# Pattern of Glomerular Disease in Patients with Nephrotic Syndrome- A Single Centre South Indian Study.

Clement Wilfred D[1], Vijaya Viswanath Mysorekar[2], Mahesh E[3], Rashmi Krishnappa[4], Radhika Kunnavil[5]

[1]Associate professor, Department of Pathology, M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.
[2]Senior professor, Department of Pathology, M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.
[3]Professor, Department of Nephrology, M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.
[4]Assistant professor, Department of Pathology, M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.
[5]Lecturer, Department of Community Medicine, M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.

## ABSTRACT

**Background:** The prevalence of primary and secondary glomerular diseases presenting as nephrotic syndrome (NS) varies according to the demography, renal biopsy practice and geographic location. To determine the morphological patterns of glomerular lesions in renal biopsies from patients manifesting with NS, in our local (South Indian) population. **Methods:** The study was conducted in a tertiary care hospital in South India between 2008 and 2014 on adults and children presenting with NS. Renal biopsies were performed in all patients and subjected to light microscopic and immunofluorescence studies. **Results:** A total of 264 cases of NS were identified of which 80.7% were adults and 19.3% were children. The mean age for the adults was 42.2 years with a male: female ratio of 1.6:1 and the mean age for children was 12.1 with a male: female ratio of 1.8:1. The most common cause of NS in adults was minimal change disease (MCD) (42.7%) followed by membranous nephropathy (MN) (24.4%) and focal segmental glomerulo-sclerosis (FSGS) (17.8%). In children MCD (88%) was the single most common cause of NS followed by FSGS (5.9%) and MN (3.9%). Compared to MCD and MN, a higher incidence of microscopic haematuria and renal insufficiency was present in FSGS. **Conclusion:** A wide range of primary and secondary glomerular disorders can present as NS, the prevalence of which varies according to the geographic area and demography. Though the frequencies of MCD, MN, and FSGS in our study were different from other studies conducted in India and other countries, these three glomerular disorders are the three major causes of NS in many geographic areas across the world.

***Keywords:*** Focal segmental glomerulo-sclerosis, Membranous nephropathy, Minimal change disease, Nephrotic syndrome.

## INTRODUCTION

Nephrotic syndrome (NS) is a common presentation of renal disease and is characterised by massive proteinuria, oedema, hypo-albuminemia and hyper-lipidemia.[1,2]

The syndrome is caused by diverse primary and secondary glomerular lesions. The distinction between the various causes of NS is important, as these glomerular diseases exhibit different clinical behaviour and prognosis and require appropriate treatment protocols.[2]

Further the aetiology and renal tissue histology of NS varies according to the demography, race and geographic location and there is scarcity of this information in the native South Indian population.[1,3]

The aim of the present study was to determine the morphological patterns of glomerular lesions in renal biopsies from patients manifesting with NS, in a tertiary care hospital in South India.

**Name & Address of Corresponding Author**
Dr Clement Wilfred D
Associate professor,
Department of Pathology,
M. S. Ramaiah Medical College and Teaching Hospitals, Bangalore, India.
Email. clement.wilfred@yahoo.com.

## MATERIALS AND METHODS

The study was a cross-sectional, hospital based study and was conducted in the department of Pathology in collaboration with the department of Nephrology, M.S Ramaiah Medical College and Hospitals, Bangalore (which caters mainly to the local South Indian population) over a duration of six years (between 2008 and 2014). Patients presenting with NS, who underwent percutaneous renal biopsy were included in the study. NS was defined as heavy proteinuria of 3.5 g or greater per day per 1.73m$^2$ surface area and hypo-albuminemia of under 2.5 mg/dl.[1-5] The renal biopsies were processed for light microscopy (LM) and immunofluorescence microscopy (IFM) as per standard protocol. For LM, 3 to 4 µm thick paraffin embedded tissue sections were stained with haematoxylin and eosin, Masson's trichrome, periodic acid Schiff and Jones silver methenamine stains. For IMF, cryo-sections were stained with fluorescein isothiocyanate (FITC) conjugated antisera (Bio Genex) specific for immunoglobulin IgG, IgM, IgA and complement component 3 (C3). The staining intensity was semi quantitatively graded from 0 to +++ and the distribution described as mesangial or membranous in a granular or linear pattern. Clinical details and relevant investigations including age, gender, 24 hour proteinuria, urinalysis, serum creatinine and serological data

[anti-nuclear antibodies (ANA), complement (C3) levels] were obtained. The histology slides were interpreted independently and blindly by two nephro-pathologists and classified into primary glomerular disease (PGD) and secondary glomerular disease (SGD). Statistical analysis: Data was entered in Microsoft excel and analysis was carried out using Statistical Package for Social Sciences version 20.0, (SPSS, IBM, USA). All the continuous variables were expressed as mean and standard deviation and all qualitative variables as proportion. The frequency and percentage of each category of renal disease was computed. Chi square test was used to compare the difference in proportions of categorical variables. $P<0.05$ was considered as statistically significant.

## RESULTS

A total of 264 cases of NS were identified of which 213 (80.7%) were adults and 51 (19.3%) were children (≤ 15 years). The mean age for the adults was 42.2 years (age range: 16 to 78 years) with a male: female ratio of 1.6:1. The mean age for children was 12.1 years (age range: 1 to 15 years) with a male:female ratio of 1.8:1. The mean 24 hour proteinuria and serum creatinine in adults, respectively, were 5.6 gm/24 hrs (range: 3.5 to 19.4 gm/24 hrs) and 1.59(±1.28) mg/dl (range: 0.25 to 8.1). The mean 24 hour proteinuria and serum creatinine in children, respectively, were 4.8 gm/24 hrs (range: 3.5 to 10.53 gm/24 hrs) and 0.5 mg/dl (range: 0.14 to 7.1). The mean serum albumin was 2.3 ± 0.34 in adults and 2.4 ± 0.33 in children. Microscopic haematuria was observed in 10.3% (17/213) of adults and 11.8% (6/51) of children. ANA was positive only in 1.9% (4/213) of the adult cases.

Table 1 and Table 2 show the histological patterns of glomerular disease and laboratory parameters in adults and children with NS, respectively. In adults PGD comprised of minimal change disease (MCD), membranous nephropathy (MN), focal and segmental glomerulo-sclerosis (FSGS), diffuse proliferative glomerulonephritis (DPGN), membrano-proliferative glomerulonephritis (MPGN) and IgA nephropathy (IgA), which accounted for 93% (198/213) of the cases. SGD comprised of lupus nephritis (LN), amyloidosis, diabetic nephropathy (DN) and light chain deposition disease (LCDD), which accounted for 5% (11/213) of the cases of NS in adults. On the other hand, in children, all the cases of NS were due to PGD. The most common cause of NS in adults was MCD (42.7%) followed by MN (24.4%) and FSGS (17.8%). In children MCD (88%) was the single most common cause of NS followed by FSGS (5.9%) and MN (3.9%).

**Table 1:** Histological patterns of glomerular disease and laboratory parameters in adults with NS.

| Histological diagnosis | Total no.of cases(%) | Mean age, years | Males | Females | Male: Female ratio | Serum:creatinine, md/dl (±SD) | 24hrs proteinuria, gm (±SD) |
|---|---|---|---|---|---|---|---|
| **MCD** | 91 (42.7) | 35 | 53 | 38 | 1.4:1 | 1.2(±0.4) | 6(±4) |
| **MN** | 52 (24.4) | 40.3 | 34 | 18 | 1.9:1 | 1.4(±1.2) | 4.6(±2.7) |
| **FSGS** | 38 (17.8) | 36.8 | 24 | 14 | 1.7:1 | 2.5(±2.1) | 6.4(±3.1) |
| **DPGN** | 7 (3.3) | 38.8 | 6 | 1 | 6:1 | 1.6(±0.7) | 4.4(±2.7) |
| **MPGN** | 6 (2.8) | 35.2 | 4 | 2 | 2:1 | 1.1(±0.2) | 5.6(±1.3) |
| **IgAN** | 4 (1.9) | 35.5 | 2 | 2 | 1:1 | 1.4(±0.1) | 5.5(±1.4) |
| **LN** | 6 (2.8) | 31.7 | 1 | 5 | 0.2:1 | 1.6(±0.7) | 3.87(±2.6) |
| **Amyloidosis** | 2 (0.9) | 55 | 2 | - | - | 3(±0.3) | 5.1(±0.7) |
| **DN** | 2 (0.9) | 57 | 2 | - | - | 4.1(±0.3) | 5.2(±1.8) |
| **LCDD** | 1 (0.5) | 60 | - | 1 | - | 3.2 | 4.9 |
| **ESRD** | 4 (1.9) | 36.3 | 3 | 1 | 3:1 | 4.5(±0.8) | 4.8(±1.5) |
| **Total** | 213 | - | 131 | 82 | - | - | - |

MCD (Minimal change disease), MN (Membranous nephropathy), FSGS (Focal and segmental glomerulosclerosis), DPGN (Diffuse proliferative glomerulonephritis), MPGN (Membrano-proliferative glomerulonephritis), IgAN (IgA nephropathy), LN (Lupus nephritis), DM (Diabetic nephropathy), LCDD (Light chain deposition disease), ESRD (End stage renal disease).

**Table 2:** Histological patterns of glomerular disease and laboratory parameters in children with NS.

| Histological diagnosis | Total no. of cases (%) | Mean age, years | Males | Females | Male:Female ratio | Serum creatinine, md/dl (±SD) | 24 hrs proteinuria, gm (±SD) |
|---|---|---|---|---|---|---|---|
| **MCD** | 45 (88) | 8.1 | 29 | 16 | 1.8:1 | 0.5(±0.2) | 4.7(±2.5) |
| **FSGS** | 3 (5.9) | 12.7 | 3 | - | - | 1.0(±0.4) | 4.6(±0.2) |
| **MN** | 2 (3.9) | 13.5 | - | 2 | - | 0.9(±0.4) | 6.2(±0.9) |
| **MPGN** | 1 (2) | 14 | 1 | - | - | 1.1 | 5.2 |
| **Total** | 51 | - | 33 | 18 | - | - | - |

**Table 3:** Salient pathologic and key clinical features of common PGD causing NS.[2,6,17]

| PGD | Pathologic features | Clinical features |
|---|---|---|
| **MCD** | No glomerular anomaly on LM; negative IFM; podocyte foot process effacement and no deposits on EM | Relatively mild or benign cases of NS |
| **FSGS** | Segmental sclerosis and hyalinosis involving <50% of all glomeruli on LM; IgM and C3 deposits in the sclerotic areas on IFM; podocyte denudation and loss of foot processes on EM | Have higher incidence of haematuria, hypertension and renal insufficiency |
| **MN** | Diffuse and global uniform thickening of glomerular basement on LM; diffuse granular membranous deposits of IgG and C3 on IFM; Sub-epithelial deposits on EM | At presentation, haematuria, hypertension and renal insufficiency are less frequent compared with proteinuria. |

PGD (Primary glomerular disease), LM (Light microscopy), IFM (Immunofluorescence microscopy), EM (Electron microscopy)

## DISCUSSION

NS results from damage to the glomerular filtration barrier with consequent proteinuria. It is caused by/ associated with a heterogeneous variety of primary (PGD) and secondary glomerular disorders (SGD). The common PGD causing NS include MCD, FSGS and MN, the salient pathologic and key clinical features of which are elaborated in Table 3. The other less common primary causes of NS include MPGN, other proliferative glomerulonephritis (GN) like DPGN, crescent GN and IgAN and chronic GN.[2,6] The common SGD which cause NS include DN, LN, amyloidosis, Henoch-Schönlein syndrome, multiple myeloma, infections like human immunodeficiency virus (HIV) infection, malaria and hepatitis B or C, preeclampsia, drugs like non-steroidal anti-inflammatory agents and malignancies (carcinoma/ lymphoma).[2,6]

The histologic spectrum of PGD and SGD clinically presenting as NS varies according to age (children vs. adults), race, socio-economic conditions, indications for renal biopsy and geographic area (tropical vs. temperate).[1,2,3] In the present study the most common cause of NS in adults was MCD (42.7%) which is in concurrence with another South Indian study (Hyderabad) and study from Morocco.[7,8] However, in a North Indian study (Chandigarh) involving 364 adult NS cases, the incidence of MCD was only 14.8%. Further many European studies and a South Indian study conducted at Vellore have shown declining incidence of MCD.[5,9,10]

The most common cause of NS in our childhood population was MCD (88%) which is in synchrony with a North Indian study (76.6%) conducted on 521 childhood NS cases and a Pakistan study (37%).[11,12] However, in an Iranian study, MCD was the second most common histo-pathological subtype (18%), FSGS being the commonest.[13] The high frequency of MCD in our study can be partly attributed to the practice patterns of doing a kidney biopsy. As the procedure is safe and pre biopsy clinical course does not always predict the histological diagnosis, we biopsy more liberally.[11] Further biopsy helps in making early diagnosis and instituting the appropriate doses of immunosuppressive medications promptly.[11]

The clinical presentation was similar in adult and childhood MCD, in the present study. A few studies have reported higher incidence of acute renal failure and hypertension in adult NS, especially in the elderly.[2] Macroscopic haematuria was not detected and microscopic haematuria was present in 5.5% (5/91) of adult and 4.4% (2/45) of childhood MCD. All the cases had normal serum creatinine levels. On histology glomerular sclerosis and arteriosclerosis were observed more often in adult MCD, which were related to the age rather than the disease process.

MN constituted the second most frequent cause of adult NS (24.4%) which is in synchrony with a North Indian study (Chandigarh), where the frequency of MN in adult NS was 24.4%.[3] Most widely used renal pathology text books have quoted MN as the most common cause of adult NS.[2,5,8] It is still the most common cause of NS in many European countries (Italy and Serbia).[5,14] In our childhood population MN was the third commonest cause of NS, constituting 3.9% of the cases. Studies conducted in Iran and Pakistan respectively, revealed the frequency of childhood MN as 5.8% and 7%.[11,13]

Microscopic haematuria and raised serum creatinine levels were present in 3.8% (2/52) and 11.5% (6/52) of the adult MN cases, respectively. One of the 2 cases of childhood MN showed microscopic haematuria (50%). There was no statistically significant difference, with respect to the incidence of microscopic haematuria and renal insufficiency (raised serum creatinine levels), between MN and MCD in adult NS cases (P=1)

In addition to the characteristic finding of diffuse and global uniform thickening of the glomerular basement membrane, mesangial hyper-cellularity, segmental glomerular sclerosis and interstitial foam cells were present in 11.5% (6/52), 3.8% (2/52) and 5.8% (3/52) of adult MN cases. Cases of MN with segmental sclerosis are said to have micro-haematuria, hypertension, renal insufficiency and lower survival rates.[2] Both the cases with segmental sclerosis, in our study, had micro-haematuria and raised creatinine levels. IFM revealed diffuse global fine granular membranous staining for IgG, IgM and C3 in 100%, 25% and 84% of the MN cases.

In the present study FSGS constituted the third most frequent cause of adult NS, occurring in 17.8% of the cases. Another South Indian study (Hyderabad) has reported a frequency of 15.2% and concluded that FSGS is the second commonest cause of NS.[7] In a North Indian (Chandigarh) study it was the most common cause of adult NS, occurring in 99 of the 364 cases (30.6%).[3] The latter study has demonstrated a five-fold increase in the frequency of FSGS as a cause of NS.[3] A recent study from Kolkata revealed that FSGS accounted for majority (27.4%) of their adult NS cases.[15] Many recent studies have demonstrated a worldwide increase in cases of FSGS, which has become the commonest cause of NS, especially in the Hispanic and African-Americans.[2,3,5,7,16] This increasing trend could be related to new environmental causes, broadened morphological definition of FSGS, changing pattern of renal biopsy indications, improving socio-economic status , increased incidence of obesity and wider use of IFM and electron microscopy.[3,16,17]

FSGS was the second commonest cause of childhood NS in our study, occurring in 5.9% of the cases, which is in synchrony with a study conducted in Pakistan,[11] whereas it was the most common subtype in an Iranian study, comprising 41% of all cases of childhood NS.[13]

In the present study, microscopic haematuria was present in 23.7% (9/38) of adult FSGS cases and 40% (2/5) of the childhood cases. Signs of renal insufficiency with raised serum creatinine levels were present in 31.6% (12/38) of adult FSGS cases and 20% (1/5) of childhood cases. Compared to adult MCD, cases of adult FSGS had increased incidence of microscopic haematuria and renal insufficiency, which was statistically significant (P=0.004). The latter findings were compatible with literature review.[17]Similarly, higher incidence of haematuria and renal insufficiency was present in adult FSGS compared to adult MN, which was statistically significant (P=0.007). On histology the commonest morphological variant in adults and children was FSGS, classical variant. Cellular, tip lesion and peri-hilar variants comprised <15% of all cases of FSGS. Collapsing variant was not encountered in our study.

The other less common PGD causing adult NS encountered in the study included DPGN (3.3%), MPGN (2.8%) and IgAN (1.9%). Other Indian studies have quoted frequencies ranging from 1.6% to 14.9% for DPGN, 5.7% to 17.9% for MPGN and 1.8% to 13.8% for IgAN.[3,7,15,18,19]

The most common SGD causing NS in the present study was lupus nephritis, accounting for 54.5% (6/11) of all SGD cases, which is similar to a North Indian study (Chandigarh) where 62.5% of the SGD cases were lupus nephritis.[3] ANA was positive in 66.6% (4/6) of these cases.

A limitation of the present study is the small sample size of childhood NS and unavailability of electron microscopy study, which is being done in a limited fashion only in a few institutes across the country. A wider use of the latter study may modify the spectrum of NS.

## CONCLUSION

A wide range of primary and secondary glomerular disorders can present as NS, the prevalence of which varies according to the geographic area and demography. In our local South Indian patient population, the commonest cause of adult NS was MCD, followed by MN and FSGS. The commonest cause of childhood NS was MCD, followed by FSGS and MN. Compared to MCD and MN, a higher incidence of microscopic haematuria and renal insufficiency was present in FSGS. Though the frequencies of MCD, MN, and FSGS were different from other studies conducted in India and other countries, these three glomerular disorders are the three major causes of NS in many geographic areas across the world. The present study represents a contribution to understanding the epidemiology of renal disease presenting as NS in South India.

## REFERENCES


1. Chijioke A, Adeniyi AB. Clinicopathological Study of Adult Nephrotic Syndrome in Ilorin, Nigeria. Nigerian Medical Practitioner. 2003;42:28-32.
2. Olson JL. The Nephrotic Syndrome and Minimal Change Disease, Chapter 4. In: Hepinstall's Pathology of the Kidney, 6th ed., pp 1287-98.
3. Jennette JC, Olson JL, Schwartz MM, Silva FG, Eds. Lippincott Williams & Wilkins, Philadelphia,2007;1:126-54.
4. Rathi M, Bhagat RL, Mukhopadhyay P, Kohli HS, Jha V, Gupta KL, et al. Changing histologic spectrum of adult nephrotic syndrome over five decades in north India: A single centre experience. Indian J Nephrol.2014;24:86-91.
5. Chang JH, Kim DK, Kim HW, Park SY, Yoo TH, Kim BS, et al. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant.2009;24:2406-10.
6. Naumovic R, Pavlovic S, Stojkovic D, Basta-Jovanovic G, Nesic V. Renal biopsy registry from a single centre in Serbia: 20 years of experience. Nephrol Dial Transplant. 2009;24:877-85.
7. Kodner C. Nephrotic Syndrome in Adults: Diagnosis and Management. Am Fam Physician. 2009;80:1129-34.
8. Das U, Dakshinamurty KV, Prayaga A. Pattern of biopsy-proven renal disease in a single center of south India: 19 years experience. Indian J Nephrol. 2011;21:250-7.
9. Aatif T, Maoujoud O, Montasser DI, Benyahia M, Oualim Z. Glomerular diseases in the Military Hospital of Morocco: Review of a single centre renal biopsy database on adults. Indian J Nephrol. 2012;22:257-63.
10. Narasimhan B, Chacko B, John GT, Korula A, Kirubakaran MG, Jacob CKJ. Characterization of kidney lesions in Indian adults: towards a renal biopsy registry. J Nephrol.,2006;19:205-10.
11. Volovăt C, Cãruntu I, Costin C, Stefan A, Popa R, Volovăt S, et al. Changes in the histological spectrum of glomerular

diseases in the past 16 years in the North-Eastern region of Romania. BMC Nephrol. 2013;14:148.
12. Absar A, Diamond M, Sonia Y, Arshalooz R, Safia A, Waqar K, et al. Ten year experience of pediatric kidney biopsies from a single center in Pakistan. Indian J Nephrol. 2010;20:190-2.
13. Srivastava RN. 50 years of nephrotic syndrome in children, and hereafter. Indian Pediatr. 2013;50:107-10.
14. Zaki SA, Shanbag P. Spectrum of childhood nephrotic syndrome in Iran: A single centre study. Indian J Nephrol. 2010;20:222-3.
15. Gesualdo L, Di Palma AM, Morrone LF, Strippoli GF, Schena FP. The Italian experience of the national registry of renal biopsies. Kidney Int. 2004;66:890-4.
16. Golay V, Trivedi M, Kurien AA, Sarkar D, Roychowdhary A, Pandey R. Spectrum of nephrotic syndrome in adults: Clinico-pathological study from a single center in India. Ren Fail. 2013;35:487-91.
17. Hanko JB, Mullan RN, O'Rouke DM, McNamee PT, Maxwell AP, Courteny AE. The changing pattern of adult primary glomerular disease. Nephrol Dial Transplant. 2009;24:3050-4.
18. Schwartz MM. Focal Segmental Glomerulosclerosis, Chapter 5. In Hepinstall's Pathology of the Kidney, 6th ed., pp 1843-9.
19. Jennette JC, Olson JL, Schwartz MM, Silva FG, Eds. Lippincott Williams & Wilkins, Philadelphia. 2007;1:156-204.

**How to cite this article:** Wilfred CD, Mysorekar VV, Mahesh E , Krishnappa R, Kunnavil R. Pattern of Glomerular Disease in Patients with Nephrotic Syndrome- A Single Centre South Indian Study. Ann. Int. Med. Den. Res. 2015;1(3):281-85.

**Source of Support:** Nil, **Conflict of Interest:** None declared