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Original Article

Long-Term Outcome of Children With Steroid-Resistant Nephrotic Syndrome: a Single Center Experience from Pakistan

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ABSTRACT

***Objective*:** To determine the long-term outcome of children with steroid-resistant nephrotic syndrome at a single center in Pakistan.

Study Design: Retrospective, observational study.

***Place and Duration of Study*:** Pediatric Nephrology Department, Sindh Institute of Urology and Transplantation, Karachi, Pakistan from July 2008 to June 2014.

Methodology: The study included 153 children aged 4 months-12 years with steroid-resistant nephrotic syndrome. We collected data at the time of diagnosis and the last follow-up. The data was entered and analyzed by SPSS version 20.

Results: Among 153 children, 84(55%) were males and 69(45%) females. At the time of diagnosis, 118(77%) were hypertensive and 65 (42.5%) had microscopic hematuria. Histopathological spectrum included focal segmental glomerulosclerosis, 63(41%); minimal change disease, 33(22%); IgM nephropathy, 9 (6%); mesangioproliferative glomerulonephritis, 26(17%), membranous glomerulonephritis, 13(8%) and membranoproliferative glomerulonephritis, 9(6%). Complete remission with cyclosporine was seen in 53(34.6%), partial remission in 36(23.5%), while 53(35%) developed chronic kidney disease, of which 26(78.8%) needed renal replacement therapy. Mortality was 21(13.7 %) and 11(7.2%) were lost to follow-up. Calcineurin inhibitors' toxicity was seen in 52(34%). One patient received renal transplant but lost the graft 6 years post-transplant due to disease recurrence.

Conclusion: Steroid-resistant nephrotic syndrome has significant long-term morbidity and mortality. Recurrence of disease in transplanted kidney is common and can result in graft loss.

Keywords: Children, nephroticsyndrome, outcome, steroids, Pakistan.

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INRODUCTION

Nephrotic syndrome (NS) is a common glomerular syndrome in children with an incidence of 2-7 cases per 100,000 children per year, with the higher incidence reported in South-Asian children.[1] It is characterized by edema, heavy proteinuria and hypoalbuminemia. Majority of these children respond to steroids. A smaller percentage (10-15%) turn out to have steroid-resistant NS (SRNS).[2] Among them, one-third children have an underlying genetic mutation while the remaining probably have immune system dysfunction.[3] Treatment with calcineurin inhibitors (CNIs) is the standard of care in patients with non-genetic SRNS.[4,5] Disease responsive to CNIs portends a better outcome4. Patients who fail to respond to immunosuppressive medications pose a considerable therapeutic challenge and have a high risk of progression to end-stage renal disease (ESRD).[4,5]

Several risk factors have been identified in patients who progress to ESRD which include onset of disease in later childhood, proteinuria that is unresponsive to therapy, hypertension and biopsy showing focal segmental glomerulosclerosis (FSGS) and tubulointerstitial disease.[6-8]

Recurrence of primary disease in transplanted patients is common and is seen in 30-50% of renal transplants. Out of them, graft loss occurs in almost half the cases.[9]

Children with SRNS form a substantial portion of patients that are regularly attended to in our pediatric nephrology clinic. Since, the data on outcome from different studies is varied, we set out to review our experience. As we have a large cohort of children with SRNS with regular follow-up and with outcome data, our experience will help inform pediatric nephrology care in the country and region.

The objective of this study was to determine the long-term outcome of children with SRNS and secondly to determine whether any of the clinical, laboratory or histopathological features at presentation correlates with the development of ESRD.

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METHODOLOGY

This retrospective, observational analysis included all children diagnosed with SRNS from July 2008 to June 2014 at the department of Pediatric Nephrology at Sindh Institute of Urology and Transplantation (SIUT). The research followed the tents of the Declaration of Helsinki. The study was approved by Ethical Review Committee of the institute (SIUT-ERC-2019/A-184). Since the study was retrospective, ERC allowed waiver of written informed consent. However, assent from all children and written informed consent from their parents were obtained at the time of renal biopsy. Patients diagnosed as SRNS, whether primary or secondary, with age of onset between 4 months to 12 years and with at least one year follow-up period were included. Exclusion criteria included NS with systemic involvement (e.g. IgA nephropathy, lupus nephritis), NS with renal failure with estimated glomerular filtration rate (eGFR)<90 ml/min and congenital nephrotic syndrome (CNS). From the review of medical records, 153 consecutive children with SRNS were identified. Their demographic, clinical, and histopathological findings and treatment were recorded on a predesigned proforma. Laboratory investigations including serum creatinine, serum albumin, urinary dipstick for proteinuria and haematuria were also noted. The details obtained from biopsy reports included the histopathological diagnosis, grade of tubular atrophy and interstitial fibrosis. Treatment options included anti-proteinuric agents (angiotensin converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]) and CNIs: cyclosporine (CyA) and tacrolimus (TAC).

At the last available follow-up, disease outcome was based on classification of patients into either complete or partial remission or progression to renal insufficiency and ESRD. If patient progressed to renal insufficiency, it was categorized according to the stage of chronic kidney disease (CKD).[8] Renal replacement therapy (RRT) or renal transplantation, if done, were also noted.

SRNS (primary) was defined as failure to achieve remission after full dose of prednisolone,i.e., 2 mg/kg/day for 4 to 6 weeks.[8]

Steroid sensitive patient with history of one or more complete remissions but later failing to respond after 4 weeks of corticosteroids treatment was considered to have secondary steroid resistance. Heavy proteinuria was defined as ≥ 3+ on urine dipstick testing. Haematuria was present if urine dipstick read 1+ or more. The eGFR was calculated using the age and gender appropriate modified Schwartz formula. Patients with an eGFR <90 ml/min/1.73 m² were considered to have renal insufficiency and classified according to the stage of CKD as per the KDOQI guidelines. ESRD was defined as the requirement for dialysis or renal transplantation. Hypertension was identified using the National High Blood Pressure Education Program Working Group 2004 guidelines, based on gender, age, and height percentiles.[10] Complete remission (CR) was defined as absence of edema, negative proteinuria on dipstick and serum albumin more than or equal to 2.5 g/dl. Partial remission (PR) was defined as serum albumin more than 2 g/dl and absence of edema regardless of grade of proteinuria on urine dipstick.[8]

Data was analyzed using SPSS version 20. All continuous variables were presented as mean and standard deviation and categorical variables as frequencies and percentages. Chi square test was applied to determine the correlation between clinicopathologic features at outset and progression to ESRD. The *p*-value≤0.05 was considered as statistically significant.

RESULTS

The records of 153 patients were studied, out of which 84(55%) were males. The mean age of all children was 6.4±3.5 years. The median follow-up duration was 6 years. In all, 21(13.7%) patients expired; 10(47.6%) were in CKD stage 5, 5(23.8%) were in CKD stages 1-3 and 6(28.5%) had normal renal functions. Eleven (7.3%) were lost to follow-up. The baseline characteristics of the enrolled patients are shown in Table 1.

According to histopathological findings and as per institutional protocol, either CNIs or anti-proteinuric agents were prescribed to all. During the course of treatment, CyA was withdrawn in 72(47%) patients. Renal impairment occurred in 52(72.2%) of them and 20(27.8%) were non-responsive to CyA. Therefore, anti-proteinuric agents were prescribed in 45(62.5%) and TAC was given in the remaining 27(37.5%). CyA toxicity was diagnosed on biochemical basis and no renal biopsy was done to document morphological features of toxicity.

Out of 153 children, complete records of 143 were subsequently found (Table 2). CR was observed in 53(34.6%) children at the last follow-up. Among them, the majority had been treated with CNIs while only

Table-I: Baseline Characteristics of 153 Children with Steroid-Resistant Nephrotic Syndrome.

Parameters	
Age (years) Mean (SD)	6.4±3.4
Gender n, (%)	
Male	84(54.9)
Female	69(45.1)
Height (cm) Mean(SD)	109.7±21.7
Weight (kg) Mean(SD)	20.7±9.3
Hypertension n, (%)	118(77.1)
Serum albumin (g/dl) Mean(SD)	1.4±0.7
Serum creatinine (mg/dl) Mean(SD)	0.40±0.14
Microscopic hematuria n, (%)	65(42.5)
Treatment choice, n (%)	
Cyclosporine	127(83)
Tacrolimus	5(3.3)
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers	21(13.7)
Histopathological diagnosis, n (%)	
Minimal change disease	33(21.6)
Focal segmental glomerulosclerosis	63(41.2)
IgM Nephropathy	9(5.9)
Mesangial proliferative glomerulonephritis	26(17)
Membranous nephropathy	13(8.5)
Membranoproliferative glomerulonephritis	9(5.9)
Tubular Atrophy n, (%)	
None	49(32)
Mild	102(66.7)
Moderate	2(1.3)

Table-II: Renal Outcome of Children with Steroid-Resistant Nephrotic Syndrome at Last Follow-Up.

Parameters	n (%)
Complete remission	53(34.6)
Partial remission	36(23.5)
Chronic Kidney Disease	53(35)
Stage 1	5(9.4)
Stage 2	5(9.4)
Stage 3	8(15)
Stage 4	2(3.7)
Stage 5	33(62.2)
Renal replacement therapy not required	7/33(21.2)
Renal replacement therapy/Transplant done	26/33(78.8)

6(11.3%) had initially been prescribed ACEIs/ARBs. In the CNI group, TAC was given in 4(7.5%) patients. FSGS was seen in one third of these patients while 10(18.8%) had mesangioproliferative glomerulonephritis (MesPGN) as the histological diagnosis. Two patients, in whom CyA was stopped after prolonged remission, relapsed. CyA was restarted in both patients; one achieved CR while the other had PR.

PR was observed in 36(23.5%) children. Seventeen (47.2%) of them were on CNIs, 10(27.7%) on TAC while the remaining were taking ACEIs/ARBs. The underlying histological diagnosis was FSGS in most 15(41.6%) of them.

In all, 53(35%) of patients followed had progressed to CKD at the last available visit. As expected, FSGS (n=32:60.3%) was the predominant underlying histology. Out of these, 33(62.2%) were in stage 5, while 2(3.7%) were in stage 4 and 8(15%) in stage 3. There were 5(9.4%) each in stages 1 and 2. Twenty six (78.8%) patients in stage 5 required RRT, out of whom 9(34.6%) expired and 1(3.8%) had a live-related renal transplant. His primary disease was FSGS, which recurred in the graft after 6 years of transplantation. The primary cause of death was infection in the majority of children.

At the last follow-up, mean serum albumin had risen from 1.4±0.7 g/dl to 2.9±1.1 g/dl, while mean serum creatinine increased from 0.40±0.14 mg/dl to 2.5±2.1 mg/dl.

On applying chi square statistic (Table 3), the correlation between age, gender, proteinuria, hematuria, serum albumin, hypertension and histopathology at presentation and progression to ESRD was not found to be statistically significant.

Table-III: Factors affecting progression to end-stage renal disease.

Parameters	End stage Renal Disease YES	N0	*p*-value
Age ≤5 years	11(42.3%)	63(49.6%)	0.497
Age > 5 years	15(57.7%)	64(50.4%)	
Gender			
Male	13(50.0%)	71(55.9%)	0.581
Female	13(50.0)	56(44.1%)	
Hypertension			
Present	22(84.6%)	96(75.6%)	0.318
Absent	4(15.4%)	31(24.4%)	
Hematuria			
Present	12(46.2%)	53(41.7%)	0.678
Absent	14(53.8%)	74(58.3%)	
Proteinuria			
Dipstick Proteinuria ≥ 3+	16(61.5%)	90(70.9%)	0.348
Dipstick Proteinuria ≤ 2+	10(38.5%)	37(29.1%)	
Serum Albumin			
Serum albumin <1.5 mg/dl	12(46.2%)	76(59.8%)	0.431
Serum albumin 1.5 -2.5 mg/dl	11(42.3%)	41(32.3%)	
Serum albumin >2.5 mg/dl	3(11.5%)	10(7.9%)	
Histopathology			
Focal segmental glomerulosclerosis	14(53.8%)	49(38.6%)	0.150
Non- Focal segmental glomerulosclerosis	12(46.2%)	78(61.4%)	

DISCUSSION

In this study, we present the clinical characteristics and outcome of childhood SRNS. FSGS was found to be almost twice as common as MCD and MesPGN, a finding consistent with the largest SRNS clinicopathologic registry till date (PodoNet registry cohort).[3]

In recent years, there has been an increase of FSGS compared to MCD observed in various studies. A similar observation was documented by Mubarak et al 11and Gulati *et al* 12 sharing the same epidemiology as our cohort.

Hypertension was a common finding at the time of diagnosis of steroid-resistant cases. It was reported in more than half of the patients in our study but, only 8% patients were found to be hypertensive by Mekahli *et al*.[13] However, a similar finding of hypertension in majority of patients was found in the cohort studied by Shatat *et al*.[14] Raised blood pressures can be due to fluid shifts, side effects of prolonged use of steroids or due to sodium retention15. Microscopic heamturia was found in 42% of our patients, similar to that of 33% reported by Otukesh *et al*.[16]

Clinicians have tried a variety of immunosuppressive treatment protocols (cyclophosphamide, CNIs, mycophenolate mofetil, rituximab) showing variable outcome.[17,18]. Almost one third of our cohort achieved CR on CyA in contrast to a 5-year prospective study showing a remission rate of 88% in the CyA group.[19] Comparable rate of remissions were seen in the PodoNet registry Cohort.[20] Only five patients in our study received TAC as an initial immunosuppressive drug and out of them, only one went into CR. This is a small number to compare; however, good results have been seen with TAC.[21]

One fourth of our patients had decrease in proteinuria and went into PR vs 6% reported in a prospective French study.[22] Various studies, though, showed PR rates ranging from 13 % to 22.5%16-18.

TAC has been tried in multidrug resistant group of patients, and response (either complete or partial) was fairly good.[22] Our patients who did not respond to CyA were switched to TAC with the possible aim to achieve remission, as has been recorded in literature. A fraction of unresponsive patients went into CR/PR on switching the regimen to TAC.

Nephrotoxicity limits the use CNIs in the treatment of SRNS. Rise in serum creatinine while on CNIs was reported in half of the patients in which immunosuppressant therapy was halted and anti-proteinuric drugs (ACEIs and ARBs) were started. None of the patients were re-biopsied. Biopsy-proven CNI toxicity is reported to be 25%.[23]

Burden of disease in the form of CKD and ESRD requiring dialysis in our study was seen in almost 35% of the cohort. There was no significant risk factor observed in patients who progressed to ESRD. Several risk factors including older age at onset, early steroid resistance, immunosuppressant resistance, hematuria, hypertension and FSGS were reported in literature in patients who progressed to ESRD.[8-18] Patients with a histological diagnosis of diffuse mesangial sclerosis and FSGS has been predicted to be at high risk of ESRD.[18] Patients responding to immunosuppressive drugs either having complete or partial remission, have a low risk of progression to ESRD.[20]

Renal transplantation is considered to be the optimal therapy for patients with ESRD. Recurrence of primary disease and graft loss is commonly seen in patients with NS secondary to FSGS.[24] Because of high risk of relapse, cadaveric organ transplant is preferred over live-related donors in patients with SRNS in many centers worldwide.[25] As cadaveric organ transplantation is not established in our country, we perform live-related organ transplants. One of our patients had a live-related transplant from his father. His primary disease, FSGS, recurred early in the post-transplant period requiring plasmapheresis and extensive immunosuppression. He lost his graft 6 years post-transplant and is now on dialysis.

CONCLUSION

In conclusion, SRNS has significant long-term morbidity and mortality. Recurrence of disease in transplanted kidney is common and can result in graft loss. FSGS on diagnosis has a high risk of progression to CKD in five years.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

LA & MA: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

NA & MM: Data acquisition, data analysis, approval of the final version to be published.

AAL & SH: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018; 392(10141): 61-74.
2. Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health 2018; 2(12): 880-90.
3. Trautmann A, Bodria M, Ozaltin F, Gheisari A, Melk A, Azocar M, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol 2015; 10(4): 592-600.
4. Lombel RM, Hodson EM, Gipson DS; Kidney Disease: Improving Global Outcomes. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatr Nephrol 2013; 28(3): 409-14.
5. Büscher AK, Beck BB, Melk A, Hoefele J, Kranz B, Bamborschke D, et al. Rapid response to cyclosporin and favorable renal outcome in nongenetic versus genetic steroid–resistant nephrotic syndrome. Clin J Am Soc Nephrol 2016; 11(2): 245-53.
6. Tsai WC, Wu HY, Peng YS, Ko MJ, Wu MS, Hung KY, et al. Risk factors for development and progression of chronic kidney disease: A systematic review and exploratory meta-analysis. Medicine (Baltimore) 2016; 95(11): e3013.
7. Plumb L, Boother EJ, Caskey FJ, Sinha MD, Ben-Shlomo Y. The incidence of and risk factors for late presentation of childhood chronic kidney disease: A systematic review and meta-analysis. PLoS One 2020; 15(12): e0244709.
8. Zagury A, Oliveira AL, Montalvão JA, Novaes RH, Sá VM, Moraes CA, et al. Steroid-resistant idiopathic nephrotic syndrome in children: long-term follow-up and risk factors for end-stage renal disease. Braz J Nephrol 2013; 35(3): 191-9.
9. Bacchetta J, Cochat P. Primary disease recurrence—effects on paediatric renal transplantation outcomes. Nat Rev Nephrol 2015; 11(6): 371-84.
10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114(2 Suppl 4th Report): 555-76.
11. Mubarak M, Lanewala A, Kazi JI, Akhter F, Sher A, Fayyaz A, et al. Histopathological spectrum of childhood nephrotic syndrome in Pakistan. Clin Exp Nephrol 2009; 13(6): 589-93.
12. Gulati S, Sengupta D, Sharma RK, Sharma A, Gupta RK, Singh U, et al. Steroid resistant nephrotic syndrome: role of histopathology. Indian Pediatr 2006; 43(1): 55-60.
13. 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(8): 1525-32.
14. Shatat IF, Schoeneman M, Flynn JT, Woroniecki RP. Association of steroid and cyclosporin resistance in focal segmental glomerulosclerosis. Pediatr Nephrol 2007; 22(6): 834-9.
15. Shatat IF, Becton LJ, Woroniecki RP. Hypertension in childhood nephrotic syndrome. Front Pediatr 2019; 7: 287.
16. Bensimhon AR, Williams AE, Gbadegesin RA. Treatment of steroid-resistant nephrotic syndrome in the genomic era. Pediatr Nephrol 2019; 34(11): 2279-93.
17. Trautmann A, Vivarelli M, Samuel S, Gipson D, Sinha A, Schaefer F, et al; International Pediatric Nephrology Association. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2020; 35(8) :1529-61.
18. Otukesh H, Otukesh S, Mojtahedzadeh M, Hoseini R, Fereshtehnejad SM, Riahi Fard A, et al. Management and outcome of steroid-resistant nephrotic syndrome in children. Iran J Kidney Dis 2009; 3(4): 210-7.
19. Hamasaki Y, Yoshikawa N, Nakazato H, Sasaki S, Iijima K, Nakanishi K, et al. Prospective 5-year follow-up of cyclosporine treatment in children with steroid-resistant nephrosis. Pediatr Nephrol 2013; 28(5): 765-71.
20. Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS, Bodria M, Ozaltin F, Emma F, et al; PodoNet Consortium. Long-Term Outcome of Steroid-Resistant Nephrotic Syndrome in Children. J Am Soc Nephrol 2017; 28(10): 3055-65.
21. Gulati S, Prasad N, Sharma RK, Kumar A, Gupta A, Baburaj VP. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant 2008; 23(3): 910-3.
22. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. J Pediatr 1994; 125(6): 981-6.
23. Sinha A, Sharma A, Mehta A, Gupta R, Gulati A, Hari P, et al. Calcineurin inhibitor induced nephrotoxicity in steroid resistant nephrotic syndrome. Ind J Nephrol 2013; 23(1): 41-6.
24. Cheong HI, Han HW, Park HW, Ha IS, Han KS, Lee HS, et al. Early recurrent nephrotic syndrome after renal transplantation in children with focal segmental glomerulosclerosis. Nephrol Dial Transplant 2000; 15(1): 78-81.
25. First MR. Living-related donor transplants should be performed with caution in patients with focal segmental glomerulosclerosis. Pediatr Nephrol 1995; 9(1): S40-2.