RESEARCH ARTICLE

Clinicopathological features and outcome of secondary steroid resistant nephrotic syndrome: A retrospective analysis

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Abstract

Objective: To determine the clinico-pathological features and long-term outcome of secondary steroid-resistant nephrotic syndrome treated with steroids and calcineurin inhibitors.

Method: The retrospective cohort study was conducted at the Sindh Institute of Urology and Transplant, Karachi, in June and July 2023, and comprised data from January 1, 2008, to December 31, 2020, of children aged 1-18 years who developed steroid resistance after initial sensitivity to steroids with at least 1-year of follow-up. Demographics as well as time taken to secondary steroid response were documented. Renal biopsy of all patients with secondary steroid resistance had been performed. Eventual outcomes after treatment with calcineurin inhibitors based on the degree of proteinuria and serum albumin levels were used to categorise complete remission, partial remission and no response. Kidney function, as determined by estimated glomerular filtration rate, was recorded. Data was analysed using SPSS 22.

Results: Of the 1,000 patients who underwent renal biopsy for steroid resistance, 48(4.8%) had idiopathic steroid-resistant nephrotic syndrome; 32(66.7%) males, 16(33.3%) females and median age of 5 years (interquartile range: 4-7.3 years). Median age at diagnosis of nephrotic syndrome was 5 years (interquartile range: 3.6-7.3 years). The median time from nephrotic syndrome to secondary steroid-resistant nephrotic syndrome was 23 months (interquartile range: 8.75-44.5 months). Biopsy results at diagnosis showed that 27(56.3%) had minimal change disease. The mean follow-up time was 6.1±3.2 years. Of the 43(89.5%) patients who received cyclosporin for 1 year, 29(67%) obtained complete remission, 5(12%) attained partial remission and no response was seen in 9(21%) patients.

Conclusion: Majority of the children had minimal change disease at the time of diagnosis of secondary steroid-resistant nephrotic syndrome. The long-term response with calcineurin inhibitors was favourable at 1 year.

Keywords: Secondary steroid-resistant nephrotic syndrome, Late non-responder nephrotic syndrome, Calcineurin inhibitors, Childhood nephrotic syndrome. (JPMA 74: 524; 2024) **DOI: https://doi.org/10.47391/JPMA.10584**

Introduction

Idiopathic nephrotic syndrome (NS) is the most prevalent glomerular disease in childhood, affecting approximately 1.15 to 16.9 out of every 100,000 children.[1] It can be categorised into two groups based on the initial response to standard steroid treatment; steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS). However, the responsiveness to steroids can change over the course of the disease. Some patients initially classified as SRNS start showing response to steroid treatment, and may later develop secondary SSNS. Conversely, some patients with initial SSNS may experience secondary SRNS during subsequent relapses.[2] Secondary SRNS, also referred to as late SRNS or late steroid non-responders, accounts for 13.8% to 35.9% of SRNS cases.[3]

Typically, a positive prognosis and eventual resolution of the relapsing NS are linked to minimal change disease (MCD) histology and responsiveness to steroid treatment. On the other hand, when NS is resistant to steroids and exhibits focal segmental glomerulosclerosis (FSGS) histology on biopsy, there is a higher likelihood of the disease progressing to chronic kidney disease (CKD). While this association is not absolute, many patients with SRNS tend to show FSGS histology on biopsy.[3]

A study showed that the predominant histopathological lesions seen in SRNS were FSGS (38.5%), followed by MCD (23.2%) and mesangial proliferation with immuglobulin M (IgM) deposits (13.6%). It did not differentiate between primary and secondary SRNS.[4]

In secondary SRNS, the main histopathological pattern has been shown to be MCD, followed by FSGS. Treatment usually includes inhibitors of the renin-angiotensin-aldosterone system inhibitors (RAASi) and calcineurin inhibitors (CNI) in patients with non-genetic forms of SRNS. With this approach, complete remission (CR) or partial remission (PR) can be achieved in 50-70% of cases.[5]

Management of SRNS is a great challenge due to its heterogeneous aetiology, frequent lack of remission induced by immunosuppressive treatment, and

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complications including drug toxicity, infections, thrombosis, the development of end-stage kidney disease (ESKD), and recurrence after renal transplantation.[6,7]

In a study, the long-term outcomes of 153 children with SRNS were examined. The results revealed that 34.6% of the children achieved CR with the use of cyclosporin, while 23.5% experienced PR. However, 35% of children developed CKD, and, among those, 78.8% required renal replacement therapy.[8]

Despite having been identified many years ago, there is still limited understanding of secondary SRNS. The current study was planned to determine the clinico-pathological characteristics and to gain insight into long-term outcomes of secondary SRNS in children treated with steroids and CNIs.

Patients and Methods

The retrospective cohort study was conducted at the Sindh Institute of Urology and Transplant (SIUT), Karachi, in June and July 2023, and comprised data from January 1, 2008, to December 31, 2020, of children aged 1-18 years who developed SRNS after initial SSNS with at least 1-year of follow-up. The sample was raised using consecutive sampling technique. Patients aged <1 year and those with secondary causes of NS were excluded.

Data with respect to demographics, clinical course, laboratory findings, biopsy findings, treatment given, and response was documented on a proforma. The end-point was death, end-stage renal disease (ESRD), or December 31, 2022.

SSNS was defined as patients who achieved CR within 4 weeks of starting prednisone at a dose of 2mg/kg/day with a maximum of 60 mg/day. Those who did not achieve remission in 4 weeks were labelled as having SRNS. Secondary SRNS was defined as patients who initially achieved remission lasting for at least 2 weeks who then developed steroid resistance on subsequent relapses. Response to CNIs was classified according to proteinuria and serum albumin levels as PR, CR, or no remission (NR) within the first year after secondary SRNS, according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[9] PR was defined as proteinuria of 1+ or 2+ with serum albumin of more than 3g/dl. CR was defined as negative, or trace proteinuria. NR was defined as persistent 3+ or 4+ proteinuria with serum albumin of <3g/dl.[10] The estimated glomerular filtration (eGFR) rate was calculated using Schwartz formula.[11] ESRD was defined as GFR <15ml/min/1.73m. Results were compared to those of another study of children with primary SRNS conducted at SIUT.[8]

Data was analysed using SPSS 22. Data was expressed as mean±standard deviation, median and interquartile range (IQR), and as frequencies and percentages, as appropriate. Chi-square test was applied to determine the correlation between clinico-pathological features at baseline and eventual outcome. Mann-Whitney U test was used to determine any difference of time to first relapse and time to secondary SRNS with response to cyclosporine, histopathological findings and progression to CKD. P<0.05 was considered significant.

Results

Of the 1,000 patients who underwent renal biopsy for steroid resistance, 48(4.8%) had idiopathic SRNS. There were 32(66.7%) males, 16(33.3%) females and median age of 5 years (IQR: 4-7.3 years). Median age at NS diagnosis was 5 years (IQR: 3.6-7.3 years). The median time to first relapse was 2 months (IQR: 1-4 months). The median time from NS to secondary SRNS was 23 months (IQR: 8.75-44.5 months). A total of 17(35.4%) cases developed secondary SRNS at the first relapse, and 31(64.5%) relapsed more than once. Biopsy results at diagnosis showed that 27(56.3%) had MCD, 11(22.9%) FSGS, 8(16.7%) IgM nephropathy and 2(4.2%) mesangial proliferative glomerulonephritis (Table 1).

All patients were treated with cyclosporin initially and 19(40%) were given tacrolimus subsequently. Out of 48(100%) patients who were started on cyclosporine, 5(10%) were switched to tacrolimus at 6 months due to no response. Of the 43(89.5%) patients who completed cyclosporin for 1 year, 29(67%) obtained CR, 5(12%)

Table-1: Clinical and histopathological characteristics (n=48).

Characteristic	n (%)
Male	32 (67)
Age median (IQR), years	5.0 (4.0-7.3)
Age of diagnosis of nephrotic syndrome median (IQR), years	5.0 (3.6-7.3)
Time to First Relapse Median (IQR), months	2 (1.0-4.0)
Frequency of relapses	
1	17 (35)
2	10 (22)
3	9 (19)
4	8 (17)
5	2 (4)
6	2 (4.)
Time to secondary SRNS median (IQR), months	23 (8.75-44.5)
Hypertension	29 (60)
Biopsy findings	
MCD	27 (56)
FSGS	11 (23)
IgM nephropathy	8 (17)
Mesangial proliferative glomerulonephritis	2 (4)

IQR: Interquartile range, SRNS: Steroid-resistant nephrotic syndrome, MCD: Minimal change disease, IgM: Immunoglobulin M.

Table-2: Predictors of secondary SRNS [n (%)].

Time duration to first relapse	CKD	Non-CKD	U=131.5
	10	38	Z=-1.50
			p=0.125
	MCD	Non MCD	U=280.5
	27 (56)	21 (44)	Z=-0.64
			p=0.949
	Single relapse	Multiple relapses	U=175.5
			Z=-1.96
	17 (35)	31 (65)	*p*=0.05
	Complete/ Partial response	No response	U=140.5
			Z=-0.387
	34 (79)	9 (21)	*p*=0.699
Duration to Secondary SRNS	CKD	Non CKD	U=149.0
	10 (21)	38 (79)	Z=-1.042
			p=0.297
	MCD	Non MCD	U= 271.0
	27 (56)	21 (44)	Z=-0.260
			p=0.795
	Single relapse	Multiple relapses	U=74.5
			Z=-4.078
	17 (35)	31 (65)	*p*≤0.001
	Complete/ Partial response	No response	U=137.0
			Z=-0.478
	34 (79)	9 (21)	*p*=0.632

CKD: Chronic kidney disease, MCD: Minimal change disease, SRNS: Steroid-resistant nephrotic syndrome. Statistical test Mann Whitney U test, U = difference between two rank totals, Z = z score, *p*=*p*-value.

attained PR and NR was seen in 9(21%) patients. There was no difference seen in patient outcomes with respect to time to first relapse and time to secondary SRNS (Table 2).

The mean follow-up time was 6.1±3.2 years. There were 10(21%) patients who reached CKD, 1(2%) patient reached ESRD and 3(6.2%) patients died due to sepsis. There was no significant difference identified between time to first relapse or time to secondary SRNS with respect to biopsy findings and progression to CKD.

Discussion

The current study had 48 patients with secondary SRNS, which, to the best of our knowledge, is the second highest number of patients with secondary SRNS reported. The study showed that the clinical features of secondary steroid resistance with respect to gender, age and blood pressure was similar compared to secondary SRNS reported in previous studies.[2] A complete or partial response to therapy in the first year after being diagnosed as secondary SRNS did not show any relation with respect to progression to CKD. The predominant histological finding of MCD in patients was similar to a previous study.[2,3,12] Other studies related to primary SRNS reported FSGS as the primary finding.[4,8]

CR and PR at 1 year the current study was similar to a study which reported CR 71.4% and PR 16%, while a multicentre study reported a remission rate of 69%.[2,12] A study of children with primary SRNS showed that patients with primary SRNS had CR 34.6% and PR 23.5%.[8]

This suggests that secondary SRNS has a more favourable response to CNIs compared to primary SRNS.

The mean time of follow-up was 6.1±3.2 years in the current study, with 10(20.8%) patients developing CKD, and 3(30%) of them reaching stage 5. Overall, 3(6.2%) deaths were documented. Ying et al. showed an overall ESRD-free survival among 56 patients at 5 years and 10 years of 90.9% and 85.8%, respectively.[2] Schwaderer et al. showed a 100% preserved renal function of 14 patients over a period of 7.8 years, and Straatmann et al showed 26 out of 29 patients maintained normal renal function over 2 years.[12,13]Trainin et al. reported that 9 out of 10 patients held stable renal function, with 1 patient dying of sepsis over a period ranging from 6 months to 9.5 years (median: 53 months).[14] In contrast, Siegel et al. reported 6 patients with secondary SRNS who developed renal insufficiency, with 1 patient developing it in the first year while the duration for others was not mentioned.[15] Srivastava et al. observed that 4 out of 12 patients developed renal insufficiency over a period ranging 1-16 years.[16] In primary SRNS, 35% progressed to CKD, with 78.8% getting initiated on dialysis therapy, and overall death of 13.7% (Table 3).[8]

The current study found no relation between of time to first relapse or time to development of secondary SRNS with long-term outcome with respect to CKD. Ying et al. showed that the only independent predictor for ESRD was no response to intensive immunosuppression in the first year.[2]

Table-3: Comparison between primary and secondary SRNS [n (%)].

	SRNS n=153	**Sec SRNS** n=48
Histopathological diagnosis		
Minimal change disease	33 (22)	27 (56)
Focal segmental glomerulosclerosis	63 (41)	11 (23)
IgM Nephropathy	9 (6)	8 (17)
Mesangial proliferative glomerulonephritis	26 (17)	2 (4)
Membranous nephropathy	13 (9)	-
Membranoproliferative glomerulonephritis	9 (6)	-
Complete remission	53 (35)	29 (60)
Partial remission	36 (24)	5 (10)
Chronic Kidney Disease	53 (35)	10 (21)
Stage 1	5 (9)	-
Stage 2	5 (9)	4 (40)
Stage 3	8 (15)	3 (30)
Stage 4	2 (4)	-
Stage 5	33 (62)	3 (30)
Renal replacement therapy/Transplant done	26/33 (79)	1/3 (33)
Total number of children expired	21/153 (14)	3/48 (6)

Trautmann et al. also identified no response to intensified immunosuppression in the first year as an independent risk factor for ESRD in patients with SRNS.[6]

The current study has several limitations. It is a single-centre study and although the SIUT caters to a large number of NS patients, this entity is rarely encountered. Due to the small sample size, the results may not be generalised to the broader population. The aetiology of CKD in these patients could not be ascertained due to the retrospective design of the study. Since CKD could result from CNI toxicity as well as progression of primary disease, further studies in this regard are warranted.

Conclusion

Clinical features with respect to demographics appeared to be heterogeneous. Response to intensive immunosuppression appeared to be favourable, with only a small number reaching ESRD. The predominant histology type was MCD, followed by FSGS.

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