JSTMU Journal of Shifa Tameer-e-Millat University

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ORIGINAL ARTICLE

Clinical presentation, histopathology, and treatment outcomes of steroid-resistant nephrotic syndrome in children presenting in a tertiary care hospital in Pakistan

Musarrat Hussain[1], Sabeen Abid Khan[2*], Muhammad Imran[3], Humaira Nasir[4]

[1] Consultant Pediatric Nephrologist, Department of Pediatrics, Shifa International Hospital, Islamabad, Pakistan

[2] Associate Professor, Department of Pediatrics, Shifa College of Medicine, Shifa Tameer e Millat University, Islamabad, Pakistan

[3] Senior Registrar, Department of Pediatrics, Shifa College of Medicine, Shifa Tameer e Millat University, Islamabad, Pakistan

[4] Consultant Histopathologist, Department of Pathology, Shifa International Hospital, Islamabad, Pakistan

Author`s Contribution

[1] Conception, data analysis, drafting
[2, 3] Data collection, analysis, drafting
[4] Compilation, analysis, drafting

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

Correspondence

**Sabeen Abid Khan*
Sabeenk45@gmail.com

Article information

Submission date: 26-02-2024
Acceptance date: 14-11-2024
Publication date: 31-12-2024

Cite this article as *Hussain M, Khan SA, Imran M, Nasir H. Clinical presentation, histopathology, and treatment outcomes of steroid resistant nephrotic syndrome in children presenting in a tertiary care hospital of Pakistan. JSTMU. 2024;7(2):124-127.*

A B S T R A C T

Introduction: Nephrotic syndrome (NS) is one of the most common glomerular diseases in children. Steroid-resistant nephrotic syndrome (SRNS), although represents a small fraction of NS is a challenging condition to manage. The study aims to review the clinical signs and symptoms, histopathology, and treatment outcomes of SRNS in children.

Methodology: This cross-sectional study was conducted in the Pediatric nephrology department of Shifa International Hospital from 1st September 2019 to February 2022. All children 1 to 18 years old fulfilling the criteria for SRNS patients were included. Their age of presentation, signs, symptoms, clinical findings, laboratory data, and histopathological findings on renal biopsy were noted. Outcomes like complete remission, partial remission, and chronic kidney disease were recorded.

Results: A total of 67 (25.8%) SRNS patients were included, mean age was 4.3 $\pm$ 3.09 years. FSGS 21 (31.3%) was the most common, and MCD was seen in 9 (13.4%). Classic signs and symptoms of edema, weight gain, and abdominal distension were present in the majority. Oliguria, hematuria, and hypertension were significantly associated with a diagnosis of SRNS ($p<0.05$). In the laboratory workup, the mean albumin was 2.03 $\pm$ 0.6 gm/l, the mean cholesterol 385.3 $\pm$ 149 mg/dl, the mean serum creatinine was 2.1 $\pm$ 1.16 mg/dl, and the mean protein creatinine ratio was 7.7 $\pm$ 4.2. CKD and ESRD developed in 10 patients, and mortality was reported in 10 patients ($P<0.005$).

Conclusion: SRNS comprises a significant number of cases of NS resulting in ESRD with high morbidity and mortality.

Keywords: *Nephrotic syndrome; Steroid-resistant; Children*

Introduction

Nephrotic syndrome (NS) is one of the most common glomerular diseases in children.[1] The incidence of NS is reported to be 2-16.9/100,000 children globally.[1] The prognosis of NS depends on the response to steroid treatment.[2] There are two categories of the disease steroid sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS). Most children with idiopathic NS respond to steroids.[3] Steroid resistance is defined as persistent proteinuria despite 4 to 6 weeks of a daily dose of oral prednisolone 2mg/kg/day. When there is no response, the treatment can be prolonged for up to eight weeks.[4] Majority of children (85-90%) with NS respond to corticosteroids, however, 10–15% remain unresponsive or later become steroid-resistant.[5] Although

these are smaller numbers of cases, patients with SRNS are more difficult to treat, with 36%–50% progressing to chronic renal disease within 10 years.[6] Appropriate treatment of SRNS requires an understanding of the historical treatment, renal histopathology findings, and the associated genetic mutations of the disease. There is a wide variation of practice in the management of NS. Initially, the International Study of Kidney Disease in Children (ISKDC) recommended oral steroid 60 mg/m^2/day for four weeks followed by 40 mg /m^2 every other day for four weeks.[7] Similarly, the use of high-dose steroids (60mg/m^2/day) for 6 weeks followed by 40 mg/m^2 on alternate days for 6 weeks has also shown a reduced number of relapses and steroid dependency. In 2012, Kidney Disease Initiative Global Outcome (KDIGO) suggested oral steroid 60 mg/m^2/day for 4–6 weeks followed by tapering over 2–5 months.[8]

Treatment of SRNS is challenging and there are multiple strategies for improving outcomes that require input from a pediatric nephrologist.[9] Calcineurin inhibitors (CNIs) are the current treatment of choice later switching to Mycophenolate mofetil (MMF) after 1-2 years of remission by CNIs. Renal biopsy is mandatory before starting CNIs in case of SRNS or steroid-dependent (SDNS) because of the high potential of renal toxicity by CNIs.[10] Use of Rituximab (anti-CD 20) is controversial in SRNS.[11] The two most reported histopathological findings are minimal change disease (MCD) in 85% of SSNS and focal segmental glomerulosclerosis (FSGS) in SRNS.[12]

Our study aims to evaluate the clinical presentation, histopathology, and clinical outcomes of SRNS in our hospital.

Methodology

The study was conducted in Pediatric Nephrology, Shifa International Hospital, and the Department of Pediatrics in Shifa Falahee Community Health Center (SFCHC) from 1st September 2019 to February 2022. Ethical approval was obtained from Shifa International Hospital's Institutional Review Board IRB (No 041-861-202). All children 1 to 18 years old who presented with signs and symptoms of nephrotic syndrome confirmed by laboratory analysis were included in the study. Further classification of NS based on response to steroid therapy was recorded using the International Pediatric Nephrology Association (IPNA) classification into SSNS, SRNS, and SDNS.[13] Children with missing data were excluded from the study. SRNS was verified as persistent proteinuria despite 4-6 weeks of treatment with oral prednisolone at a dose of 2mg/kg/day. In cases where there is a decrease in the quantity of proteinuria and edema after 4 weeks, the treatment would be prolonged up to 6 weeks to include any late responders. SRNS patients were recruited in the study. Their age of presentation, signs, symptoms, clinical findings, and laboratory data were recorded. Histopathological findings on renal biopsy were noted. The outcome in terms of complete remission, partial remission, chronic kidney disease, and end-stage renal disease (ESRD) was noted.

Data was analyzed on SPSS version 23. Continuous variables were noted as mean and standard deviation and categorical variables as number and percentage. The chi-square test was used to study the significance of association. A $p<0.05$ was considered as statistically significant. Informed consent was taken from parents.

Results

A cohort of 260 children with NS was reviewed. Males were 172 (66.2%) and females were 88 (33.8%). The majority of our patients had SDNS/FRNS 105 (40.4%), infrequent relapsing (IRNS) 77 (29.6 %) and SRNS 67 (25.8%). In the SRNS group, 36 were male and 31 were female. The mean age of our study population was 8.3$\pm$4.3 years. The mean age of diagnosis was 4.3$\pm$3.09 years. The mean height was 109+23 cm, and the mean weight was 23.4$\pm$13 kg. FSGS 21 (31.3%) was the most common finding on renal biopsy followed by MCD 9 (13.4%). Histopathological types are shown in Table 1. In the laboratory workup for SRNS, mean albumin was 2.03 $\pm$ 0.6 gm/l, mean cholesterol 385.3$\pm$149 mg/dl, mean serum creatinine was 2.1$\pm$1.16 mg/dl, and mean protein creatinine ratio was 7.7$\pm$4.2. Signs and symptoms of SRNS are shown in Table 2.

ANA was positive in 5 patients. All patients initially received prednisolone at 60mg/m^2 or 2 mg/kg every day for 8 weeks. Cyclosporin was given to 44 (65.6%) patients, 12 (18%) received tacrolimus and 18 (26.8%) MMF. Two patients were resistant to tacrolimus, one patient developed hypertrichosis to cyclosporine and switched to MMF, and one patient was last responded (8 weeks). One patient who was resistant to CNI (both tacrolimus and Cyclosporine) received rituximab. One

patient MSGN (Membranosclerosing glomerulonephritis) achieved partial remission on cyclosporine for 1 year and was shifted to MMF, continues to be in partial remission. ESRD developed in 10 patients and mortality was reported in all 10 patients (P<0.005) shown in Table 3.

Table 1: Histopathological findings in steroid-resistant nephrotic syndrome

Histopathology	N 67 (100%)
FSGS	21 (31.3)
MCD	9 (13.4)
Ig M nephropathy	6 (8.9)
Membranous nephropathy	5 (7.4)
C1q nephropathy	8 (11.9)
IgA nephropathy	2 (2.9)
MPGN	4 (5.9)
MSGN	1 (1.49)
Lupus nephritis	3 (4.4)
Not done	8 (11.9)

Table 2: Clinical symptoms in SRNS

Sign& symptoms	N (%)	P value
Edema	67(100)	0.51
Oliguria	23(34.3)	0.002
Weight gain	44(65.6)	0.18
Rash	3(4.4)	0.005
Abdominal swelling	44(65.6)	0.15
Hypertension	23(34.3)	0.009
Hematuria	18(26.8)	0.002

Table 3: Outcome of SRNS

Outcome	N (67) percent (%)
Remitted	18 (26.8)
Alive on treatment	12 (17.9)
CKD	10 (14.9)
Dead	10 (14.9)
Partial remission	9 (13.4)
Renal transplant	2 (2.9)
Lost to follow	7 (10.4)

The outcome is significantly associated with the type of nephrotic syndrome (0.04). Amongst SRNS highest mortality was associated with FSGS 4 patients (p 0.001). Complete remission was reported in 18 (26.8%) patients only. One patient with SRNS (MCD) developed dural vein thrombosis. Other complications reported were stroke, and post-capsular cataract in one patient each.

Discussion

SRNS constituted 25% of our study population, being a tertiary care center, we receive more referrals for atypical nephrotic syndrome. Literature shows that 10% of NS are steroid-resistant in children.[14] FSGS (31.3%) was the predominant histopathological type accounting for SRNS. It is estimated that 80% of FSGS are resistant to steroid treatment.[15] FSGS is associated with poor outcomes as the majority of patients progress to ESRD in SRNS.[16] However, a study from Karachi reported MCD as the predominant histopathological type followed by FSGS.[17] C1 q nephropathy was seen in a significant number of patients (8) MCD was the second most common histopathological finding in our study population. The age of presentation for FSGS was higher 10.2 $\pm$ 4.2 years as compared to children with MCD/SRNS 7.6 $\pm$ 3.8 years (0.02).

Classic signs and symptoms of edema, weight gain, and abdominal distension were present in the majority. Oliguria, hematuria, and hypertension were significantly associated with a diagnosis of SRNS. Renal insufficiency as suggested by raised creatinine was seen in the SRNS group. The rash was seen in 3 patients with lupus nephritis. Low C3 was noted in 22 (32%) patients, 4 had FSGS, 3 had MPGN, and one each had C1q and membranous nephropathy. However, C4 was low in 2 patients only, 1 had MPGN and the other had lupus nephritis. These findings should raise the concern for atypical NS necessitating the need for renal biopsy.[18] Calcineurin inhibitors are the mainstay of treatment for SRNS.[19] Majority of studies prove that the use of cyclosporine along with steroids reduces the number of relapses and halts the progression of chronic kidney disease (CKD). Cyclosporine was used in 44 (65.6%) patients, and hypertrichosis was reported in only one patient. Complete remission was noted in 18 (26.8%) patients. Eleven of these had underlying MCD/SRNS, 4 had FSGS, 2 had MPGN and 1 had IgA nephropathy. The renal transplant was done in two patients only with FSGS SRNS. There is a risk of post-transplant FSGS in 30% of patients. However, none of our patients have reported recurrence of Nephrotic syndrome symptoms within 5

years. Cost of treatment, limited renal transplant centers, and donor availability are major hurdles for low-middle-income countries (LMICs) like Pakistan.

Genetic factors are thought to be responsible for SRNS in 30% of the patients.[20] It is postulated that response to treatment outcomes depends on the underlying genetic mutations.[21] Until now more than 50 monogenic causes of SRNS have been identified.[22] Identification of genes will help towards precise medicine and a better understanding of disease pathogenesis. Genetic testing was not done in our cohort of patients due to lack of availability.

Conclusion

SRNS comprises a significant number of cases of NS resulting in ESRD with high morbidity and mortality requiring Renal replacement therapy either hemodialysis or renal transplant.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018; 392(10141):61-74. DOI: https://doi.org/10.1016/s0140-6736(18)30536-1
2. Dossier C, Lapidus N, Bayer F, Sellier-Leclerc AL, Boyer O, de Pontual L, et al. Epidemiology of idiopathic nephrotic syndrome in children: endemic or epidemic? Pediatr Nephrol. 2016; 31(12):2299-2308. DOI: https://doi.org/10.1007/s00467-016-3509-z
3. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018; 392(10141):61-74. DOI: https://doi.org/10.1016/S0140-6736(18)30536-1.
4. Mekahli D, Liutkus A, Ranchin B, Yu A, Bessenay L, Girardin E, et al. Long-term outcome of idiopathic steroid-resistant nephrotic syndrome: a multicenter study. Pediatr Nephrol. 2009; 24:1525-32. DOI: https://doi.org/10.1007/s00467-009-1138-5
5. Kemper MJ, Valentin L, Husen M. Difficult-to-treat idiopathic nephrotic syndrome: established drugs, open questions and future options. Pediatr Nephrol. 2018; 33:1641-9. DOI: https://doi.org/10.1007/s00467-017-3780-7
6. Bensimhon AR, Williams AE, Gbadegesin RA. Treatment of steroid-resistant nephrotic syndrome in the genomic era. Pediatr Nephrol. 2019; 34(11):2279-2293. DOI: https://doi.org/10.1007/s00467-018-4093-1
7. Cattran DC, Feehally J, Cook HT, Liu ZH, Fervenza FC, Mezzano SA, et al. Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl. 2012; 2(2):139-274. DOI: https://doi.org/10.1038/kisup.2012.9
8. Kemper MJ, Valentin L, Husen M. Difficult-to-treat idiopathic nephrotic syndrome: established drugs, open questions and future options. Pediatr Nephrol. 2018; 33:1641-9. DOI: https://doi.org/10.1007/s00467-017-3780-7
9. Gruppen MP, Bouts AH, Jansen-van der Weide MC, Merkus MP, Zurowska A, Maternik M, et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int. 2018; 93(2):510-8. DOI: https://doi.org/10.1016/j.kint.2017.08.011
10. Iijima K, Sako M, Kamei K,. Rituximab in steroid-sensitive nephrotic syndrome: lessons from clinical trials. Pediatr Nephrol. 2018; 33:1449-55. DOI: https://doi.org/10.1007/s00467-017-3746-9.
11. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatric Nephrol. 2001; 16:27182. DOI: https://doi.org/10.1007/s004670000523.
12. Hahn D, Hodson EM, Willis NS. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2015; (3):Cd001533. DOI: https://doi.org/10.1002/14651858.CD001533.pub5.
13. Trautmann A, Vivarelli M, Samuel S. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2020; 35(8):1529-1561. DOI: https://doi.org/10.1007/s00467-020-04519-1
14. Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS, et al. Long-Term Outcome of Steroid-Resistant Nephrotic Syndrome in Children. J Am Soc Nephrol. 2017; 28(10):3055-3065. DOI: https://doi.org/10.1681/ASN.2016101121
15. Han KH, Kim SH. Recent Advances in Treatments of Primary Focal Segmental Glomerulosclerosis in Children. Biomed Res Int. 2016; 2016:3053706. DOI: https://doi.org/10.1155/2016/3053706.
16. Zagury A, Oliveira AL, Montalvão JA. Steroid-resistant idiopathic nephrotic syndrome in children: long-term follow-up and risk factors for end-stage renal disease. J Bras Nefrol. 2013; 35(3):191-9. DOI: 10.5935/0101-2800.20130031
17. Moorani KN, Hotchandani HM, Zubair AM. Immunosuppressive therapy in children with primary nephrotic syndrome: single center experience, Karachi, Pakistan. BMC Nephrol. 2019; 20(1):239. DOI: https://doi.org/10.1186/s12882-019-1347-5.
18. Vivarelli M, Massella L, Ruggiero B. Minimal change disease. Clin J Am Soc Nephrol. 2016; 12(2):332-45. DOI:https://doi.org/ 10.2215/CJN.05000516
19. Lee JM, Kronbichler A, Shin JI, Oh J. Current understandings in treating children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2021; 36(4):747-761. DOI: https://doi.org/10.1007/s00467-020-04476-9
20. Kamei K, Ishikura K, Sako M, Ito S, Nozu K, Iijima K. Rituximab therapy for refractory steroid-resistant nephrotic syndrome in children. Pediatr Nephrol. 2020; 35:17-24. DOI: https://doi.org/10.1007/s00467-018-4166-1.
21. Mason AE, Sen ES, Bierzynska A, Colby E, Afzal M, Dorval G, et al. Response to first course of intensified immunosuppression in genetically stratified steroid resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2020; 15(7):983-94. DOI: https://doi.org/10.2215/CJN.13371019
22. Bensimhon AR, Williams AE, Gbadegesin RA. Treatment of steroid-resistant nephrotic syndrome in the genomic era. Pediatr Nephrol. 2019; 34(11):2279-2293. DOI: https://doi.org/10.1007/s00467-018-4093-1