DOI: 10.7860/IJNMR/2021/50264.2320

Original Article

Paediatrics Section

Clinical Pattern and Course of Nephrotic Syndrome in Children: An Observational Study

RAHUL KADAM[1], VIDYA SINGARAVELU[2], SUSHAMA S BAI[3], MADHUSUDHAN[4]

ABSTRACT

Introduction: Chronic renal diseases not only affects the personal life of an individual but also results in social and financial burden on their families too. Nephrotic syndrome is most common in the paediatric age group contributing to significant illness related morbidity and even mortality if not identified early and treated promptly. This common disease has shown varying clinical trends with studies attempting to document them.

Aim: To study the clinical pattern and course of nephrotic syndrome in children.

Materials and Methods: The study was a retrospective analysis of medical records of diagnosed nephrotic syndrome patients in the Paediatrics and Nephrology Departments of a Tertiary Care Medical college hospital. The patients were prospectively followed-up for a period of two years. A total of 90 patients were enrolled into the study and their case records were systematically reviewed to obtain the details regarding age, sex distribution, number of admissions, hospital stay during first admission, complications and interim problems, histopathology finding where indicated, diagnostic classifications based on traditional operational definitions, treatment received, duration of remission after first episode and its relation to future relapses and the final outcome were noted and then statistically analysed.

Results: Of the 90 cases of nephrotic syndrome, 14 were lost during follow-up, so remaining 76 patients were included. There were 49 males (64.5%) and 27 females (35.5%). Steroid-Sensitive Nephrotic Syndrome (SSNS) was the most common type (59%). It was found that 67 (88.1%) patients had first episode within 1-5 years of age, 31(40.8%) had only 1st time admission, 35 (46%) had 2-4 times admissions, while the rest (13.2%) required more than 4 times admissions. Majority of the cases {48 (63.2%)} had hospital stay between 7-14 days. Infectious complications were the most common (35.3%) and 48 (63.1%) cases showed frequent relapse, while 16 (21%) never had a relapse. The final outcome showed 64 (84.2%) of the cases were in remission, 12 (15.8%) were still relapsing, and there was no mortality.

Conclusion: Age of onset for nephrotic syndrome was 5 years in majority of cases. Males were more affected than females. Majority of the patients had hospital stay for 7-14 days. SSNS was the most common type of nephrotic syndrome and Urinary Tract Infection (UTI) was the most common infectious complication. As respiratory and UTIs account for majority of relapses, prevention of respiratory infections by observing respiratory etiquettes, early and aggressive treatment and respiratory protective vaccines will go a long way in prevention of relapses.

Keywords: Relapse, Remission, Steroid-sensitive nephrotic syndrome

INTRODUCTION

Nephrotic syndrome is the most common chronic glomerular disease in children [1,2]. It is 15 times more common in children than adults. The annual incidence in children has been estimated to be 1-3 per 100,000, with a cumulative prevalence of 16 per 100,000 [3] in children less than 16 years. Geographic or ethnic differences are well known with six-fold greater incidence in Asian than in European children [4], this is also true for Indians [5]. In the Indian subcontinent, the incidence is 90-100/million population and 2-3/100,000 children per year [6]. This illness specially affects school going age group children and produces significant morbidity in them. If not recognised early and treated properly, it produces significant mortality around 1-4 % which is mostly due to infections and hypovolemia which is preventable [7] also leads to school absenteeism.

A 90% children with nephrotic syndrome have a form of the idiopathic nephrotic syndrome which reveals Minimal Change Disease (MCD) in 85% cases, Mesangial Proliferation (MP) in 5% and 10% cases of Focal Segmental Glomerulosclerosis (FSGS). The remaining 10% of children with nephrotic syndrome

have secondary nephrotic syndrome related to systemic or glomerular diseases such as membranous nephropathy or membranoproliferative glomerulonephritis [8].

A three to four fold increased incidence of HLA-DR7 (human leukocyte antigen HLA) in children with idiopathic nephrotic syndrome has been reported [9]. Children with atopy and HLA-B12 have a 13-fold increased risk of developing idiopathic nephrotic syndrome [10].

The disease is characterised by insidious onset of oedema which increases gradually and becomes clinically detectable when fluid retention exceeds 3 to 5% of body weight. A diagnosis other than Minimal Change Nephrotic Syndrome (MCNS) should be considered in the presence of age <1 year, a family history, extrarenal findings (arthritis, rash, anaemia), hypertension or pulmonary oedema, acute or chronic renal insufficiency, and haematuria [11]. By studying the clinical presentation and proper clinical categorisation, appropriate treatment can be given which will improve the prognosis, thus improve the quality of life and decrease the mortality. Hence, the aim was to study clinical pattern of nephrotic syndrome in the paediatrics age group and to evaluate their response to the treatment.

MATERIALS AND METHODS

The study was conducted on diagnosed nephrotic syndrome patients, in the Departments of Paediatrics and Nephrology in a Tertiary Care Medical College and Hospital of Pushpagiri Institute of Medical Sciences, Thiruvalla, Kerala, India. The study was a retrospective analysis of medical records and prospective follow-up of patients were conducted over period 2 years (February 2009 to January 2011). After approval from the Institute Ethics Committee (PIMSRC/2009/IEC/24),informed written consent was taken from all the participants.

Inclusion criteria: Children <18 years diagnosed to have nephrotic syndrome (based on their medical records) and those who were admitted and received treatment in the study institute were included.

Exclusion criteria: Patients diagnosed to have other renal disorders and those not willing to participate in the study were excluded.

Ninety patients were selected for retrospective analysis among which 14 did not respond to follow-up. So finally, the study was conducted on 76 patients. Case sheets and documents of previous medical records were retrieved and information regarding onset of illness, clinical course, duration, investigations done, treatment taken and response to treatment collected as per proforma.

These patients were called for follow-up. Aim and objectives of the study were explained to them and their parents, and were enrolled into the study after obtaining informed written consent from the parent and assent from the child. Patients were re-evaluated for a detailed history, physical examination, growth assessment and relevant investigations.

Re-evaluation of Patients

- **Detailed history:** regarding onset of illness, duration, number of relapses, any interim problems encountered, family history, treatment history including drug toxicity and treatment for same.
- **Physical examination:** growth assessment, sexual maturity rating, developmental assessment, drug toxicity in the form of mooning, hirsutism, posterior cataract, truncal obesity, striae, hypertension.
- Investigation and treatment details obtained from patients were re-evaluated
- Following investigations were performed in patients at the time of follow-up as per relevance: early morning urine protein, spot urine P/C (Protein to Creatinine ratio), serum albumin, hemogram, urine culture, serum electrolytes, renal function tests.
- Renal biopsy was performed, when indicated in patients in whom it was not performed earlier.

Patients were categorised using these operational definitions [12,13]:

Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, having been in remission previously.

Infrequent relapses: Three or less relapses within one year.

Frequent relapses: Two or more relapses in initial six months or more than three relapses in any twelve months.

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks.

STATISTICAL ANALYSIS

Collected data was entered in the Microsoft (MS) excel 2007 and Statistical Package for Social Sciences (SPSS) version 19.0 was used to analyse. The outcome variables were summarised using mean, standard deviation.

RESULTS

Of the 76 patients, 49 were males (64.5%) and 27 were females (35.5%). It was found that 67(88.1%) children had first episode within 1-5 years of age, 3(3.9%) were of 5-11 years and 6(7.9%) were above 11year of age and there were no cases

of congenital nephrotic syndrome [Table/Fig-1]. A positive family history was elicited in 6 patients, 5 of these had Steroid-Sensitive Nephrotic Syndrome (SSNS) and 1 had Steroid Dependent Nephrotic Syndrome (SDNS) with MCD based on histopathological findings. It was found that 67 (88.1%) patients had first episode within 1-5 years of age, 31 (40.8%) had only 1-time admission, 35 (46%) had 2-4 times admissions, while the rest (13.2%) required more than 4 times admissions. [Table/Fig-2] shows that majority 48 (63.2%) of cases had hospital stay of 7-14 days.

Variables	n (%)
Age of onset (years)	
1-5	67 (88.15)
>5	3 (3.94)
>11	6 (7.89)
Gender	
Males	49 (64.5)
Females	27 (35.5)

[Table/Fig-1]: Distribution based on age and gender.

Duration of hospital stay	n (%)
<7 days	7 (9.2)
>7 days	48 (63.2)
>14 days	19 (25)
> 21 days	2 (2.6)

[Table/Fig-2]: Duration of hospital stay at 1st admission.
Mean±SD: 12.14±4.85

Infectious complications were reported in majority of the patients (35.3%) [Table/Fig-3]. [Table/Fig-4] shows that majority of the cases in which biopsy was done showed MCD on histopathological examination.

Complications and interim problems	Cases n (%)
Infections	27 (35.3%)
• Urinary tract infection	15 (19.7%)
• Spontaneous bacterial peritonitis	6 (7.9%)
• Varicella	3 (3.9%)
• Progressive pulmonary disease	3 (3.9%)
Drug toxicity	25 (32.9%)
Acute renal failure	7 (9.2%)
Poststreptococcal glomerulonephritis	4 (5.3%)
Late onset hypothyroidism	4 (5.3%)
Electrolyte disturbances	14 (18.4%)
• Hypocalcaemia	10 (13.1%)
• Hypokalemia	2 (2.6%)
• Hyponatremia	2 (2.6%)

[Table/Fig-3]: Complications and interim problems.

Histopathological findings	Cases n (%)
Minimal change disease	13
Focal segmental glomerulosclerosis	8
IgM Nephropathy	1

[Table/Fig-4]: Histopathological findings.
n=22

[Table/Fig-5] shows the final diagnostic classification of the 76 cases of nephrotic syndrome, with SSNS being seen in majority of cases.

Diagnostic classification	n=76 (%)
Steroid-sensitive nephrotic syndrome	45 (59)
Steroid dependent nephrotic syndrome	20 (26.3)
Steroid resistant nephrotic syndrome	7 (9.2)
Secondary nephrotic syndrome	4 (5.3)

[Table/Fig-5]: Diagnostic classification.

[Table/Fig-6] shows that steroids and diuretics were used as the treatment modality in all the cases (100%) in the study, and 56 (73.7%) cases required the use of immunomodulators of which levamisole was the most commonly used agent. Mycophenolate mofetil and tacrolimus were used only in those cases that failed therapy with first line (levamisole + cyclophosphamide) immunomodulators.

Modality of treatment	Number of cases n (%)
Prednisolone	76 (100)
Diuretics	76 (100)
Albumin	1 (40.8)
Immunomodulators	
• Levamisole	56 (73.7)
• Cyclophosphamide	26 (46.4)
• Mycophenolate mofetil	20 (35.7)
• Tacrolimus	3 (5.4)

[Table/Fig-6]: Treatment received.

The average time taken for remission to occur during first episode was 11 days and 61 cases had relapses following remission. Study shows that 64 (84.2%) of the cases were in remission, 12 (15.8%) were still relapsing and there was no mortality at the end of the study.

DISCUSSION

This study aimed to record the clinical course of nephrotic syndrome in children. Total 76 children with nephrotic syndrome were retrospectively analysed and prospectively followed-up and observations were made with few of them contrary to the available literature.

The present study showed that 88.1% of the cases were less than 5 years at disease onset. This is comparable to many other studies which also showed most cases having disease onset at <5 years of age [8,11,14,15]. No cases of congenital nephrotic syndrome were found in this study which is comparable to the findings in the Chowdhury EUA and Huq MN study, which also did not have a case of congenital nephrotic syndrome, whereas one Iranian study by Safaei A and Maleknejad S, found one case of congenital syndrome in their study [8,11].

In the present study, 63.2% of cases had to stay at hospital for 7-14 days. This is comparable to the study by Chowdhury EUA and Huq MN, which also found that hospital stay of 7-14 days was seen in majority of cases (45%) which reflects disease severity and responsiveness to treatment [8].

In the present study, drug toxicity was found to be the most common non infectious complication followed by electrolyte disturbances (18.4%). Urinary Tract Infection continues to be a major complication of children with nephrotic syndrome, especially in the developing countries such as India which is concurrent with the study by Chowdhury EUA et al., [8]. A study by Senguttuvan P et.al., which included 199 children with nephrotic syndrome, showed UTI was the commonest infection (46%) followed by peritonitis (25.8%), acute respiratory infection (13.5%), tuberculosis (5%) [16].

In present study, biopsy was conducted in 22 of the 76 cases. It showed that MCD was the most common lesion (59%) followed by FSGS (36.4%), which conforms to MCD being the most common type which therefore conveys a better responsiveness to therapy and carries a better prognosis. In contrast, the study by Safaei A and Maleknejad S and Reshi AR et al., found FSGS to be the most common histopathological finding in 41% and 38% of cases, respectively [17,18]. To distinguish MCD, especially among children, from other causes of nephrotic syndrome is important because the clinical course and management would vary. As the non MCD subtypes and becoming common, a histological diagnosis is crucial to the management and outcome of the disease [19].

In this study, SSNS accounted for majority of the cases (59%) of which 22.3% were frequent relapses. Most patients with SSNS have frequent relapses as one of the main problem is its association with a high incidence of complications [20]. This is comparable to other studies in literature [11,14,15]. In Ali A et al., study, 87% cases showed steroid sensitive nephrotic syndrome [21]. All the 76 patients were treated as per standard protocol (Prednisolone). Diuretics were used in all the cases as they presented with severe oedema. Chowdhury EUA and Huq MN also used diuretics in cases with severe oedema [8].

In the present study, 73.7% of cases required immunomodulator therapy which is in contrast to the study by Chowdhury EUA and Huq MN, where all cases responded to steroids and immunomodulation was not required [8]. This might be explained based on the fact that almost all cases in the other study were of idiopathic nephrotic syndrome which responded to steroids. Hence, most first time cases usually responded well to steroids and frequent relapsers were the usual candidates for immunomodulation.

This study shows that shorter the remission period after the 1st episode higher was the number of relapses and number of relapse-free cases were more in those patients with a longer duration of remission after 1st episode. The study by Dakshayini B et al., also showed similar results [22]. The final outcome at the end of the study period revealed that 84.2% of the cases were in remission, and 15.8% were relapsing. This was comparable to the study by Ali A et al., in which the remission rate was 68.4% [21]. In contrast, Chowdhury EUA and Huq MN, reported that 100% of the cases had full remission [8]. This may be explained based on the fact that the latter study had a small study population of 199 (N).

CONCLUSION(S)

This study concludes that the age of onset of nephrotic syndrome was around 5 years with a male predilection. SSNS was the commonest type with majority of the patients having a hospital stay of 7-14 days. Among the complications, UTI was the most common infectious complication, whereas drug toxicity was the non infectious complication. Most of the relapses were triggered by respiratory infections, which leads us to conclude that prevention of respiratory infections by observing respiratory etiquette, early and aggressive treatment of infections and respiratory protective vaccines could minimise the occurrence and number of relapses. Though, this study conforms to the prior knowledge that we have in many respects, it would be good to study patterns of a common disease like nephrotic syndrome from time to time to see the evolution of the course of the disease and also in the backdrop of emerging infections like the COVID-19 pandemic, to see if the restrictions imposed by the pandemic have affected relapses and other aspects.

REFERENCES

[1] Behrman RE, Kliegman RM, Jenson Hd. Nephrotic Syndrome. In: Nelson Textbook of Paediatrics. 17th ed. Philadelphia. PA: Saunders: 2004;1753-1.
[2] Coovadia HM, Eke F, Luta M, eds. Nephrotic Syndrome. In: Pediatric Nephrology. 4th ed. Baltimore. MD: Lippincott Williams and Wilkins: 1999;1362-1367.
[3] Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003;362:629-39.
[4] Sharples PM, Poulton J, White RHR. Steroid responsive nephrotic syndrome is more common in Asians. Arch Dis Child. 1985;60:1014-17.
[5] Srivastava RN, Mayekar G, Anand R, Choudhry VP, Ghai OP, Tandon HD. Nephrotic syndrome in Indian children. Arch Dis Child. 1975;50(8):626-30. Doi: 10.1136/adc.50.8.626.

[6] Srivastava RN, Bagga A. Nephrotic syndrome. In: Pediatric nephrology, 3rd ed. New Delhi: Jaypee Brothers, 2001.

[7] Ghai OP, Paul VK, Bagga A, et al. Nephrotic syndrome. Essenial Paediatrics, 7th ed. New Delhi; 15:450-454.

[8] Chowdhury EUA, Huq MN. Pattern of nephrotic syndrome in children admitted in Bangladesh medical college hospital. Bangladesh Med Coll J. 2010;15(2):67-73.

[9] De Mouzon-Cambon A, Bouissou F, Dutau G, Barthe P, Parra MT, Sevin A, et al. HLA-DR7 in children with idiopathic nephrotic syndrome. Correlation with atopy. Tissue Antigens. 1981;17:518-24.

[10] Alfiler CA, Roy LP, Doran T, Sheldon A, Bashir H. HLA-DRW7 and steroid responsive nephrotic syndrome of childhood. Clin Nephrol. 1980;14:71-74.

[11] Safaei A, Maleknejad S. Spectrum of childhood nephrotic syndrome in Iran: A single center study. Indian J Nephrol. 2009;19(3):87-90.

[12] Consensus Statement on Management of Steroid Sensitive Nephrotic Syndrome. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics. Indian Pediatr. 2001;38:975-86.

[13] Consensus Statement on Management and Audit Potential for Steroid Responsive Nephrotic Syndrome. Report of a Workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. Arch Dis Child. 1994;70:151-57.

[14] Madani AB. Clinicopathologic and drug response in children with idiopathic nephrotic syndrome in pediatric medical center. J Tehran Univ Med Sci. 2003;1:71-79.

[15] Srivastava RN, Mayekar G, Anand R, Choudhry VP, Ghai OP, Tandon HD. Nephrotic syndrome in Indian children. Arch Dis Child. 1975;50:626-30.

[16] Senguttuvan P, Prabhu N Ravanan K, Tamilarasi V. Infections encountered in childhood nephrotics in a pediatric renal unit. Indian J Nephrol. 2004;14:85-88

[17] Safaei AA, Maleknejad S. Clinical and laboratory findings and therapeutic responses in children with nephrotic syndrome. Indian J Nephrol. 2010;20(2):68-71.

[18] Reshi AR, Bhat MA, Najar MS, Banday KA, Naik MA, Singh DP, et al. Etiological profile of nephrotic syndrome in Kashmir. Indian J Nephrol. 2008;18:09-12.

[19] Arif MK, Arif M, Amjad N. A histopathological outlook on nephrotic syndrome: A pediatric perspective. Indian J Nephrol. 2016;26(3):188-91. Doi: 10.4103/0971-4065.159555.

[20] Ali SH, Ali AM, Najim AH. The predictive factors for relapses in children with steroid-sensitive nephrotic syndrome. Saudi J Kidney Dis Transpl. 2016;27(1):67-72.

[21] Ali A, Ali D, Mehran H, Ali Z. Idiopathic nephrotic syndrome in Iranian Children. Indian Pediatrics. 2008;45:52-53.

[22] Dakshayini B, Lakshmanna M, Premalatha R. Risk factors for relapse in Childhood steroid sensitive nephrotic syndrome. Turk Pediatri Ars. 2018;53(1):24-30. www.iapindia.org/ files/ abstracts 2006/ NEP.doc.

PARTICULARS OF CONTRIBUTORS:

1. Consultant, Neonatologist, Department of Paediatrics, Yashoda Hospital, Hyderabad, Telangana, India.
2. Associate Professor, Department of Paediatrics, Malla Reddy Institue of Medical Sciences, Hyderabad, Telangana, India.
3. Retired Professor and Head, Department of Paediatrics, Pushpagiri Institute of Medical Sciences, Thiruvalla, Kerala, India.
4. Assistant Professor, Department of Physiology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Vidya Singaravelu,
Associate Professor, Department of Pediatrics, Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad, Telangana, India.
E-mail: viddu7@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: May 19, 2021
- Manual Googling: Sep 21, 2021
- iThenticate Software: Sep 30, 2021 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. None

Date of Submission: **May 18, 2021**
Date of Peer Review: **Aug 25, 2021**
Date of Acceptance: **Sep 22, 2021**
Date of Publishing: **Dec 31, 2021**