Original Article

DOI: 10.7860/IJNMR/2019/42502.2256

Paediatrics Section

Clinical Spectrum of Nephrotic Syndrome and Correlation with Histopathology and Immunofluorescence Findings

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ABSTRACT

Introduction: Nephrotic syndrome is characterised by altered permselectivity of the glomerular filtration barrier which is a common chronic renal disorder in children. In children, it is characterised by oedema, hypoalbuminemia and proteinuria.

Aim: To study the clinical profile of nephrotic syndrome in patients and also to study histopathological and immunofluorescence findings and correlation with clinical response to treatment.

Materials and Methods: A prospective clinical study was undertaken to study the 'Clinical Spectrum of Nephrotic Syndrome with special reference to Histopathology and Immunofluorescence. Children with nephrotic syndrome upto the age group of 18 years admitted in the Nephrology ward over a period of one year from January 2008 to December 2008 were included. All patients who met the criteria for nephrotic syndrome (proteinuria >40 mg/m^2/hr serum albumin <2.5 gm/dL, serum cholesterol >200 mg/dL) were eligible for the study. The results were analysed based on the clinical profile histopathology and immunoflorescence findings of the cases.

Results: A total of 72 cases with Nephrotic syndrome were included in this study, gross haematuria was noticed in 9 cases (12.5%), hypertension was noticed in 21 cases (29.2% of children).Upper Respiratory Tract Infection (URTI) was seen in 34 cases (77.27%), Urinary Tract Infection (UTI) seen in 03 cases (06.81%), viral fever was seen in 9 cases (12.5%), peritonitis seen in 3 cases (4.2%) and it was seen as the precipitating causes for relapse. Hypertension was seen in 46 cases (63.6%) of steroid resistant group and 24 hour urine protein excretion was more in steroid resistant group. Renal biopsy was done in 29 out of 72 children (42.7%). Minimal change nephrotic syndrome was seen in 11 cases (37.9%) that underwent biopsy irrespective of the indication. Mesangio-proliferative nephrotic syndrome was the most common type in non minimal change nephrotic syndrome, 13 cases (45%) out of 18 cases of nonminimal change nephrotic syndrome (62%).

Conclusion: Immunofluorescence is very important in diagnosing secondary nephrotic syndrome and plays a very important role where light microscopy alone cannot help in diagnosis such as IgA and IgM nephropathy, and Lupus nephritis.

Keywords: Henoch-Schonlein purpura, Minimal change disease, Proteinuria, Systemic lupus erythematosus

INTRODUCTION

Nephrotic syndrome is characterised by altered permselectivity of the glomerular filtration barrier, is a common chronic renal disorder in children characterised by oedema, hypoalbuminemia and proteinuria which ranges from milligrams to grams [1]. Minimal Change Disease (MCD) is a renal or kidney disease in which protein is lost in the urine in moderate to severe amounts. It is one of the most common causes of nephrotic syndrome worldwide. The most noticeable clinical symptom of MCD is often oedema, or swelling, which can range from mild, moderate or profound. Oedema typically starts in the feet and legs, but can move into the hips and abdomen, and also causes puffiness of the face. Proteinuria develops very rapidly in minimal change nephrotic syndrome when compared to other systemic causes. Other clinical or laboratory findings of nephrotic syndrome include elevated blood pressure, high cholesterol, and altered coagulation profile. Renal biopsy and histopathological examination provides and confirms the nature of the disease as all the types of nephrotic syndrome commonly present with similar clinical features. Renal biopsy tissue is sampled to histology by light microscopy and immunofluorescence provides clear demarcation between MCD where the glomeruli are normal or nearly normal in MCD under microscopy and in Non-MCD glomeruli show significant changes depending upon

the type of the disease [2]. The most definitive diagnosis will be on Immunofluorescence because Nephrotic syndrome is a result of immune reaction and clear understanding of the nature of the disease is important to effectively manage the case and prevention of complications by timely intervention and addition of immuno-suppressive drugs. Recognising the underlying renal histopathology in a nephrotic syndrome has significant implications for response to treatment and for prognosis. Due to the recent advances in the investigating modalities, a change in the trend of idiopathic nephrotic syndrome from MCD to Non-MCD is seen [3]. The objective of this study was to know the clinical profile of nephrotic syndrome patients, histopathological and immunofluorescence findings and correlation with clinical response to treatment.

MATERIALS AND METHODS

This prospective study was conducted in the Paediatric Nephrology unit of Indira Gandhi Institute of Child Health (IGICH), a tertiary care center South Hospital Complex, Dharmaram college post, Bangalore, Karnataka, India. Children with nephrotic syndrome up to the age group of 18 years who were admitted in the Nephrology ward over a period of one year from January 2008 to December 2008 were included in this study. All patients who met the criteria for Nephrotic syndrome (proteinuria > 40 mg/m^2/hr serum albumin <2.5 gm/dL, serum cholesterol >200 mg/dL) were eligible for the study. They were no exclusion criteria. Written and Informed consent from parents or guardians of all the children were taken for the study with the Institute Ethics Committee (IEC) reference No: IGICH/Ped/1501/T2008. The data was entered into the proforma drafted for the study. The details of the patient's demographics and underlying illness were obtained. Data was also collected regarding, age of onset, total duration of nephrotic state, any precipitating factors, previous treatment and complications. All children in the study were subjected to the complete blood picture, blood urea, serum creatinine, serum electrolytes, serum total protein and Albumin, serum cholesterol, serum C3 level, urine-microscopy, albumin, 24 hour urine protein, and protein: creatinine ratio and Mantoux test was done. In some cases, additional investigations like urine culture and sensitivity, peritoneal tap and ascitic fluid analysis, blood culture and sensitivity, ultrasound abdomen and pelvis, prothrombin time and activated partial thromboplastin time were done. Viral screening for Anti-HCV antibody, HbsAg, anti nuclear antibody and dsDNA was done. Renal biopsy was done as per the following clinical criteria.

- Age of onset <1 year.
- Gross Haematuria, or persistent microscopic Haematuria
- Low serum C3.
- Sustained hypertension.
- Renal failure not attributable to hypovolaemia.
- Suspected secondary causes of nephrotic syndrome.
- Steroid resistance.
- Before treatment with cyclosporine A or tacrolimus.

Percutaneous renal biopsy was done using 18 gauge trucut biopsy needles. Under ultrasound guidance and marking of the kidney (left kidney), biopsy was done. Two specimens were obtained, which were transported in formalin and normal saline containing bottles to the Pathology lab. The specimens were fixed in 10% formalin. Paraffin-embedded tissue was sectioned serially at 2-3 micron thickness and stained with Haematoxylin and Eosin (H&E). The specimen in saline was subjected to Immunofluorescence. For the purpose of analysis, adequate clinical information was provided to the Pathologist. A biopsy tissue with minimum of 5 glomeruli per field should be present to call the biopsy specimen adequate [4].

STATISTICAL ANALYSIS

Descriptive statistical analysis has been carried out in the present study by Statistical Product and Service Solutions (SPSS) version 14. Results on continuous measurements were presented on Mean±SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5% level of significance. Chi-square/Fisher-Exact test and Analysis of Variance (ANOVA) had been used to find the significance of study parameters on categorical scale between the groups. Confidence Interval had been computed to find the significant features. Confidence Interval with lower limit more than 50% is associated with statistical significance.

RESULTS

The study group included a total of 72 patients. Male children were 44 (61.1%) and female children were 28 (38.9%); age of onset of the disease as tabulated in [Table/Fig-1]. The maximum number of children who were studied had their first episode of nephrotic syndrome between the ages 12 months to 60 months. The youngest child noted was one-month-old and the oldest was 14 year. The Mean±SD: 49.16±38.41 months, respectively. Among the study group of 72 cases, 33 cases (45.8%) were first episode cases, 20 cases (27.8%) were frequent relapses and 19 cases (26.4%) were infrequent relapses. Among the cases with nephrotic syndrome 93% were primary nephrotic syndrome and the remaining 7% were secondary nephrotic syndrome 3 cases of Henoch Schonlein Purpura, 1 case of SLE, 1 case of congenital rubella syndrome. Oliguria (subjective, as described by the patient's parents of decreased urine output at presentation) was seen in 62 patients (86%), facial puffiness was seen all 72 cases (100%) and pedal oedema was noted in 70 cases (97.2%). Macroscopic haematuria was seen in 9

patients (12.5%). Hypertension was present in 21 (29.2%) of cases as per task force 4 criteria for hypertension. Rashes in the form of Purpura were seen in 4 children (5.6%).

Age of onset	Number	Percentage
<1 year	2	2.8
1.1-5 years	52	72.2
5.1-8 years	9	12.5
>8 years	9	12.5
Total	72	100

[Table/Fig-1]: Age of onset of cases.

In this study, various co-morbid associations were seen and are tabulated in [Table/Fig-2]. Eight (10.9%) of cases had urea >40 mg/dL which was transient and only one patient had persistent high urea. A 1.4% of cases had high creatinine. This accounts for 1.4% of renal failure cases in the study group. Hypercholesterolemia was noted in 69 cases (96%). A total of 49 cases (68.05%) were steroid responsive, 12 cases (16.66%) were steroid dependent and 11 cases (15.27%) were steroid resistant.

Complaints	Number (n=44)	Percentage
Upper Respiratory Tract Infection (URTI)	34	77.27
Urinary Tract Infection (UTI)	3	06.81
Peritonitis	3	06.81
Tuberculosis	2	4.55
Pneumonia	1	2.28
Cellulitis	1	2.28

[Table/Fig-2]: Associated co-morbidities.

In this study, among 72 cases only 29 cases had indications for biopsy and among the 29 biopsy cases, 11 cases (37.9%) were minimal change nephrotic syndrome and in the remaining 18 cases (62.1%) it was non-minimal change nephrotic syndrome and other histopathological examination findings are tabulated in [Table/Fig-3].

Histopathological findings	Number of cases	Percentage
Minimal change NS (MCNS)	11	37.9
Non-minimal Change NS (Non MCNS)	18	62.0
Mesangioproliferative GN (MES P GN)	13	44.9
Focal segmental glomerular sclerosis (FSGS)	2	6.9
Diffuse proliferative GN (DIFF PRO GN)	1	3.4
Membranous GN (MEM GN)	1	3.4
Membrano-proliferative GN (MEM P GN)	1	3.4

[Table/Fig-3]: Histopathological findings.

The immunofluorescence studies showed that, C3, IgA, IgM and IgG were absent in 100% of minimal change nephrotic syndrome and positive in 38.9% of non-minimal change nephrotic syndrome. Immunofluorescence was positive in 4 out of 13 cases of mesangioproliferative glomerulonephritis and they were positive for IgA in 3 cases and all three were Henoch Schonlein Purpura. Immunofluorescence in FSGS was positive for one case and it showed IgM deposits in the other case tissue were insufficient. In a child with SLE light microscopy showed diffuse proliferative glomerulonephritis and IF showed evidence of full house (stain positive for all IgA, IgM, IgG, C3) which is characteristic of SLE. In a child with membranoproliferative glomerulonephritis IF showed coarse granular deposits for IgG(3+) and C3(1+) [Table/Fig-4-10]. Haematuria was positively associated with non-MCNS group and was statistically significant with p-value of 0.001. There was a significant statistical association between hypertension and non MCNS group with p-value of 0.001. Among the 18 case with positive urine RBC 12 of them belonged to non-MCNS group and this was statistically significant with p-value of 0.001. No statistically significant association was noticed between the 24 hour urine protein and histopathology. When the other blood parameters like urea, creatinine, serum albumin, cholesterol was compared between MCNS and non-MCNS group no statistically significant association was noticed, except for urea. A 63% of the case with urea >40 mg/dL will belong to non MCNS group and this is statistically significant with p-value of 0.011.

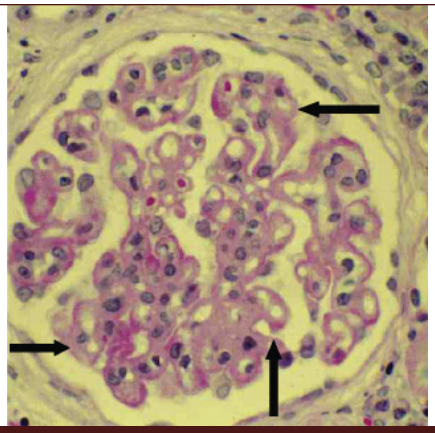
DISCUSSION

Richard Bright first demonstrated the correlation of oedema and proteinuria were due to the changes in the kidney in the year 1827, and later the disorder was named as “Bright’s disease” [5]. The term ‘lipoid nephrosis’ was coined by Munk in 1913 to describe a group of patients with oedema, heavy proteinuria, hypoproteinemia, and hyperlipidemia, in whom microscopic examination of the kidney showed normal Glomeruli but lipid droplets in the cells of the proximal tubule. Finally in 1929, Henry Christian included the phrase “Nephrotic syndrome” in his writings [5]. Nephrotic syndrome requires the presence of oedema, hypoalbuminemia less than 2.5 g/dL, and proteinuria greater than 40 mg/m^2/h (or a protein/creatinine ratio of greater than 200 mg/m.mol or 2.0 mg/dL) with hyperlipidemia (cholesterol of >200 mg/dL) with or without oedema [6,7].

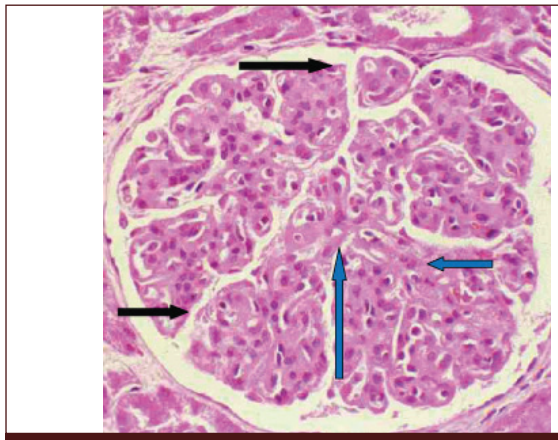
The major basic histological and functional defect in nephrotic syndrome is an increased threshold of the glomerular basement membrane to macro-molecules that are ordinarily not filtered by kidneys. The recent discovery of genetic abnormalities, particularly mutation of genes that encode for several slit diaphragm proteins, has aided researchers in understanding the molecular mechanisms involved in the development of the nephrotic syndrome. Theoretically, albuminuria of nephrosis

Histopathological findings	Number of cases	Immunoflourescence		Positive				
		Negative	Positive	C3	IgA	IgM	IgG	No tissue
MCNS	11	11 (100.0%)	0	-	-	-	-	-
Non MCNS	18	11 (61.1%)	7 (38.9%)	1	2	1	2	1
MES P GN	13	9 (69.3%)	4 30.7%)	1	3	-	-	-
FSGS	2	1 (50%)	1 (50.0%)	-	-	1	-	1
DIF PRO GN	1	0	1 (100.0%)	1	1	1	1	-
MEM GN	1	1(100.0%)	0	-	-	-	-	-
MEM P GN	1	0	1 (100.0%)	1	-	-	1	-

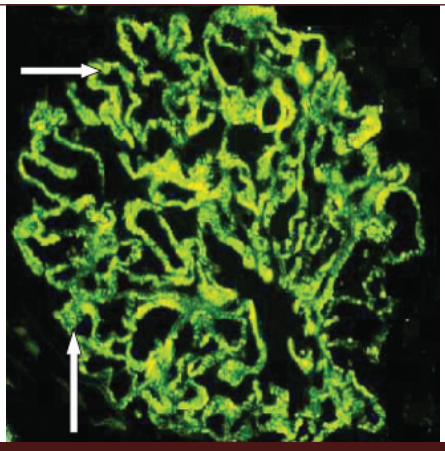
[Table/Fig-4]: Histopathological findings and immunofluorescence.



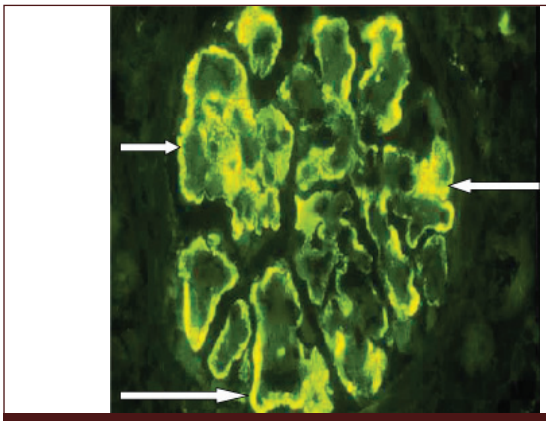
[Table/Fig-5]: Light microscopy (H&E stain-40X view) - membranous glomerulopathy shows marked thickening of the glomerular basement membrane (black arrows).



[Table/Fig-7]: Light microscopy (H&E Stain-40X view) of membranoproliferative glomerulonephritis type -1 showing global and diffuse thickening of capillary walls (black arrows) and hypercellularity due to mesangial proliferation (blue arrows).



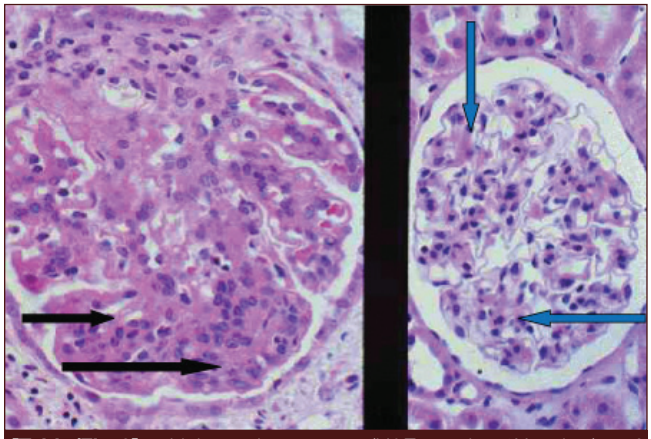
[Table/Fig-6]: (IF stain-40X view)-immunofluorescence in membranous glomerulopathy showing diffuse global granular staining of capillary walls (white arrows).



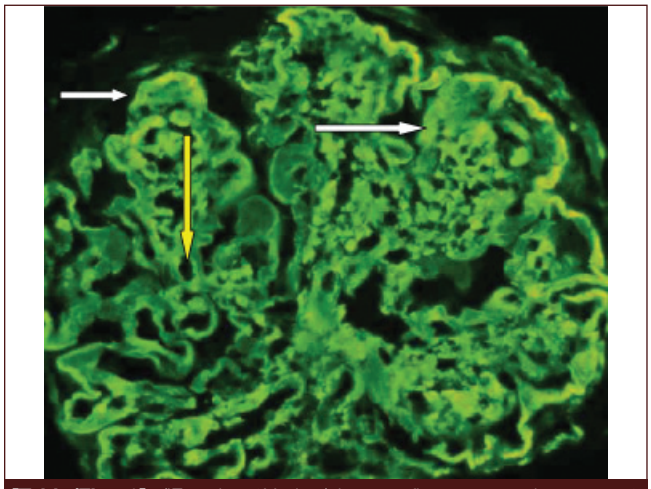
[Table/Fig-8]: (IF stain-40X view)-immunofluorescence- in mpgn -1 showing peripheral granular or band-like staining that outlines the hypersegmentation (white arrows).

might be due to loss of the glomerular polyanion, less anionic serum albumin, or both. In any of these situations the electrochemical disturbance could be due to a circulating factor. Additionally, vascular permeability factor may induce increased permeability of the Glomerular Basement Membrane (GBM) [8]. International Study of Kidney Disease in Children (ISKDC) reported that the majority of children with nephrotic syndrome had MCD and almost all these children demonstrated response to corticosteroids with disappearance of proteinuria and for sometime steroid responsiveness was being taken as the hallmark of benign disease [9]. Further studies have shown that not all nephrotic syndromes in children are MCD. It is difficult to clinically differentiate MCD from non-MCD [10]. In India, Srivastava RN et al., have found a male to female ratio of 3:1

[11]. This study showed a male to female ratio of 3:2, whereas the ISKDC report shows a ratio of 2:1 [9].



[Table/Fig-9]: Light microscopy (H&E stain-40X view) of membranoproliferative glomerulonephritis type 2 showing hypercellularity and thickening of capillary walls (black arrows) as compared to normal glomerus (blue arrows).



[Table/Fig-10]: (IF stain-40X view)-immunofluorescence in mpgn- 2 showing linear and bilinear capillary wall staining (white arrows), and also showing spherical or ring-shaped mesangial deposits (yellow arrow).

Infections	Present study	Gulati S et al., [21]	Ahmadzadeh Ali et al., [16]
Urinary tract infection	16.7%	13.7%	10.5%
Upper respiratory tract infection	45.8%	5.2%	65.9%
Lower respiratory tract infection	1.4%	3.9%	
Peritonitis	4.2%	9.4%	16.5%
Tuberculosis	2.8%	10.4%	-
Skin infection	1.4%	5.2%	7.3%
Pyogenic meningitis	-	0.6%	-
Thrush	-	-	7.3%

[Table/Fig-11]: Comparison of associated co-morbidities with other studies.

Corticosteroids have been the mainstay of therapy for nephrotic syndrome for nearly 50 years. The medication is administered after meals to reduce its gastrointestinal side effects. It is necessary to treat infections before starting treatment with prednisolone. Deflazocort, a steroid analogue, is as effective as prednisolone and has fewer corticosteroid side effects but has not been widely employed [12]. Various studies suggested that extension of initial steroid treatment for 12 weeks or longer significantly reduce the risk for subsequent relapses but this regimen is associated with higher frequency of adverse events [7,13].

This study had a youngest of one-month-old and oldest 168 months (14 years) old. Most of our patients had an age of onset ranging to 12 to 60 months (66%). Age of initial presentation has an important impact on the type of histopathological distribution and response to steroid [14].

Among the cases 33 patients (45.8%) presented to us at the first episode. In the remaining 39, 19 children were infrequently relapsing (26.4%) and 20 (27.8%) were frequently relapsing. This correlates with the study published by Iyengar A et al., study explains that most children with Idiopathic Nephrotic Syndrome (INS) show good response to corticosteroid therapy, 40-90% have subsequent relapses. About a quarter of patients with INS can have a single relapse and 33.33% relapse occasionally and 50% of them become steroid dependent over the years of continuous therapy [15]. This is also similar to the study done by Ali A et al., among 201 steroid responders, 70 (34.8%) were frequent relapses, 78 (38.8%) were non-relapses, and 53 (26.4%) infrequent relapses [16]. Among the 72 children, 61 (68.1%) were steroid responsive which included 12 steroid dependent children (16.6%) and the remaining 11 (15.27%) were steroid resistant. In this study, 84.6% of children had steroid sensitive nephrotic syndrome, which was more than the data from Churg J et al., (77%), and Ozkaya N et al., (76%) [17,18]. The incidence of steroid resistance in this study was 15.2%. Bagga A et al., have reported incidence of SRNS to be 20% in his study [19].

Facial puffiness and pedal oedema were present in all patients. Oliguria was seen in 62 patients (86%). Macroscopic haematuria was seen in 9 patients (12.5%). Macroscopic haematuria in the presentation of nephrotic syndrome should be suspected in cases associated with UTI, acute PSGN, renal vein thrombosis, MPGN, SLE and congenital renal diseases.

In our study, hypertension was present in 29.2% of cases. The ISKDC had documented that at the first presentation high blood pressure was noted in approximately 21% of patients [7]. Strauss J et al., described that 20.7% and 13.5% of MCNS patients have systolic and diastolic BP that were in the 98 percentile for age prior to the initiation of corticosteroid therapy

[20]. Hypertension was present in 23.5% of the children as reported by Nammalwar BR et al., [10].

Four children presented with rashes and joint pains as the presenting symptom and three of them were cases of Henoch Schonlein Purpura and the other child was a case of SLE, one child presented with congenital rubella syndrome, accounting for 6.9% of cases of secondary nephrotic syndrome. Urine analysis of the study population showed significant microscopic haematuria in 18 patients which constitutes 25% of the study group. Strauss J et al., have reported that 25% of children had microscopic haematuria at the onset [20] and 10.9% of cases had urea >40 mg/dL which was transient and only one patient had persistent high urea.1.4%of cases had high creatinine. This accounts for 1.4% of renal failure cases in the study group. As similar findings were also reported by Gulati S et al., [21] [Table/Fig-11]. Sakaracan A et al., showed a 5% incidence of ARF in their study [22]. Steele BT et al., have described a case report of reversible acute renal failure in minimal change nephrotic syndrome which accounts for 3.8% [23].

Among the 72 children, biopsy was done in 29 (42.7%) children. The histopathological spectrum is as follows, 38% of children had minimal change nephrotic syndrome and the remaining 62% had non-minimal change nephrotic syndrome. This study is in close correlation with the studies conducted by ISKDC, Srivastava T et al., Gulati S et al., Bonila-Felix M et al., and White RHR et al., [7,24-27].

It was seen that there is a marked difference in the incidences of MCNS and FSGS groups in the present study and previous studies. The reason for the higher prevalence of non-MCNS, in this study could be due to referral bias. This being a tertiary care referral center, the numbers of complicated nephrotic syndromes were higher. The steroid response in relation to the histopathology is comparable with the other studies and it was in close correlation.

Haematuria was positively associated with non MCNS group and this was statistically significant with p-value of 0.001. This correlates with the study done by Nammalwar BR et al., where haematuria was observed in 63 of 112 patients with the p-value of 0.001 [10]. In our study, there was statistically significant association between hypertension and non MCNS group with p-value of 0.001 whereas the study done by Nammalwar BR et al., did not prove so [10]. The immunofluorescence results noted in this study is in correlation with the study conducted by Buch AC et al., [28].

LIMITATION

Study group and the duration of the study was less; more studies can be done involving large sample size.

CONCLUSION

Immunofluorescence is very important in diagnosing secondary nephrotic syndrome as some of the nephrotic syndromes cannot be diagnosed by light microscopy alone. Treatment selection and strategy depends upon the immunoflorescence findings; treatment in these cases should be aggressive and should affect the further progression of the disease. Multi-modality approach with direct immunofluorescence microscopy and correlation with histopathology findings, clinical, biochemical and serological markers should be done on a regular basis for the correct diagnosis and treatment of glomerular diseases.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Publishing: **Jul 01, 2019**