ORIGINAL ARTICLE

CHILDHOOD IDIOPATHIC STEROID RESISTANT NEPHROTIC SYNDROME, DIFFERENT DRUGS AND OUTCOME

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Background: The management of steroid resistant nephrotic syndrome (SRNS) is quite difficult in paediatric patients. Not only the remission is difficult but also these patients are at risk of progression to end stage renal disease (ESRD). The goal of treatment is either to achieve complete remission or even partial remission as it is the most important predictor of disease outcome. **Methods:** This study was conducted at The Children's Hospital, Lahore from February 2014 to May 2015. The SRNS patients of either sex between ages of 1–12 years were included with histology showing mesangioproliferative glomerulonephritis (MesangioPGN), focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD). Patients were given different immunosuppressant drugs and steroid 30 mg/m^2 alternate day therapy on case to case basis and kept on regular follow up to check for response and adverse effects. **Results:** Total of 105 patients included, 63 (60%) male and 42 (40%) female patients. The age ranges from 1.08 to 12 years, mean age of 6.53 years and SD of ±3.17. Tacrolimus was the most common drug used 43 (41%) patients followed by cyclosporine in 38 (36.2%) patients, while Mycophenolate mofetil (MMF) was prescribed in 21 (20%) patients. Complete response was in 96 (91.4%) initially while partial response was seen in 8 (7.6%) patients. On follow up, 92 (87.6%) patients showed complete response and partial response was in 5 (4.7%) patients. Cushingoid features and hypertrichosis were the most common adverse effect seen. **Conclusion:** Steroid resistant nephrotic syndrome can be managed well with various immunosuppressant drugs and steroids but treatment should be individualized according to clinical presentation, disease histology and cost/social factors.

Keywords: Steroid Resistant Nephrotic Syndrome, cyclosporine, tacrolimus, immunosuppressant, outcome

J Ayub Med Coll Abbottabad 2016;28(2):249–53

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is characterized by hypoalbuminemia, proteinuria, hypercholesterolemia and oedema in children.[1] It is the most common chronic disease which affects paediatric population all over the world with increased prevalence in children form subcontinent.[2] When patients do not show response to treatment despite taking full dose of prednisone for four weeks then then they are labelled as Steroid Resistant Nephrotic Syndrome (SRNS).[3] The SRNS accounts for about 10% of paediatric INS.[4] The management of SRNS is daunting task for paediatric nephrologists as not only remission is difficult but also these patients have got significant risk of progression to end stage renal disease (ESRD).[5] Prognosis of SRNS is not good as if it is not responding to treatment and there is persistent proteinuria.[6] The goal of treatment in SRNS is either to achieve complete remission or even partial remission as it is the most important predictor of disease outcome.[7] Mostly idiopathic SRNS histopathology is either focal segmental glomerulosclerosis (FSGS) or mesangio-proliferative glomerulonephritis (MesangioPGN) or it may be minimal change disease (MCD). During last few decades there is increase in incidence of focal segmental glomerulosclerosis (FSGS) all over the world.[8] Though rare yet FSGS is one of the important causes of ESRD in children as about 50% of paediatric patients with FSGS progress to ESRD over a time period of 5–10 years.[9] The drug options for treatment of SRNS include calcineurin inhibitors (tacrolimus, cyclosporine), angiotensin converting enzyme inhibitors (ACEI), cyclophosphamide, chlorambucil, mycophenolate mofetil and IV methylprednisolone as remission is reported to achieve in 50–60% of patients with SRNS.[10] Other treatment option for SRNS management is Rituximab.[11] The optimal treatment option with combination of various drugs is not known as various studies showed variable response and adverse effects of different drugs.[12] In this study we studied the response to treatment of various drugs given in management of SRNS and out come at end of six months of follow up.

MATERIAL AND METHODS

This study has been conducted in the Department of Paediatric Nephrology at The Children's Hospital and The Institute of Child Health Lahore over a period of sixteen months from February 2014 to May 2015. Patients of either sex between age of one year and twelve years were included in study. Patients were managed as SRNS when patient showed no response to medication in in terms of clearance of urine protein despite getting four weeks treatment of oral

prednisolone. Patient renal biopsy was also done and only patients with idiopathic nephrotic syndrome as MCD, FSGS and MesangioPGN were included. Patients having atypical nephrotic syndrome features as hypertension, deranged renal function tests, gross haematuria, and low complement levels were excluded from study. Patients whom renal biopsy report show Membrano-proliferative glomerulonephritis were excluded along with secondary nephrotic syndrome. Oral steroids were also prescribed in dose of 30 mg/m^2/day on alternate day along with immunosuppressant drugs used for treatment of SRNS. Patients were called for regular follow up in terms of response to treatment and for monitoring of drug adverse effects. Parents/patients were educated for urine protein monitoring, the response to treatment and keep record of it in written form. Urinary protein excretion was monitored either with urine dipstick or by boiling on the first morning voided urine sample. Patients first morning urine protein was monitored for response to treatment as patients achieving complete remission defined as urine protein nil or trace. Partial response was taken when urine protein was on +2 and no response when patient still having +3 urine proteins. Response to treatment was monitored up to three months of initiating the treatment and if patient was showing response then patient was followed for six months from start of treatment. Blood pressure was regularly monitored on each visit and if there was increase in blood pressure from base line then patients were added captopril as antihypertensive. Other groups of antihypertensive medications were also added if blood pressure not is controlled with single drug having maximum dose. There was also regular monitoring of renal function tests, liver function tests, blood sugar, electrolytes, magnesium and uric acid for different adverse effects of different drugs. Patients who showed any adverse effects which could not be managed were dropped from study. Data regarding the age of presentation, age of diagnosis, follow up, histopathology, cholesterol, albumin, follow up duration, histopathology, drug used for treatment and response to treatment was recorded on specified *pro forma*. Data was analysed SPSS 20.0. Results were taken significant if p-value <0.05.

RESULTS

In this study there were total of 105 patients included after exclusion of patients who were dropped from study while doing data audit. Out of total 105 patients, 63 (60%) patients were male and 42 (40%) patients were female. The age range was from 1.08 to 12 years with mean age of 6.53 years and SD of ±3.17 years. The weight range was from 8 kg to 47 kg with mean of 21.76 kg and SD of ±8.23 kg. The descriptive statistics are given in table-1. Family history of nephrotic syndrome was present in only one patient (1%) while there was no family history in 104 (99%) patients. Two patients (1.9%) had history of associated allergy. Microscopic haematuria was present in 33 (31.4%) patients and the no microscopic haematuria was observed in 72 (68.6%) patients. Out of total 105 SRNS patients, 60 (57.1%) patients were late non responders as these patients initially responded to oral steroid therapy and later on developed steroid resistance. Only 45 (42.9%) presented as SRNS as these patients did not show response to full induction dose of oral steroids at presentation. The most common diagnosis on histopathology was MesangioPGN followed by FSGS (Table-2).

The most common drug used for the treatment of SRNS was tacrolimus which was given in 43 (41%) patients followed by cyclosporine which was given in 38 (36.2%) patients. Mycophenolate mofetil (MMF) was prescribed in 21 (20%) patients. Mendoza protocol (Table-9) and triple regimen (prednisolone, vincristine, and cyclophosphamide) was used for management for two and one patient respectively (Table-3). Out of total 105 patients, 96 (91.4%) patients showed complete response after three months for start of treatment as there was no proteinuria. Partial response was seen in 8 (7.6%) patients and one (1%) patient showed no response to treatment (Table-4). Regarding response to treatment and histopathological diagnosis, out of 74 patients with MesangioPGN, 67 patients showed complete response and 7 patients showed partial response and response vs histology is shown in table-5. Different drugs response to treatment is shown in table-6 as overall drug response p-value is 0.286 (Table-7) which is not significant but individual drug response p-value for all drugs like tacrolimus, cyclosporine, mycophenolate mofetil, Mendoza protocol and triple regimen is 0.000 which is very significant (significant p-value <0.05) (Table-8). Patients were followed up to six months after start of treatment and at the end of six months follow up, 92 (87.6%) patients showed complete response. Partial response was shown was by 5 (4.7%) patients. One patient showed no response till end of six months and one patient lost follow up. Five patients expired during course of follow up as they presented with septicaemia and could not survive.

The most common adverse effect was related to steroids as 67 (63.8%) patients were having cushingoid features. One patient also got bilateral cataract due to prolong use of steroids as patient was late non responder and later on during course of treatment was managed as SRNS. The cyclosporine related adverse effects include hypertrichosis which was present in 22 (57.9%) patients. Gum hypertrophy was present in 3 (7.9%) patients. Hypertension secondary to use of cyclosporine was noticed in two (5.2%) patients and one (2.3%) patient on tacrolimus got hypertension. Hyperuricemia was detected in one (2.6%) patient taking cyclosporine.

Table-1: Descriptive statistics

	Minimum	Maximum	Mean	SD
Age(years)	1.08	12.00	6.5330	±3.17015
Weight(kg)	8.00	47.00	21.7667	±8.23135
Systolic Blood Pressure(mm Hg)	90.00	130.00	105.0286	±9.97348
Diastolic Blood Pressure(mm Hg)	50.00	96.00	70.3238	±9.15307
Urea(mg/dl)	12.00	90.00	29.5143	±15.24802
Creatinine(mg/dl)	.1	5.0	.670	±.4944
Cholesterol(mg/dl)	3.4	786.0	383.937	±127.8235
Albumin(mg/dl)	1.1	3.8	2.203	±.5231

Table-2: Frequency of histopathology

Histopathology	Frequency	Percent
FSGS	20	19.0
MCD	11	10.5
MesangioPGN	74	70.5
Total	105	100.0

Table-3: Different drugs used for treatment of SRNS

Drugs	Frequency	Percent
Cyclosporine	38	36.2
Mendoza protocol	2	1.9
Mycophenolate mofitil	21	20.0
Tacrolimus	43	41.0
Triple regimen	1	1.0
Total	105	100.0

Table-4: Response to treatment

Response to treatment	Frequency	Percent
Complete response	96	91.4
Partial response	8	7.6
No response	1	1.0
Total	105	100.0

Table-5: Response and histology

Response	Histology			Total
	FSGS	MCD	MesangioPGN	
Complete response	19	10	67	96
Partial response	1	0	7	8
No response	0	1	0	1
Total	20	11	74	105

Table-6: Different drugs and treatment response

Drugs	Response to treatment			Total
	Complete response	Partial response	No response	
Cyclosporine	36	2	0	38
Mycophenolate mofetil	18	2	1	21
Tacrolimus	40	3	0	43
Triple regimen	1	0	0	1
Total	96	8	1	105

Table-7: Chi-square tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.707[a]	8	.286
Likelihood Ratio	6.457	8	.596
N of Valid Cases	105		

a. 12 cells (80.0%) have expected count less than 5. The minimum expected count is .01.

Table-8: Pearson Chi-Square for different drugs

Drug	Value	Asymp. Sig. (2-sided)
Tacrolimus	105.000	.000
Cyclosporine A	105.000	.000
Mycophenolate Mofetil	105.00	.000
Mendoza protocol	105.000	.000
Triple regimen	105.000	.000

Table-9: The mendoza protocol[13]

Week	Methylprednisolone 30 mg/kg	Prednisone
1–2	Three times per week	None
3–8	Every week	2 mg per kg OD
11–18	Every other week	Without/with tapering
19–50	Every four weeks	Slow tapering
51–82	Every eight weeks	Slow tapering

DISCUSSION

Though in literature the exact definition of SRNS varies yet we took the patients as SRNS when there was no response to full dose of prednisolone given for four weeks.[3] In different centres paediatric nephrologists do give three pulses of methylprednisolone on alternate day after four weeks of oral steroids before considering patient as case of SRNS.[14] There is no definite therapy proposed for management of SRNS as it's a chronic disease having challenging management with poor outcome.[15] In this study we followed the patients with SRNS taking different drugs and the response to treatment was followed.

In our study we checked for the response to treatment up till three months from start of treatment and followed patients up to six months after initiation of treatment. In our study the complete response was observed in 91.4% patients and partial response was seen in 7.6% patients. In literature[5] complete response to treatment has been reported in between 30–84% in management of patient with FSGS. In comparison to our study, one study done at tertiary care centre in Saudi Arabia by Kari JA *et al*[16] in which patients with SRNS were followed as complete response was seen in 45% patient and partial response was seen in 19% patients. While in our study the complete response was seen in 91.4% patients. The literature[17,18] shows cyclosporine is the most common drug used for the treatment of SRNS and there is also response to treatment but patients have to be monitored for drug toxicity especially regarding nephrotoxicity and relapse is also significant when therapy is discontinued. In one study by Plank[19] *et al* which was randomized control trial included patients with SRNS and response to cyclosporine was compared with cyclophosphamide pulse therapy. And it showed better response to cyclosporine and there was recommendation that to use cyclosporine as first line medication in management of SRNS. In our study complete response to cyclosporine was seen in 94.7% (p-value <0.05) and partial response was observed in 5.3% patient and it is also comparable to the study done by Plank *et al*[19]. One another study done by Ulinski T[20] *et al* showed that mycophenolate mofetil (MMF) is also one of effective drug for treatment of SRNS. As in our

study the response to MMF was also significant as P value for the response is <0.05.

In one study[21] by the International Study of Kidney Disease in Children (ISKDC) showed that there is no extra advantage and increase in response as compare to single drug treatment given in form of prednisone when compare with combination of oral cyclophosphamide and prednisone. Other drug which has been used extensively in management of SRNS in our study is tacrolimus. There are current recommendations of Kidney Disease Improving Global Outcome (KDIGO) that calcineurin inhibitors be used as initial therapy for treating SRNS.[22] In our study there was complete response to treatment in 40 (93%) patients, while partial response was seen in about 7% patients. In comparison to our study one study conducted by Gulati S *et al*[23] showed that tacrolimus was one of effective management in SRNS patients as in their study, out of total 22 patients, 84% showed complete response while 10.5% went into partial remission and only 4.55% patients showed no response. While in our study there was no patient with any response to treatment. We also followed the patients for response at end of six months as 92 (87.6%) patients showed complete response and partial response was in 5 (4.7%) patients. Mortality during follow up was 4.7%.

There were also limitations of our study as we did drug level only in case of cyclosporine and tacrolimus in patients with SRNS due to financial aspects and also we only followed patients for six months after start of treatment as we could not determine the optimum duration of immunosuppressant to be given in management of patients with SRNS. Other short coming in our study was genetics, as there is no facility available in our part of country to screen patients for genetic mutations. It is known that mutations in NPHS2 Encoding Podocin showed not good prognosis and identifying the mutation would enable the paediatric nephrologists to avoid unnecessary use of immunosuppressant medications on trial basis in patients with SRNS.[24]

CONCLUSION

This study concluded that management of SRNS in paediatrics patients is difficult task as it involves high morbidity in form of drug adverse effects apart from complications of disease itself. Though remission can be achieved with various immunosuppressant drugs yet treatment for individual patient is based on clinical presentation and histological features along with consideration of social and cost factors.

AUTHOR'S CONTRIBUTION

SS: Data collection, Data analysis, article writing.
FH: Supervision

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