases of generalized edema due to causes other than nephrotic syndrome will be excluded.

Variables : Clinical and Biochemical presentation, response to Prednisolone therapy, difference in clinical and biochemical presentation as well as clinical course between Atypical and Classical presentations and infection profile.

Study Population: Pediatrics patients of age group 1yr to 15yrs visiting OPD and admitted to ward in S.B.K.S.M.I.R.C, Vadodara.

Sample Size: 40 cases.

Statistical Methods: The data was analyzed using Statistical Package for Social Sciences version 20.0. Statistical tests employed were Mean, Standard Deviation, Chi square test, Student 't' test and Level of significance($p < 0.05$ Significant).

Study was done after clearance from institutional Ethics committee.

RESULT

On the basis of present study, the following findings have been obtained:

Age of pediatric patients with nephrotic syndrome ranged from 1-15 years. Majority of patients (82.5%) were aged 1-10 years. Mean age of patients was 6.28±3.82 years. Male to female ratio of study population was1.35:1.

Presenting complains and investigations are mentioned in table 1 and table 2 respectively.

Table 1: Presenting Complaints.

SN.	COMPLAINT	NO. =40	PERCENTAGE(%)
1.	**Edema**	40	100%
	Generalized (Anasarca)	16	40 %
	Facial only	23	57.5%
	Scrotal	1	2.5%
2.	**Abdominal Pain/ Distension**	33	82.5%
	Abdominal Pain	11	27.5%
	Abdominal Distension	13	32.5%
	Abdominal Pain & Distension	9	22.5%
3.	**Breathlessness**	21	52.5%
4.	**Urinary complaints**	33	82.5%
	Oliguria	23	57.5%
	Burning Micturition	19	47.5%
	No urinary complain	7	17.5%
5.	**OTHER**	36	90%
	Fever	29	72.5%
	Cough and cold	7	17.5%

Table 2: Investigations.

Sl. No	Parameters	Cut off	Percentage (n=40)
1.	**Vitals**		
	Blood pressure	>/=95th percentile	60%
2.	**Blood investigations**		
	Haemoglobin	<11 g/dl	70%
	total leukocyte count	>11000	55%
	ESR	<20 mm/hr	75%
	Serum albumin levels	<2.5 g/dl	97.5%
	Sr. cholesterol	>200 mg/dl	90%
	Serum sodium	<135 or >155	37.5%
	Serum potassium	<3.5 or >6	5%
3.	**Urine investigation**		
	24-hr urinary protein	>40 mg/m^2/hr	100%
	Spot urine protein/creatinine ratio	>2	100%
	Urinary albumin	3+ or above	90%
	urinary RBC	>5/hpf	25%
	pus cells	>5/hpf	55%
	Urine culture	Positive	60%

On admission, 26 patients were case of first episode (65%), 9 (22.5%) had frequent relapse and 5 (12.5%) had infrequent relapse. All patients (100%) were steroid sensitive in which 4 (10%) were steroid dependent. None of the patients were steroid resistant.

USG findings and infection rate in typical and atypical are described in table 3.

Table 3: USG findings and infection rate

SN	Characteristic	Atypical (n=19)	Typical (n=21)	Total (n=40)	Significance
1.	USG Renal involvement	5 (26.3%)	7 (33.3%)	12(30%)	χ^2=0.234; π=0.629
2.	USG Hepatic involvement	4 (21.1%)	3 (14.3%)	7(17.2%)	χ^2=0.316; π=0.574
3.	USG Renal/Hepatic involvement	10 (52.6%)	8 (38.1%)	18(42.8)	χ^2=0.852; π=0.356
4.	Biopsy done	3 (15.8%)*	Not done	3(7.5%)	-
5.	Infection during proteinuria	19 (100%)	17 (81.0%)	36(90%)	χ^2=4.021; π=0.045
6.	Infection during remission	9 (47.4%)	9 (42.9%)	18(45%)	χ^2=0.082; π=0.775

*showed MCNS.

Serum C3 estimation was done in 30 cases. Out of 30 cases, 21(70%) had normal C3 levels and 9 (30%) had low C3 level. There were 6 (15%) Mantoux positive cases and X-ray chest were positive for tuberculosis in 12 (30%) cases. UTI was the most common infection (27.5%) followed by URTI and LRTI (25% each). Other infections were present in 22.5% patients. During remission, Upper respiratory infection, lower respiratory infection and viral fever were seen in 28%, 14% and 3% patients.

Differences between Atypical and Typical type of Presentation are given in table 4.

Table 4: Differences in Atypical and Typical type of Presentation

SN	Characteristic	Atypical (n=19)	Typical (n=21)	Significance
	Demographic			
1.	Age	(2-15) 5.21±2.44	(1-10)7.24±4.58	t=1.720; p=0.094
2.	Gender			
	Male	11 (57.9%)	12 (57.1%)	χ^2=0.002; π=0.962
	Female	8 (42.1%)	9 (42.9%)	
3.	SES (mod. kuppuswami)			
	Lower	14 (73.7%)	16 (76.2%)	χ^2=0.033; π=0.855
	Lower Middle	5 (26.3%)	5 (23.8%)	
	Symptoms			
1.	Abdominal distension	11 (57.8%)	11 (52.3%)	χ^2=0.129; π=0.720

2.	Breathlessness	11 (57.8%)	12 (57.1%)	χ^2=3.879; p=0.049
3.	Oliguria	7 (37%)	16 (76.2%)	χ^2=0.302; π=0.583
4.	Cough and cold	3 (15.7%)	8 (38.1%)	χ^2=0.631; π=0.427
5.	Fever	16 (84.2%)	14 (66%)	χ^2=2.489; π=0.115
6.	Burning micturition	12 (63%)	7 (33.3%)	χ^2=0.928; π=0.335
Examination and Investigations				
1.	BP>95th centile	16 (84%)	2 (9.5%)	χ^2=2.934; π=0.087
2.	Generalized edema	7 (36.8%)	3 (14.3%)	χ^2=2.707; π=0.100
3.	Facial edema	12 (63.1%)	11 (52.4%)	χ^2=0.422; π=0.516
4.	S. Albumin low (<2.5gm/dl)	19 (100%) 2.04±0.73	21 (100%) 2.07±0.66	t=0.124; p=0.902
5.	Cholesterol (high)	15 (78.9%) 399.6±110.5	21 (100%) 421.9±100.7	t=0.667; p=0.509
6.	Ur. Albumin >3+	19 (100%)	17 (81.0%)	χ^2=4.021; π=0.045
7.	RBC 5-10	12 (63.1%)	6 (28.5)	χ^2=4.829; π=0.028
8.	Pus cells >5	9 (47.4%)	12 (57.1%)	χ^2=0.382; π=0.536
9.	Positive urine culture	12 (63.2%)	12 (57.1%)	χ^2=0.150; π=0.698

Biochemical profile of two groups was also similar except for S. creatinine levels which were significantly higher in atypical type (p=0.001) as compared to typical type. Atypical type of patients had steroid response (urine dipstick negative) earlier as compared to that of typical type of patients. The atypical patients also had significantly (p=0.001) low C3 levels and high infection rate (p=0.045) However, they did not show a significant difference in treatment response but frequencies of relapse were more common with atypical type of presentation.

Treatment, follow up and complications of treatment are mentioned in table 5.

Table 5: Treatment, follow-up and complications

SL NO.		Atypical (n=19)	Typical (n=21)	Total (n=40)	Total Percentage (%)
TREATMENT					
1.	Routine Steroid therapy	15 (78.9%)	21	36	90%
2.	Levamisole with alt day prednisolone	3 (15.7%)	0	3	7.5%
3.	Cyclophospham ide with alt day prednisolone	1 (5.3%)	0	1	2.5%
6 MONTH-FOLLOW UP FINDING					
1.	Remission	9 (47.2%)	12 (57.2%)	21	52.5%
2.	Infrequent relapse	6 (31.8%)	9 (42.8%)	15	37.5%
3.	Frequent relapse (dependent)	4 (21%)	0	4	10%
COMPLICATION OF STEROIDS					
1.	Abnormal weight gain, Moon Face	4 (21%)	0	04	10%
2.	No Complication	15 (78.9%)	21 (100%)	36	90%

All the patients received Tab. Prednisolone 6 week daily and on every alternate day for 6 weeks. In 4 steroid dependent patients, 3 were given tab. Levamisole (n=3) and 1 was given Syrup cyclophosphamide (n=1) were given in addition to alternate day prednisolone.

After starting prednisolone (2mg/kg/day), out of 40 cases, 18 cases (45%) were urine protein free within 10 days and 17 cases (42.5%) were urine protein free between 10-20 days, and 5 cases (12.5%) were urine protein free between 20-30 days.

There was not any case of steroid resistance (persistent urinary proteinuria beyond 30 days of steroid therapy).

DISCUSSION

In present study, we studied the clinical and biochemical profile, treatment response and infection rate among pediatric patients presenting with nephrotic syndrome and found out factors responsible for poor treatment response and higher risk of infection.

In present study, though the age range of patients was 1-15 years yet age group 1-10 years was most commonly affected and comprised 82.5% of our sample and mean age was 6.28±3.82 years. Several other workers also observed it to be more common in younger age groups. Similar to our study, Safaei and Maleknejad (2009)[10] in their study on Iranian children aged up to 14 years of age also found the mean age to be only 4.87±3.24 years, thus indicating the skewed age profile towards younger age groups. A number of other studies also reported the mean age of patients to be close to 5-6 years range.[13,14] Relatively higher proportion of younger children in nephrotic syndrome patients could also be attributed to high relapse rate in younger children.[9,15,13]

In present study, majority of patients were males (57.5%). Male to female ratio of study population was 1.35:1. The findings of the study thus support gender-differences in incidence of nephrotic syndrome, with a male predominance, more prominently in younger children below 8 years of age.[16,17] The male-female ratio in different studies has shown a variability ranging from as low as 1.18:1 to 5.67:1.[10,13,14,18,19,20,21] The high variability in gender ratio in different studies can be attributed mainly to three reasons – 1) gender related biological and physiological differences, 2) population differences in gender ratio and 3) gender-biased differences in health services utilization. In present study, the gender differences are reflective of population differences in gender proportions and as such do not indicate a higher gender related susceptibility difference or gender discrimination in health services utilization trend.[22]

Edema is the characteristic finding in nephrotic syndrome.[1] In present study too, we encountered edema as the characteristic finding in all the cases – it was of generalized nature in 40%, 2.5% had scrotal edema and 57.5% had edema limited only to face. Similar to results of present study Reshi *et al.* (2008)[23] have also seen facial edema to be the most common finding followed by pedal edema. In several other studies edema in general and facial edema in particular, have been shown as the characteristic finding in more than 90% of nephrotic syndrome children.[10,24]

Urinary complaints were also quite common in our cohort of patients. Oliguria was seen in 57.5% cases and hematuria was seen in 25% of cases. Similar to results in present study, Reshi *et al.* (2008)[23] and Najam-ud-Din *et al.* (2013)[21] also showed presence of urinary symptoms such as hematuria and oliguria in majority of their patients. A high prevalence of urinary symptoms was also reported by other workers too.[10,18]

In present study, majority of patients also complained of breathless ness (52.5%). The reason for this might be a high susceptibility to pneumonias and respiratory tract infections as well as cases with massive ascitis.[25, 26, 27] Amongst other systemic manifestations, fever and cough /cold were seen in 72.5% and 17.5% patients respectively. A large number of patients also reported with complaints of burning micturition (47.5%). As far as fever, cough and cold are concerned; these have been reported to be presenting complaints in other clinical studies too[21,14] and might be attributed to both systemic changes as well as infectious etiology.

On admission, 26 patients were case of first episode (65%), 9 (22.5%) had frequent relapse and 5 (12.5%) had infrequent relapse. Similar to our study, Soeiro *et al.* (2014)[26] also found a higher proportion of

frequent relapsers as compared to infrequent relapsers, however, proportion of relapse patients was relatively lower in their study (20.65%). Contrary to this, Safaei and Maleknejad (2009)[10] had 63% of their sampled population as relapsers with 38.8% being frequent relapsers and 26.4% being infrequent relapsers.

In present study, 100% of patients were steroid sensitive of which 10% were steroid dependent while none of the patients was steroid resistant. Contrary to our findings, Soeiro *et al.* (2004)[26] found a high proportion of patients to be steroid-dependent (50%) and steroid-resistant (18.5%). On the other hand Safaei and Maleknejad (2009)[10] had 20.5% steroid resistant and 13.5% steroid dependent patients. The findings of present study are close to those observed by Mortazavi and Khiavi (2011)[13] who had only 8.2% steroid dependent patients in their study and did not report of any steroid resistant patient. In present study, 60% of patients were hypertensive. Similar to our study Reshi *et al. (2008)*[23] also observed nearly 73% of their patients to be hypertensive. However, Safaei and Maleknejad *(2009)* [10] reported the proportion of hypertensive patients to be only 11.2% while Najam-ud-Din *et al.(2013)*[21] and Obiagwu *et al.* (2014)[18] reported it to be 43.20% and 30% respectively.

In present study C3 levels were below normal range in 9 (30%) of the 30 cases in whom this assessment was done. C3 levels are affected generally in atypical nephrotic syndrome.[28] In present study, on subsequent evaluation, they were also found to be significantly associated with atypical presentation. In a study, C3 levels have been shown to be positively correlated hyperlipidemia.[29] Although we found C3 levels to be raised in atypical cases however, we did not find a significant difference in lipid parameters of atypical and typical groups.

In present study, USG abnormalities were seen in 92.5% of cases. In maximum (45%) both liver and kidneys were involved. A total of 12 (30%) showed renal involvement only while 7 (17.5) showed liver involvement only.

In present study, 4 cases did fit into biopsy criteria as per recommended guidelines but biopsy was performed only in 3 cases since one dint get parent's consent. All the 3 cases had MCNS. However, in the study by Safaei and Maleknejad (2009), [10] FSGN was seen in 41% of cases in whom biopsy was performed. Results similar to our study Gulati *et al*.[30] conducted, study in 290 children, in which FSGS was the most common histopathological subtype, occurring in 38% cases, MCD in 33% cases, MPGN in 15% cases, mesangioproliferative glomerulonephritis in 11% cases, membranous glomerulonephritis in 2% cases and diffuse mesengial sclerosis in 1% cases. MCD was most common entity where FSGS predominated in children with age greater than 8 years.[30]

The chief complication of nephrotic syndrome is infection.[31] Findings of present study tended to substantiate this fact. The profile of infections included in present study showed a predominance of UTI alone but if URTI and LRTI are considered together then respiratory tract infections (25% each of LRTI and URTI) predominate. – a finding supported by previous studies.[10, 25, 26, 27] In present study, infection rate was also significantly higher in atypical type as compared to typical type.

In present study, all the patients received Tab. Prednisolone 6 week daily and on every alternate day for 6 weeks. In 4 steroid dependent patients, 3 were give tab. Levamisole (n=3) and 1 was given Syrup cyclophosphamide (n=1) were given in addition to alternate prednisolone. This is the recommended treatment strategy[3, 7] and we followed the same. In present study, after six months of follow up a total of 21 (52.5%) had no relapse, 15 (37.5%) had infrequent relapse while 4 (10%) frequent relapse respectively. In present study, the response was monitored as relapse free survival over 6 months. Overall response rate was 52.5%. Compared to present study, a higher response rate was reported by Wong (2007)[32] who reported a response rate of 80.4% but their targeted response was defined as in-hospital symptomatic response with a median time of response of 8.4 days. Mortazavi and Khiavi (2011)[13] in a study among idiopathic nephrotic syndrome patients also reported a response rate of 75.2%. Although in present study response rate was close to this figure yet we did not find any difference in response rate for typical and atypical groups. Alharthi *et al.* (2016)[33] also showed a response rate of 76%. The difference in response rate in present study might primarily be attributed to a smaller sample size in which chance fluctuations might vary the proportions heavily.

Highlighting the differences between atypical and typical presentations, the present study found that atypical type of patients had significantly earlier remission as compared to that of typical type of patients, had significantly higher proportion of patients with raised urinary albumin levels (3+ or above)(p=0.045), higher proportion of patients with hematuria (p=0.028). The atypical patients also had significantly (p=0.001) low C3 levels, high infection rate(p=0.045). However, they did not show a significant difference in treatment response but frequencies of relapse were more common with atypical type of presentation.

Limitation of the study: Present study was carried out in a relatively smaller number of patients and some of the findings in present study may only be a chance occurrence which needs further substantiation in larger studies.

CONCLUSION

The present study showed male predominance in nephrotic syndrome with variable clinical presentation and biochemical findings during hospitalization in both typical and atypical cases of nephrotic syndrome. C3 levels were lower and serum creatinine levels were higher in atypical type of patients. Rate of infection was higher during proteinuria phase of disease, UTI being the most common, while during remission infection rate was low, URTI being most common. Study showed no difference in outcome of steroid therapy in atypical and typical cases of nephrotic syndrome, however, the response rate during 6 month follow up was 52.5% which was a matter of concern. Frequent relapse was more common in patients with atypical presentation.

DECLARATION

Funding: None
Conflict of interest: None declared
Ethical approval: Study was done after clearance from institutional Ethics committee.

ABBREVIATION

1. UTI - Urinary tract infection
2. URTI - Upper respiratory tract infection
3. LRTI – Lower respiratory tract infection
4. CS - Corticosteroids
5. ESRD - End Stage Renal Disease
6. MCNS- Minimal change Nephrotic syndrome
7. SRNS- Steroid resistant nephrotic syndrome
8. FSGS - Focal Segmental Glomerulosclerosis
9. MPGN – Membranoproliferative Glomerulonephritis
10. C3- Serum complement 3

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