Original Article

Childhood Steroid-resistant Nephrotic Syndrome: Long-term Outcomes from a Tertiary Care Center

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Abstract

Introduction: Steroid-resistant nephrotic syndrome (SRNS) is a rare condition that accounts for about 10% to 20% of all nephrotic syndromes in children. While calcineurin inhibitors induce remission in the majority, the data on long-term outcomes are limited. This retrospective study aimed to look at the clinical profile, biopsy findings, and long-term treatment outcomes in children with SRNS. **Methods:** The records of all children (1–18 years) with SRNS with biopsy findings of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), or mesangioproliferative glomerulonephritis, who received treatment for a minimum period of 12 months and were in follow-up during the years 2007–2018 at a tertiary care teaching hospital were retrieved. The clinical, histopathological, and biochemical factors and treatment outcomes were recorded and analyzed. **Results:** Ninety-one (72 boys) children with a median (interquartile range [IQR]) age of onset of nephrotic syndrome as 48 (24–87) months were included. MCD and FSGS were the most common histopathological types (57.1% and 36.3%, respectively) and 62 (68.1%) patients had late steroid resistance. Calcineurin inhibitors (CNIs) were used in 86.8% of the children, and response rates with cyclosporine and tacrolimus for complete remission (CR) were 80% and 73.7%, respectively, with median (IQR) time to response being 3 (2–4) months. The presence of MCD on histology and the use of CNIs were significantly associated with CR ($P < 0.01$). At a median (IQR) follow-up of 5 (3–7) years, 76 (83.5%) children had either CR or partial remission, four (4.4%) developed chronic kidney disease and five (5.5%) died (three due to end-stage renal disease and two of infective complications). **Conclusion:** SRNS children with MCD on biopsy, late resistance, and response to CNIs have better long-term outcomes. Most patients respond to CNIs within the first 6 months of use and need therapy for at least 24 to 36 months.

Keywords: *Calcineurin inhibitors, CKD, MCD, remission, SRNS, steroids*

Introduction

Nephrotic syndrome is a chronic disorder in children characterized by edema, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia. The annual incidence of the condition is 2–7 in 100,000 in children under 15 years of age with a prevalence of 16 in 100,000; the Asian population appears to have a higher prevalence.[1,2] While most children respond to daily prednisolone therapy, failure to respond after 4 weeks of compliant steroid therapy indicates steroid-resistant nephrotic syndrome (SRNS) seen in about 10% to 20% of all children with the condition.[3] There is variability in the prevalence of SRNS depending on the ethnicity with a prevalence of about 20% among European children to 27% to 54% among Asians.[4,5]

Patients with steroid-resistant disease pose the most difficult therapeutic challenge. These children are at risk for complications of unremitting nephrotic syndrome and developing end-stage kidney disease (ESKD) in the long term. Medications like cyclosporine, tacrolimus, intravenous cyclophosphamide, intravenous steroids, and most recently rituximab are used for inducing and maintaining remission in these patients; these drugs cause intense immunosuppression.

The largest data till date reported outcomes of SRNS from the PodoNet registry, which primarily had European children of Caucasian ancestry (90.3%). The same publication also showed 10-year ESKD-free survival rates of 43%, 94%, and 72% in children with nonresponse (NR), complete remission (CR), and partial remission (PR), respectively, with 79% and 52% in children with biopsy findings

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of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS).[6,7] Non-responders are at high risk of developing chronic kidney disease (CKD) with a prevalence of up to 50%.[8] While the information on long-term outcomes of SRNS is available for Caucasian and African American children, studies from India have looked mostly at the short-term outcomes after the administration of different immunosuppressive agents.[9,10] Ethnicity appears to influence the outcomes, and as most children with SRNS receive calcineurin inhibitors (CNIs), the long-term outcome is also dependent on the response to these agents and their inherent nephrotoxicity.[8,9] This retrospective study was done to determine the clinicopathological profile and long-term outcomes of Indian children with SRNS.

Methods

This study was done in the department of pediatrics of a tertiary care teaching hospital located in the northern part of India. The records of all children with SRNS (initial and late resistance) with biopsy findings of MCD, FSGS, or mesangioproliferative glomerulonephritis (MesPGN), who were treated and were in follow-up in pediatric nephrology clinic during the period 2007–2018 were retrieved. Patients with a minimum follow-up of 12 months and complete records were included for the study analysis; children with congenital and secondary nephrotic syndrome were excluded. The study protocol was approved by the institute's ethical committee.

A study pro forma was filled for each patient that included information related to demographics, onset of nephrotic syndrome, histopathological features, therapy details, and outcomes.

Definitions

SRNS was defined as failure to respond to 4 weeks of compliant steroid therapy in the absence of any documented infection. Children who failed to respond in the first episode were termed as initial resistance, whereas late resistance was defined as failure to achieve remission after initial response to steroids.[3] Standard definitions were used for defining steroid-dependent nephrotic syndrome (SDNS), frequently relapsing nephrotic syndrome (FRNS), and infrequently relapsing nephrotic syndrome (IFRNS).[10]

Complete remission (CR) was defined as the presence of trace or negative dipstick proteinuria or spot urine protein to creatinine ratio less than 0.2 mg/mg on follow-up. ***Partial remission (PR)*** was defined as the presence of 1–2+ dipstick proteinuria or protein to creatinine ratio from 0.2 to 2 mg/mg, serum albumin >3.0 g/dL, and no edema. The persistence of 3–4+ proteinuria or protein to creatinine ratio >2, albumin less than 2.5 g/dL, or edema constituted ***nonresponse (NR)***.[11]

Treatment protocol

Children with SRNS underwent renal biopsy and were treated with immunosuppressants other than steroids based on the biopsy findings. Children with MCD, FSGS, and MesPGN were treated with CNIs (cyclosporine or tacrolimus) along with alternate-day prednisolone in tapering doses. Cyclosporine was given in doses of 4–5 mg/kg/day as two divided doses while tacrolimus was given in doses ranging from 0.08 to 0.15 mg/kg/day as two divided doses. Most patients received concomitant alternate-day prednisolone (0.25–1 mg/kg) in tapering doses for at least the first 12 months of therapy and angiotensin-converting enzyme inhibitor (enalapril 0.2–0.5 mg/kg/day). Both CNIs were given for a period of 2 to 3 years; rarely longer in some patients dependent on these drugs. Nonresponse to CNI was defined as lack of CR or PR after 6 months of compliant therapy. Serum levels of CNI for all patients could not be done due to in-house nonavailability and financial constraints. However, levels were done sparingly for patients who did not respond or showed clinical features of toxicity. Repeat biopsy was done for patients requiring CNI for more than 3 years to look for features of toxicity. Intravenous cyclophosphamide in doses of 500 mg/m² as an infusion was given every month for six such pulses in some patients who did not respond to 6 months of compliant CNIs therapy or showed toxicity (hypertension, significant gum hyperplasia, or hypertrichosis) or had contraindications to them (acute kidney injury or tubulointerstitial damage on biopsy >20%). Those who responded but remained FRNS or SDNS subsequently received second-line alternative agents that included mycophenolate (MMF), rituximab, or interchange of CNIs. The patients were followed up regularly every 3 months with kidney function tests, serum albumin, and cholesterol and evaluated for clinical and biochemical response and side effects. Genetic testing could not be performed in any child due to financial constraints.

Data collection

Demographic data such as the age of onset and presentation, gender, type of resistance, biopsy findings, treatment received, and response to therapy were recorded. In case of late resistance, the prior disease type such as FRNS or SDNS was noted. Complications such as the presence of cushingoid habitus, gum hyperplasia, hypertrichosis, hypertension, infections (numbers, site), cataract, glaucoma, diabetes, and anthropometric parameters were recorded. The final long-term outcome was recorded as a steroid-sensitive nephrotic syndrome (IFRNS/FRNS/SDNS) or persistence of resistance (PR/NR), progression to CKD, or death.

Statistical analysis

The collected data were transformed into variables, coded, and entered into Microsoft Excel. The data were analyzed and statistically evaluated using SPSS (Statistical Package

for the Social Sciences) Version 21 (IBM SPSS Statistics, Version 21.0. Armonk, NY, IBM Corp.). Quantitative data were expressed as mean and standard deviation, and median and interquartile range (IQR); the difference between two comparable groups with quantitative variables was tested by Student's *t*-test (unpaired) or Mann–Whitney *U* test. Qualitative data were expressed as proportions and compared with the Chi-square test or Fisher's exact test. A binary logistic regression model was used to assess factors predicting CR with clinical parameters and renal biopsy as independent variables. A *P* value less than 0.05 was considered statistically significant. Kaplan–Meier (KM) survival curves were drawn for the long-term outcomes.

Results

During the study period of 12 years, 135 children were treated as SRNS; 91 (72 boys) were finally included in the study after excluding two children with congenital nephrotic syndrome, 18 with secondary nephrotic syndrome, and 24 with nonavailability of complete data. The median (IQR) age at the onset of illness was 48 (24–87) months. While 31.9% had initial resistance, the remaining (68.1%) developed resistance after the initial response (late resistance) after a median (IQR) period of 12 (6.5–33) months. None of the patients had any family history of nephrotic syndrome. The demographic and clinical features of the study population are provided in Table 1.

Table 1: Demographic profile of the study population

Parameter	Values (*n*=91)
Age of onset (months)	48 (24, 87)
Age at presentation (months)	72 (48, 120)
Age at enrollment (months)	156 (108, 180)
Males	72 (79.1%)
Females	19 (20.9%)
Weight SDS (at presentation)	−0.6 (−1.45,0)
Weight SDS (at last follow-up)	−0.9 (−1.5, −0.2)
Height SDS (at presentation)	−1.65 (−2.6, −0.8)
Height SDS (at last follow-up)	−1.3 (-2.75, −0.15)
eGFR at presentation (mL/minute/1.73 m²)	98.1 (77.3, 125.4)
eGFR at last follow-up (mL/minute/1.73 m²)	90.9 (67.5, 121.5)
Initial resistance	29 (31.8%)
Late resistance	62 (68.2%)
Course before developing resistance	IFRNS 10 (16.1%) FRNS 33 (53.2%) SDNS 8 (12.4%) Not available 11 (12%)
Time to resistance in late resistance (months)	12 (6.5,33)
Biopsy findings	
MCD	52 (57.1%)
FSGS	33 (36.2%)
MesPGN	6 (6.6%)

Continuous data are expressed as median (IQR); proportions as percentage. SDS=standard deviation score, eGFR=estimated glomerular filtration rate; IFRNS=infrequently relapsing nephrotic syndrome; FRNS=frequently relapsing nephrotic syndrome; SDNS=steroid-dependent nephrotic syndrome; MCD=minimal change disease; FSGS=focal segmental glomerulosclerosis, MesPGN=mesangioproliferative glomerulonephritis

Response to immunosuppression

Sixty (65.9%) patients received cyclosporine and 19 (20.9%) received tacrolimus as the first-line therapy for SRNS, and CR was achieved in 48/60 (80%) and 14/19 (73.7%), respectively, within a median (IQR) duration of 3 (2–4) months. Twelve (13.2%) patients received cyclophosphamide due to contraindication to CNI, adverse reaction or nonresponse to CNI, and only one of them achieved CR. At the end of 1 year, CR was achieved in 63 (69.2%) patients and PR in nine (9.9%), while 19 (20.9%) remained nonresponsive to any therapy; the median (IQR) duration of CNI treatment was 2 (1.5–3) years.

Long-term course

Eighty-three patients had a follow-up of more than 2 years, and 66 (79.5%) of them were in CR, nine (10.8%) had PR, and eight (6.8%) had NR. Of those who achieved CR, 46/63 (73%) subsequently had IFRNS, whereas 14 (22.2%) had FRNS and three (4.8%) had SDNS. Forty-seven patients had a follow-up of more than 5 years and 27 (57.4%) were in CR, while four (8.5%) and 16 (37%) had PR and NR, respectively.

Final Outcome: After a median (IQR) follow-up of 5 (3–7) years, 63 (69.2%) of the patients had become infrequently relapsing, nine (9.9%) remained FRNS whereas four (4.4%) were SDNS; overall 83.5% patients had a favorable course. Seven (7.7%) children had a partial response to the therapy, whereas eight (8.8%) children remained nonresponsive, and of them, four developed CKD; five (5.5%) children died (three with ESKD and two with sepsis). There was an improvement in the height standard deviation score (SDS) from −1.65 at initial presentation to −1.3 at the last follow-up, whereas the weight SDS declined from −0.6 to −0.9.

About 46 (50.5%) patients required modification of immunosuppressive therapy during the follow-up period. The indications for use of MMF, rituximab, or another CNI were primarily NR in 19 (31.9%), PR in nine (12.7%), and FRNS or SDNS course after becoming steroid sensitive in 17 (27.6%) and CNI toxicity in one child. A comparison of clinical and biopsy features in children with CR or PR with NR is provided in Table 2. Use of CNIs was significantly associated with CR/PR ($P < 0.0001$). Biopsy findings were not significantly different between CR/PR and NR ($P = 0.33$), but when compared between CR and non-CR (PR/NR), MCD on biopsy was significantly associated with CR ($P = 0.001$). Also, the age of onset was significantly higher in the CR/PR group compared

Table 2: Comparison of patients achieving CR and PR/NR

Parameter	CR/PR (*n*=72)	NR (*n*=19)	OR (95%CI)	*P*
Gender				
Male	55 (76.4%)	17 (89.5%)	0.38 (0.07-1.8)	0.22
Female	17 (23.6%)	2 (10.5%)		
Age of onset of NS (years) Median (Q1, Q3)	4 (2.2, 8)	2.5 (1.5, 4)		<0.001[#]
Age of onset of SRNS (Years) Median (Q1, Q3)	6 (3.7, 9)	3.5 (2, 4.5)		<0.001[#]
Type of resistance				
Initial resistance	23 (31.9%)	6 (31.6%)	1.01 (0.34-3.0)	0.97
Late resistance	49 (68.1%)	13 (68.4%)		
Biopsy findings*				
MCD	43 (59.8%)	9 (47.4%)	1.6 (0.59-4.55)	0.33
FSGS	27 (37.5%)	6 (31.5%)		
MesPGN	2 (2.7%)	4 (21.1%)		
Immunosuppressants**				
Tacrolimus	15 (20.8%)	4 (21.1%)	38 (7.3-206)	<0.0001
Cyclosporine	55 (76.4%)	5 (26.3%)		
IV Cyclophosphamide	2 (2.7%)	10 (52.6%)		

*Odds ratio were calculated for MCD and non-MCD. **Odds ratio were calculated for Cylcosporine/tacrolimus and IV Cyclophosphamide. [#]Mann–Whitney *U* test. CR=complete remission, PR=partial remission, NR=nonresponse, OR=odds ratio; CI=confidence interval; NS=nephrotuc syndrome; Q=quartile; MCD=minimal change disease, FSGS: focal segmental glomerulosclerosis, MesPGN: mesangioproliferative glomerulonephritis

with the NR group. There was no significant association of gender and type of resistance with the remission rate. There was no significant difference in the response rates of cyclosporine and tacrolimus (odds ratio [OR]; 95% confidence interval [CI] = 0.34; 0.08–1.4; P = 0.14). A regression analysis with CR as the dependent variable showed the R^2 value as 0.298 and the biopsy findings of MCD and use of CNI predicted CR significantly unlike other factors [Table 3]. KM analysis was performed for survival times of CR (event) for the groups based on initial or late resistance and use of CNI or alternative agents. The mean survival time was compared using log-rank test. Figure 1 shows the KM curve for the type of resistance where the mean (95% CI) time period for CR with initial resistance was 6.43 (5.42, 7.43) and 6.61 (4.75, 8.47) years for late resistance; P = 0.76. The survival curves showed much better chances of CR in patients receiving CNI as first-line agents compared with those receiving other alternative agents [Figure 2], the mean (95% CI) time period for CR being 12.08 (9.02, 15.15) years for CNI and 5.79 (4.95, 6.63) years with other agents; $P < 0.001$.

Table 3: Logistic regression for the predictors of complete remission (*n*=91)

Variable	OR	95% CI	*P*
Gender (male)	0.79	0.19-3.3	0.75
Age at onset	1.07	0.89-1.3	0.46
Type of resistance (initial)	0.38	0.1-1.4	0.15
Biopsy (MCD)	6.16	1.6-23.3	0.007*
Use of CNIs	15.5	2.07-116.4	0.008*
Duration of therapy	1.68	0.94-2.99	0.08

*P<0.05 OR=odds ratio; CI=confidence interval; MCD=minimal change disease, CN=: calcineurin inhibitor

Side effects of therapy

Side effects of therapy observed were hypertension in 22.7% (Stage 1 in 80% and Stage 2 in 20%), hypertrichosis (40%), and cushingoid habitus (34.1%); 31% developed significant gum hypertrophy. These children were normotensive to begin with but developed hypertension during the course of therapy. None of them had any features of end-organ damage (eye evaluation and echocardiography done for them). One child developed diabetes mellitus on tacrolimus and was subsequently shifted to cyclosporine, achieved CR, and the insulin requirement ceased in 3 months. Five (5.5%) patients developed cataracts and two needed surgery for it and another two (2.2%) developed glaucoma. Repeat biopsy was done in seven patients who received CNI for more than 3 years and four (57.1%) of them had features of chronic CNI nephrotoxicity. The incidence of infections and hypertension were similar in both cyclosporine and tacrolimus groups (P = 0.33 and 0.47, respectively).

Complications

Fifty-one episodes of infections were documented in 29 (31.9%) patients; 37 episodes of peritonitis occurred in 27 (29.7%) patients, eight (8.8%) patients had tuberculosis, four (4.4%) had pneumonia, and two had cellulitis during

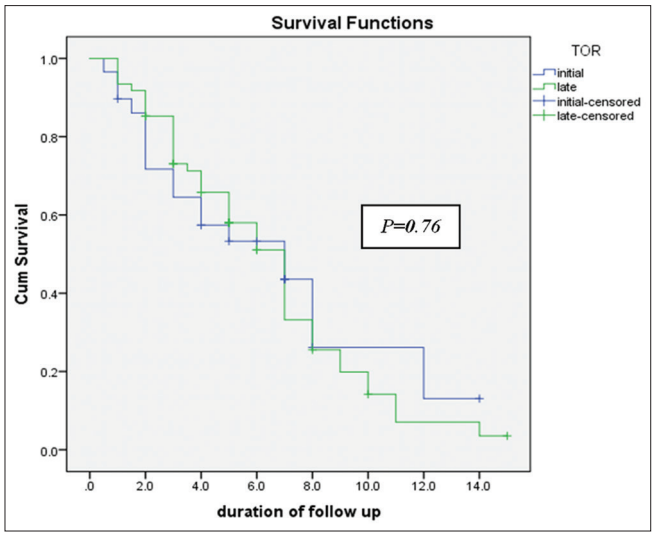

Figure 1: Kaplan–Meier survival curve showing the chances of complete remission (CR) in follow-up (in years) in patients with initial resistance (IR) and late resistance (LR)

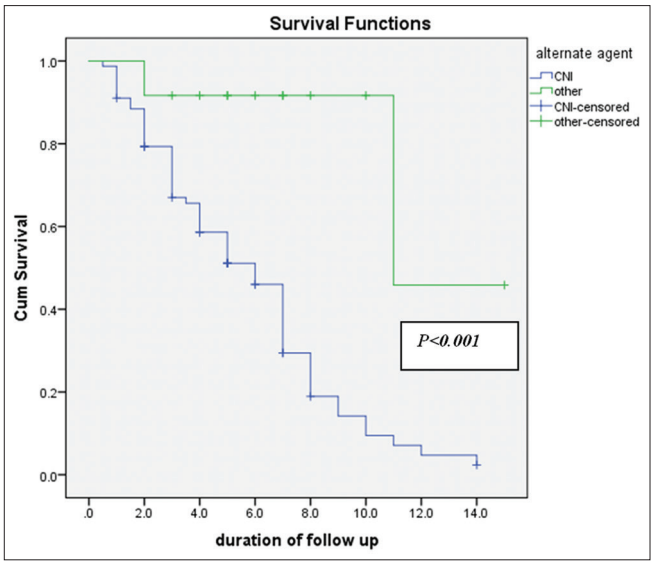

Figure 2: Kaplan–Meier survival curve showing the chances of complete remission (CR) in follow-up (in years) in patients having received calcineurin inhibitors or other agents

treatment and last follow-up. Only two (2.2%) children developed venous thrombosis during this period.

Discussion

While various studies have reported the response rates with the use of CNI in children with SRNS, the information on long-term outcomes from India is lacking.[7,12,13] Most guidelines recommend treatment of SRNS with CNIs for a duration lasting 2 to 3 years.[11,14] Treatment often changes the disease course, and the long-term renal outcomes are dependent on the achievement of prolonged remission and appearance of drug toxicity with prolonged use of CNIs. Ethnicity and genetics of SRNS too influence the long-term outcomes.[4,5]

The median (Q1, Q3) age of onset of nephrotic syndrome in our study was 48 (24, 87) months and 79.1% were boys; earlier studies too have shown similar results.[7,15] Most (68.1%) patients had late resistance and developed resistance after a median (Q1, Q3) period of 12 (6.5, 33) months; other studies have shown a higher proportion of initial resistance, and time to develop late resistance has not been described previously.[7,15] Underlying histopathology usually affects the clinical presentation and also the outcomes of children with SRNS; a higher proportion of MCD (57.1%) compared with 36.3% FSGS could have contributed to a lower prevalence of initial resistance in this study. Srivastava *et al.*[16] reported the incidence of MCD and FSGS as 52.7% and 23%, respectively, in a cohort of children biopsied between 1984 and 1995. Later, Banaszak *et al.*[17] compared the histopathology of childhood nephrotic syndrome over two consecutive decades (1985–1995 and 1996–2005) and reported a tendency toward increasing proportional incidence of FSGS and fall in the incidence of MCD. They also reported a simultaneous significant increase in steroid resistance, which they attributed partially to the rising incidence of FSGS. In 2005, an Indian study reported FSGS to be the most common histopathological finding in children with SRNS accounting for 59% of the total cases.[15] A higher incidence of FSGS was further reported in later studies. A randomized controlled trial (RCT) from India reported the incidence of FSGS and MCD as 69% and 31%, respectively.[9] A higher incidence of FSGS was also reported by the PodoNet registry (primarily European countries) data that looked at SRNS in children (n = 1,368) and documented a higher proportion of FSGS (56%) compared with MCD (21.1%).[7] Almost 50.9% of children in their cohort had an onset of nephrotic syndrome between 1 and 5 years of age. The lower incidence of FSGS in our study could be due to the lower median age of the study population and were similar to one by Inaba *et al.*,[18] where the median age of onset was 3.2 years and also due to a higher proportion of late resistance. Besides the difference in the histopathology in our study may also be attributable to genetic and ethnic factors.[4]

Overall, 69.2% of patients attained CR with CNIs within a median period of 3 months in our patient cohort. Children who achieved CR/PR were older than the children who did not achieve any response. This finding is in contrast with Trautmann *et al.*,[6] who did not find any significant difference in the age of onset of the children achieving CR, PR, or NR. Inaba *et al.*[18] also showed that higher age of onset of SRNS (>11 years) was an independent risk factor for progression to ESKD. Genetic diagnoses were identified in 23.6% of the children with SRNS in the PodoNet registry, and chances of detecting a genetic etiology reduced with increasing age (35.6% in children 3–12 months of age compared with 15.6% in children 6–11 years of age). Only 10.4% of these children responded

to immunosuppressive therapy.[7] It is possible that in our study, some of the children with NR had underlying genetic etiology, although this could not be ascertained. RCTs and cohort studies show that therapy with cyclosporine or tacrolimus results in CR in 30% to 40% and CR or PR in 60% to 80% of patients.[19,20] A higher proportion of CR in our study population could be due to a larger number of children having late resistance and MCD on biopsy. Other studies too have shown better response in patients with MCD.[21,22]

Attaining PR is an important predictor for a good outcome in children with SRNS; the risk of ESKD decreases by 85% to 90% if CR was achieved and by 50% for those with PR. Ten-year renal survival rates were 94% and 72%, respectively, for those with CR and PR, and only 43% for those with NR to immunosuppression in one cohort.[6] After a median follow-up of 5 years, 83.5% of our patients had a favorable course (69.2% had IFRNS and 14.3% had FRNS/SDNS); four (4.4%) developed CKD, and the mortality was 5.5%, which was contributed by ESKD and complications of SRNS course. The better outcomes observed in the present study appear to be due to a higher proportion of late resistance, MCD on biopsy, and the treatment with CNIs as first line in 86.8% of children. The PodoNet registry reported 33% CR and 22.5% PR after a median follow-up of 3.7 years among SRNS children, and 78.5% of patients had received CNI.[7]

Similar efficacy of cyclosporine and tacrolimus in inducing remission was observed in the present study (median time 3 months) consistent with the findings of a previous study.[18] Büscher *et al*.[23] also reported a good response with cyclosporine in nongenetic forms of SRNS (78% by 2.5 months), whereas the response was poor in the genetic form of SRNS (CR only in 3%). The side effects observed during therapy were comparable between the two CNIs although the incidence of hypertrichosis in 40% was exclusively among children on cyclosporine. Repeat biopsies for CNI toxicity were done in seven patients who required CNI for more than 3 years, and four (57.1%) of them showed features of CNI toxicity; a previous study on Indian children showed toxicity in 25% of biopsies after a median (Q1, Q3) duration of 30 (26, 35) months.[24] The difference may be due to the very small number of biopsies performed in our study. Cyclophosphamide was used less commonly and accounted for only 12% of the immunosuppressive regimen; response rates were low (8.3%) consistent with the earlier report of >80% failure rate with these regimens.[25]

The infection rates observed over a 5-year period were about 10 per year, and 72.5% of infections were spontaneous bacterial peritonitis, and 4.4% of children were treated for tuberculosis during the follow-up period. Also, the incidence of venous thrombosis was 2.2%. A previous RCT on comparison of tacrolimus and intravenous cyclophosphamide too observed a higher number (45%) of peritonitis episodes over a 12-month observation period.[15] An incidence of 3.8% for thrombosis has been described in children with SRNS from Bulgaria.[26]

A major limitation of the present study is its retrospective nature, and a significant number of patients had to be excluded due to incomplete records. Also, we were not able to do the genetics for patients with initial resistance (31.9%) due to nonavailability and financial constraints, although none of the patients had any family history of nephrotic syndrome or other renal diseases. However, considering the fact that SRNS is a rare disease in childhood and patient attrition is expected in long-term follow-up and this being a single-center study, these limitations are not completely unavoidable.

Conclusions

Based on the results of this study, we conclude that Indian children with SRNS, especially those with late resistance and MCD on biopsy, are more likely to respond to CNIs and have good long-term outcomes. There appears to be a higher occurrence of late resistance and MCD in this part of the world and with the early use of CNIs, the chances of complications decrease, and the overall growth parameters too improve.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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