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Clinical and Histopathological Spectrum of Childhood Onset Nephrotic Syndrome- Prospective Study

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1. Introduction

Nephrotic Syndrome is one of the most common forms of renal disease in the paediatric population. Nephrotic syndrome is defined as a pentad of proteinuria (nephrotic range), hypoalbuminemia (serum albumin < 2.5gm/dl), edema , hyperlipidemia (serum cholesterol > 200mg/dl) and increased lipiduria. Although not commonly thought of as part of the syndrome, hypertension, hematuria, and azotemia may be present.

The incidence of nephrotic syndrome varies with geography . In western countries the incidence of nephrotic syndrome reported to be 2-3 / 100000 children while its incidence in South Asia is slightly higher i.e 2-7/100000 children and its prevalence is 12-16 per lakh children .However , the incidence in the Indian Sub-Continent is estimated at 9 to 10 /100000 children.[1]

Nephrotic Syndrome is a clinical manifestation of different histopathologic subtypes, hence several glomerular diseases may have the same type of syndromic presentation .Eg : MCNS, FSGS, MN– all present as nephrotic syndrome. Also one particular type of glomerular disease may have multiple syndromic presentations Eg: IgA nephropathy may present as a case of AUA, recurrent macroscopic hematuria or even RPGN at times.

Nephrotic Syndrome is usually due to a glomerular disease and is currently categorized into primary and secondary forms. Hence a renal biopsy is absolutely essential for the correct characterization of the various types of glomerular diseases. The ISKDC report, demonstrated that response to corticosteroid was highly predictive of renal histology in paediatric cases of nephrotic syndrome. Hence thereafter renal biopsy has been largely limited to children with glomerular diseases, other than the steroid sensitive NS.

Certain diseases like Idiopathic nephrotic syndrome, post infectious GN can be strongly suspected on basis of their clinical and serological findings, also they are known to have a benign course. Hence they are not biopsied.

Among the group of children who are biopsied, MCNS is the most common histological finding , followed by FSGS , MesGN, MPGN etc but over the years there has been a change in the spectrum of glomerular diseases Nephrotic Syndrome diagnosed on biopsy , with FSGS showing a gradually increasing trend especially among the older children and remarkably in the steroid resistant group of NS. Also its prevalance varies in different populations and ethnic groups. The pattern of glomerular disease also varies geographically.

There are also differences in the types and patterns of glomerular diseases that may present to a primary care centre from the ones that present to a tertiary care centre, as it is naturally expected that more difficult cases will be referred to higher tertiary care centers. Hence national renal biopsy registers are very important to understand the pattern of glomerular diseases in the respective countries. Not all countries have biopsy registries. In their absence, demographic studies of glomerular diseases help in adding valuable information to the pool of existing knowledge. Our study has also been designed to fulfill similar aims, attempting to understand the spectrum of glomerular diseases in Nephrotic Syndrome in children of this region.

Aims and objectives

1) To study the clinical profile of childhood onset Nephrotic syndrome presenting to our institute.
2) To evaluate the biochemical and other laboratory abnormalities in childhood onset nephrotic syndrome.
3) To study the histopathological spectrum in childhood onset Nephrotic syndrome presenting to our institute.
4) To study the short term outcomes of these children.

2. Materials and Methods

This study has been conducted in the Department of Nephrology, Andhra Medical College/King George Hospital in Visakhapatnam, Andhra Pradesh. This study is a single center, prospective, observational study conducted between April 2018 to November 2019.

The study included all children, birth to 16 years of age presenting with clinical or laboratory features suggestive of Nephrotic Syndrome and whose duration of onset of illness was less 48 children who presented with nephrotic syndrome than 1 year.

The study excluded patients with diabetic nephropathy, those who did not require biopsy. Patients with other causes of volume overload like cardiac and hepatic causes, renal causes other than nephrotic syndrome, malnutrition, etc and those children whose parents were not willing to give consent for the study.

The demographic characteristics of these children were studied. This included their age distribution, sex ratios, place of residence (urban or rural), their economic status, education standards, including that of their parents.

This cohort of children were studied with the aim of understanding their clinical presentation, particularly in relation to any aggravating or inciting factors, their responses to steroid therapy, risk factors for relapses, indications for biopsy and their short term outcomes. For this a detailed history of the first episode of nephrotic state was recorded, the blood pressures, height, body mass index (BMI) and other relevant clinical parameters of these children were recorded as well. Laboratory tests – complete blood counts (CBC), serum creatinine, total protein with fractions, serum lipid profile, urine analysis, urine protein creatinine ratio (UPCR), serological tests (as and when relevant) were performed. The children in the age group of 2 to 15 years were treated with 4 - 6 weeks of daily prednisolone at the dose of 60mg/m^2, followed by 4 - 6 weeks of alternate daily prednisolone at the dose of 40mg/m^2, as per the present day standards of practice guided by KGIDO guidelines for glomerulonephritis, 2012, as well as the Indian academy of pediatrics (IAP) guidelines. Some children were already receiving prednisolone therapy at the time of presentation to us, their prescriptions were reviewed and dose corrections were done wherever it seemed needful. They were followed up for a period of 6 months . When relapses occurred, they were recorded, treated and risk factors for the relapses were studied. Towards the end of our study period we could classify these children into subgroups based on their responsiveness to steroid, such as – steroid sensitive nephrotic syndrome (SSNS), steroid sensitive nephrotic syndrome with frequent relapse (SSNS-FR), steroid sensitive nephrotic syndrome with infrequent relapse (SSNS-IFR), steroid dependent nephrotic syndrome (SDNS), steroid resistant nephrotic syndrome (SRNS), late non-responders to steroid (LNR).

Renal Biopsy was not routinely done for all children with Nephrotic syndrome. It was indicated in the following situations:

- SRNS
- Late non-responsiveness to steroid in a case of INS
- In a case of INS when clinical and laboratory features strongly suggested pathology other than MCD. Eg: Hypertension, low C3, active urinary sediment.

Statistical analysis

Data analysis was carried out with percentage, mean, standard deviations etc. Unpaired t-test was used to find the significance between the means of two groups. For non-parametric data, Chi-square test, Fishers exact was applied to test an association between two variables. Analysis was done using SPSS version 17.0 software and a p value of less than 0.05 was considered significant.

3. Observations and Results

Out of 48 patients, 30(62.5%) were male patients and 18(37.5%) female patients male patients outnumbered female patients.

Incidence of the various syndromic presentations varies in different age groups. The mean age of presentation of nephrotic syndrome was 6.95±3.71 years, Nephrotic children present at much younger age than Nephritic or RPGN. Most patients with nephrotic syndrome were in the age group of 1 – 6 years. Majority of patients came from rural areas (66.6%) and belonged to low socio economic and middle class.

We had 48 cases of Nephrotic syndrome, 4 cases were biopsied at presentation due to indications as listed in table 1. Out of the 4 children, 2 had APIGN, 1 had LN, 1 had IgA nephropathy. One of the cases of APIGN, LN and IgA nephropathy cases were given antihypertensives. Only LN case received Steroid + Cyclophosphamide

The other 44 children were considered as cases of idiopathic nephrotic syndrome treated with steroids. They were eventually followed up, their response to steroid was assessed and then subgrouped into SSNS-NR (steroid sensitive nephrotic syndrome – no relapse till the duration of observation), SSNS-IFR, SSNS-FR, SDNS, SRNS and L NR (late non responder). (As represented in the flow chart-1)

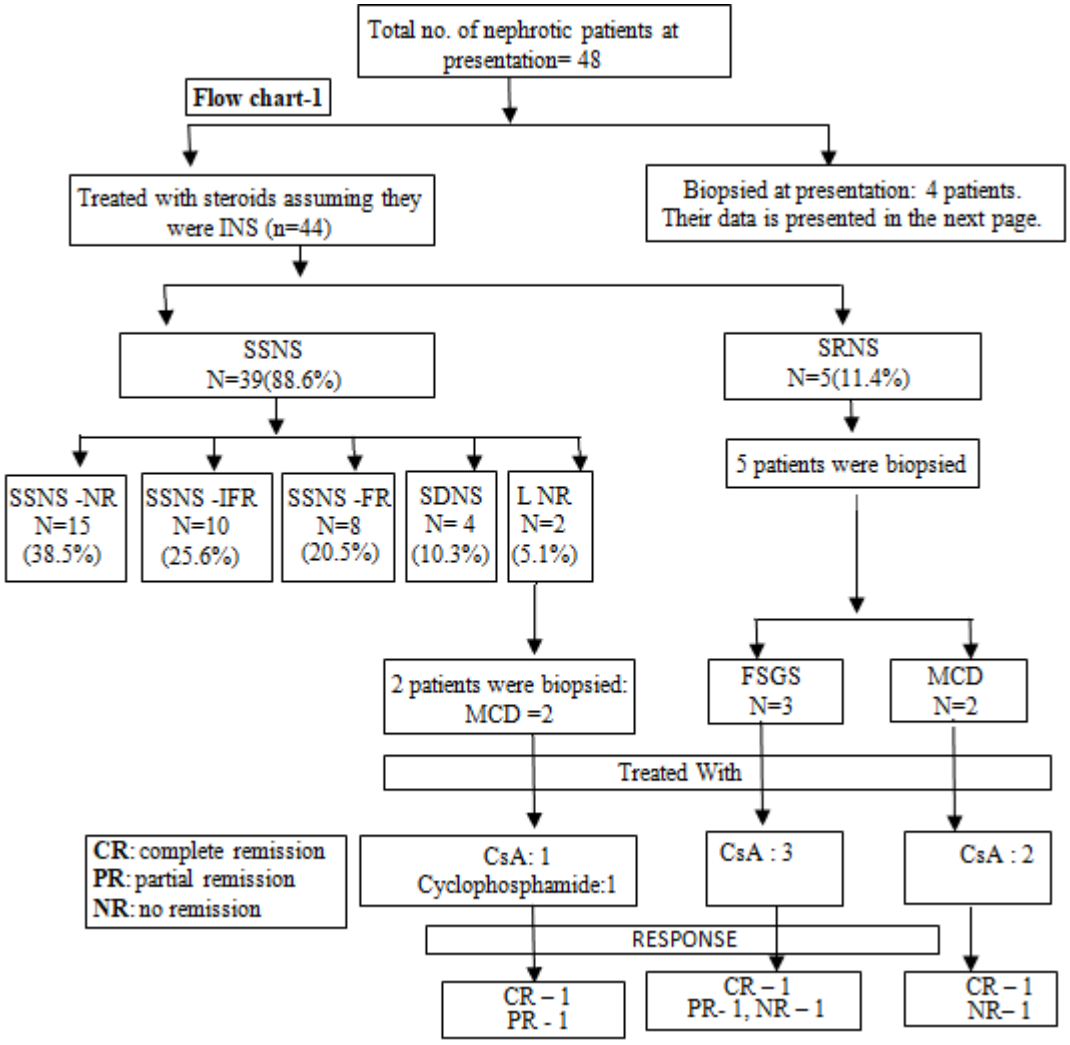

Table 1: Indications and Biopsy findings, treatment and response in cases of Atypical Nephrotic syndrome (n=4)

Indications	Findings	Treatment	Response
HTN +Low C3 + Microscopic hematuria (n=2)	APIGN (n=2)	Supportive = 1 Steroid = 1	Described in later tables
HTN + Low C3, Low C4, ANA positive Microscopic haematuria (n=1)	LN Class-IV+V (n=1)	Supportive	
HTN + Microscopic haematuria (n=1)	IgA nephropathy (n=1)	Supportive	

Amongst these 44 children, 7 children had indications for a renal biopsy. 5 were steroid resistant (SRNS) and 2 were Late steroid non-responders (L NR). Thus, finally among the 44 children, 7 children were biopsied.

In the 5 children with SRNS who were biopsied, the most common histopathologic findings were FSGS and MCD. The 2 cases of late non-responders had MCD on biopsy.

The flow chart also shows what treatment was received by the children who were biopsied and their current status of response to treatment at their last follow up.

Excluding the 4 atypical cases of nephrotic syndrome at presentation (table 1) , the remaining 44 cases have been sub-grouped on the basis of steroid responsiveness as shown in fig-1.

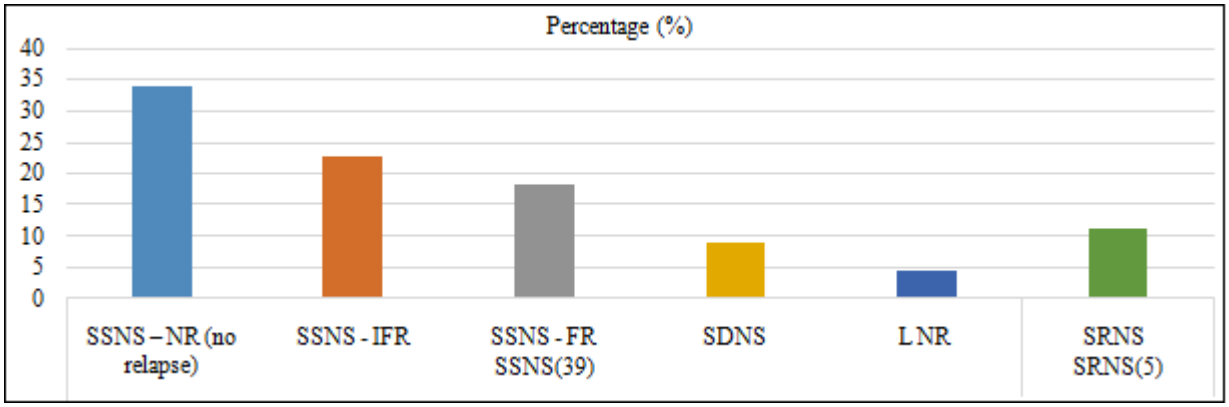

Figure 1: Proportion of different subsets of Nephrotic syndrome

The duration of follow up of the nephrotic children was 6 months. During this follow up period it was observed that 34 % of patients did not have any relapse. They have been named as SSNS-NR (no relapse) in this study. 22.7% of the cases were infrequent relapsers, 18.1% were frequent relapsers, 9% cases were steroid dependent, 4.5% cases developed late steroid non responsiveness and 11.3% cases were steroid resistant.

In this study there was no significant difference between the ages of onset of symptoms in children with SSNS and SRNS. In both groups slight male preponderance was seen. Mean arterial blood pressures were higher in the SRNS group as compared to the SSNS group which is statistically significant. Serum creatinine, serum total protein and serum albumin at presentation were not significantly different in either groups. Greater proportion of children with SRNS had microscopic hematuria, 2 out of 5 cases, while none of the cases of SSNS had microscopic hematuria, the p value was <0.05 in this case. (Table-2)

Table 2: Table showing demographic, clinical and biochemical characteristics of the two major subsets of nephrotic syndrome

	SSNS (N= 39)	*SRNS (N= 5)*	*p- value*
Age of onset <=5 6-10 >10	 15 16 8	 2 1 2	>0.05 (N.S)
Mean age of onset	6.72±3.29	8.80±6.34	>0.05 (N.S)
Sex ratio (M:F)	2:1	4:1	
Blood pressure (MAP)	70.92±5.90	85.60±11.06	<0.05 (Sig)
Serum Creatinine (mg/dl)	0.68±0.34	0.43±0.47	0.55 (N.S)
Serum Total Protein (g/dl)	4.80 ± 0.49	4.3 ± 0.52	0.06 (N.S)
Serum albumin (g/dl)	2.12± 0.46	1.74 ± 0.39	0.086 (N.S)
Serum Cholesterol (mg/dl)	442.92±47.06	409.40±27.29	> 0.05 (N.S)
Serum Triglycerides(mg/dl)	347.64±38.98	360.40±44.29	0.501 (N.S)
Microscopic hematuria : Yes No	 0 39	 2 3	 <0.05 (Sig)
UPCR	7.49 ± 1.60	8± 2.55	0.533 (N.S)
Family H/O renal disease: Yes No	 0 31	 0 5	

N.S = Not Significant
Sig = Significant

Relapses are associated with infectious or allergic triggers, however some may occur without any identifiable triggers. We found that URTI was the commonest trigger, it was associated with 50.0% of relapses. AGE and UTI was associated with 23.5% and 2.9% of relapses respectively. 23.5% of relapses were not associated with any identifiable triggers. Further it was observed that late non responders had more of non identifiable triggers. (Fig-2)

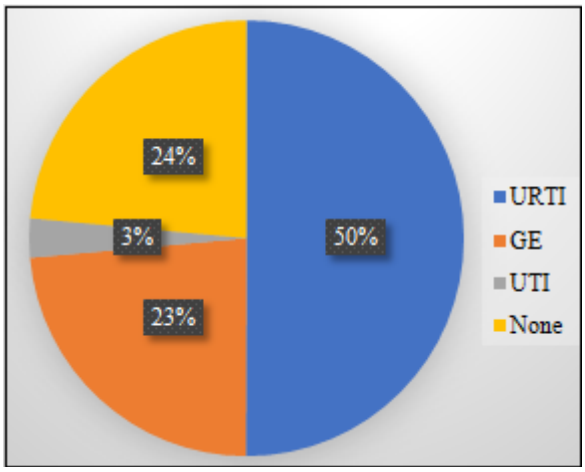

Figure 2: Infection related relapse

Table 3: Table showing treatment of nephrotic syndrome

	1st line Treatment (steroid)	2nd line treatment		
		Cyclophosphamide (N=2)	Levamisole (N=4)	CsA (N=6)
SSNS - NR	15	0	0	0
SSNS - IFR	10	0	0	0
SSNS - FR	8	0	3	0
SDNS	4	2	1	0
L NR	2	0	0	1
SRNS	5	0	0	5

It was observed that for some frequent relapsers there was use of second line agents, 3 out of 8 SSNS-FR were treated with levamisole as second line agent. Out of 4 SDNS children, 2 received cyclophosphamide and 1 received levamisole as second line agents and the remaining 1 child was still being given gradually tapering doses of steroid. One case of late steroid non responders was given CNI. In steroid resistant cases the preferred choice of second line agents is Cyclosporine, which was prescribed in 5 out of 5 cases.(Table-3)

Complications are common in nephrotic syndrome, AKI and SBP are common complications. In our study of nephrotic syndrome 3 patients (6.8%) had AKI, their mean creatinine

was 1.6 mg/dl. One patient was steroid sensitive with persistent response, who had AKI on presentation, one was IFR, one was FR. The proportion of patients with AKI having serum albumin less than or equal to 2 mg/dl was 83.3%. None of them had microscopic hematuria. All of them recovered uneventfully.

SBP was encountered in 4 (9%) patients with nephrotic syndrome. 2 patients had SRNS, one each were IFR and FR. The proportion of patients with SBP having serum albumin less than or equal to 2 mg/dl was 75%. One patient (25%) had microscopic hematuria. All of them recovered uneventfully. Pneumonitis was a serious infective complication. Two patients had pneumonitis. Besides these 3 complications, No patient had IVC thrombosis, 1 patient had varicella zoster. 3 were Recovered in AKI group, 4 Recovered in SBP group and 2 from pneumonitis group.

Renal biopsy

Out of 48 patients with nephrotic syndrome, 11 were biopsied. All the biopsies were processed for light microscopy and IF, all biopsy samples were adequate, the histopathological findings of these adequate biopsy samples are shown in table 4:

Table 4: Different glomerular pathologies in Nephrotic Syndrome

Pathology	Number	Percentage (%)
Minimal change disease (MCD)	4	36.3%
Focal sclerosing glomerulosclerosis (FSGS)	3	27.2%
APSGN/ APIGN	2	18.1%
Lupus nephritis (LN)	1	9.0%
IgA Nephropathy	1	9.0%
Total	11	100%

Minimal change disease was the commonest diagnosis on renal biopsy, found in 4 (36.3%) patients, followed by FSGS 3 (27.3%) and APSGN/ APIGN 2 (18.1%), LN 1 (9.0%). IgA Nephropathy in 1 case (9.0%). (Table-5)

Table 5: Spectrum of glomerular diseases and their clinical presentation in Nephrotic Syndrome

Glomerular disease	N	Nephrotic range proteinuria	Non nephrotic range proteinuria	Hematuria	HTN
Minimal change disease (MCD)	4	4	0	0	0
Focal sclerosing glomerulosclerosis (FSGS)	3	3	0	0	0
APSGN/ APIGN	2	2	0	2	2
Lupus nephritis (LN)	1	1	0	1	1
IgA Nephropathy	1	1	0	1	1
TOTAL	11	11	0	4	4

Table 6: Table showing clinical and biochemical improvements on follow up visits in the 4 atypical cases of nephrotic syndrome

Clinico-biochemical parameters	At presentation	At 1 month	At 3 months	At 6 months
Hypertension	3	2	2	1
Elevated Serum Creatinine	1	1	0	0
Proteinuria	4	4	1	0
Microscopic hematuria	3	3	1	1
Low complement level	3	2	1	0
Available for follow ups	4	4	4	4

The median duration of follow up of these 4 cases of nephrotic syndrome was 6 months. There was 100% follow up of patients. At 6 months of follow up, it was observed that renal functions recovered in all the 4 patients. 1 patient remained hypertensive requiring low dose of a single anti-hypertensive agent, 1 patient had proteinuria and 3 patients had microscopic hematuria, all 3 resolved at ≥ 6 months follow-up, Complement levels normalized in almost all patients by 3 month. Their outcome at the last follow up is shown in table-6

4. Discussion

In the present study the Gender ratio of M:F is 1.6:1, hence nephrotic syndrome is more common in males than females .Male preponderance with sex ratio of 1.28 to 2:1 was also found in other studies done in Tunisie, Nigeria, Saudi Arabia .[2,3,4] The present study also reveals similar gender ratio.

In the present study the most common age of presentation of Nephrotic syndrome is 1 to 6 years and mean age of presentation is 6.95±3.71 years. Most of the patients of this age group was observed in other studies as well. In a study done by Kumar et al [5] the mean of presentation was 7.9 ± 5.1 years is marginally higher than the present study whereas in another study Kari JA it was found to be lower than present study .[5]

In the present study, hematuria was observed in 6.25 % (3) of the patients. Hypertension was observed in 6.25 % (3) of the patients whereas in a study conducted by Basnet S et al the percentage of hematuria and Hypertension was 21.2% and 50 % respectively .[6] In a study done in Chowdhary EUA et al 0.5 % of patients had hypertension .[7]

Clinical response to therapy (Steroid Sensitive and Steroid Resistant)

In the present study SSNS is seen among 88.6 %, SRNS is 11.4 % and SDNS is 10.3 % whereas in study conducted by A. Safaeietal observed 66% were steroid sensitive and 20.5% steroid resistant, and 13.5% were SDNS.[8] Similar finding was reported by Aditi Sinha et al[9] in their retrospective study of 15 years duration where they found that early steroid resistance in 12.5% of cases. Amongst SSNS, in our study we found persistent response/ no relapses (NR) in 38.5% cases, IFR in 25.6 %, FR in 20.5 %, SDNS in 10.3% and L NR in 5.1% cases. Similar rates were reported by the same authors for IFR, FR, L NR cases, but in

our study the proportion of patients with SSNS-NR was much higher and that of SDNS was much lower. This difference is perhaps due to the much longer follow up period of their study as compared to ours. Findings from our study confirm that an early age at onset of nephrotic syndrome is associated with risk of frequent relapses**.** Mean age of onset of SSNS-IFR cases was 6.7 (+/- 3.5) years, while that of SSNS-FR cases was 5.37 (+/- 1.9) years, which was similar to other studies.[9] Also, early response to steroid treatment predicted lesser relapses in our study that was similar to the findings of Kasim Rahi et al.[10] URTI was seen to be the commonest trigger for relapses in our study. Gulati S et al,[11]Moorani KN et al [12] and Mc Donald et al [13] also found that Respiratory tract infections are the commonest trigger for relapses. In some other studies [14]urinary tract infections (UTI) were found to be more common associations with relapses, which in our case was only 2.9% compared to RTI which comprised 50 % of triggers. Patients with SRNS had higher mean arterial pressures than those with SSNS which is significant , also proportion of patients with microscopic hematuria was greater in the SRNS group than in the SSNS groupwhich was also significant . Patients bearing such features at presentation may be suspected to have steroid resistance.

Complications of Nephrotic Syndrome

In a study conducted by Nimisha K. Pandya et al [15], serious complications were observed in 40% of patients. Infections were seen in 27 % patients, commonest infection being UTI, 13.5% followed by pneumonia, tuberculosis and peritonitis. A study by Basnet S[6] found that infection observed in 32.5% patients among them pneumonia was the most common complication attributing to 18.8 %. UTI was the second commonest infection in the subjects 8.8% (7). Peritonitis was present in (3.8%) whereas in our study peritonitis was seen in 9 % of patients , 2 patients had pneumonitis .

Histopathology

The underlying histopathologic characteristics in nephrotic syndrome are of immense significance in determining steroid responsiveness and long-term prognosis.Out of the 48 patients we had in our study group, 11 patients underwent renal biopsy, based on established criteria for renal biopsy in pediatric population. Minimal change disease was the commonest diagnosis on renal biopsy, found in 4 (36.36%) patients, followed by FSGS in 3 (27.27 %), APSGN/ APIGN in 2 (18.18%) cases, LN was found in 1 case (9%), IgA was observed in one case. Similar findings were found in studies from North India by Irneet Mundi et al [16] and Sanjeev Gulati et al,[14] and from East India by V Golay et al [17] and Pawan Pradeep Mutalik et al [18]and also from South India by Das U et al.[19] In all of these studies MCD closely followed by FSGS was the commonest histopathological finding, similar to our study,whereas in a Study conducted by A. Safaeietal of the biopsied children, FSGS was the most common histopathological subtype (41%).[20] In the study by Madani et al, minimal change disease was the most common histopathological subtype (34.4%). Study conducted by Mubarak etal[21] observed that minimal change disease (MCD) and its variants contribute to 43.8%; focal segmental glomerulosclerosis (FSGS), 38.14%; membranous glomerulonephritis (MGN), 7.96%; mesangioproliferative GN (MesPGN), 4.81%; mesangiocapillary GN (MPGN), 3.14%; IgA nephropathy (IgAN), 1.11%.

In a study conducted by Agnieszka Bierzynska et al [22] most patients had FSGS (54.1%; >98 of 181) or minimal change disease (MCD) (23.8%; >43 of 181) on Histopathological examination .They have concluded by saying deep phenotyping combined with whole exome sequencing is an effective tool for early identification of SRNS etiology, yielding an evidence-based algorithm for clinical management.

Earlier, the international study of kidney diseases in children (ISKDC) have also shown that MCD is the most common type of NS in children.[23] However in this study all children with nephrotic syndrome were biopsied and hence MCD had greatly outnumbered FSGS, 74.6% vs 18.8%. After MCD and FSGS, post-infectious GN was the second most common glomerular pathology found in our biopsies, in 18.18 % of biopsy samples. This is in contrast to reports from developed countries[24]where the incidences are lower. Also in India, V Golay et al[17] reported an incidence of 6.45%, AK Garg et al [25] reported 2.8%, U Das et al [19] reported 8.1% and Pawan Pradeep Mutalik et al [18] reported 5.71%. These reports show lower incidences than our study, this may be due to differences in case selections for biopsies.

In the present study FSGS (60%)was more common among SRNS group than others . In a study conducted by Asim Sadaf [26] among SRNS patients, FSGS was 38% and among SDNS patients MCD is common. Present findings were supported by Bakr A and Piotto GH et al.[27]

5. Summary and Conclusions

This study Clinical Profile and Histopathological Spectrum of Nephrotic Syndrome in children was carried out at Andhra Medical College/King George Hospital in Visakhapatnam was a prospective and observation study carried out on children upto 16 years of age with Nephrotic Syndrome.

The following conclusions were drawn from the study:

1) Nephrotic syndrome is the commonest presentation of glomerular disease in children. A large majority of cases are idiopathic nephrotic syndrome.
2) Time to respond to steroids is a strong predictor of chances of relapse in INS. Lesser the time required to achieve remission with adequate doses of steroids, lesser are the chances of relapse.
3) Presence of microscopic hematuria and hypertension point towards possibility of steroid resistance.
4) Minimal change disease was found to be the most common Histopathological finding among the Nephrotic children who were biopsied.
5) In children with steroid resistance, FSGS is the commonest histopathological finding.
6) There are also Atypical/unusual presentations of nephrotic syndrome.

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