ORIGINAL ARTICLE

CLINICAL, BIOCHEMICAL AND HISTOPATHOLOGICAL PROFILE OF ADULT NEPHROTIC SYNDROME PATIENTS IN A TERTIARY CARE HOSPITAL
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HOW TO CITE THIS ARTICLE:
S. Krishnamoorthy, S. R. Ramakrishnan, Bavya Vivek, L. Suja. “Clinical, Biochemical and Histopathological Profile of Adult Nephrotic Syndrome Patients in a Tertiary Care Hospital”. Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 71, September 03; Page: 12361-12375, DOI: 10.14260/jemds/2015/1785

ABSTRACT: BACKGROUND: The nephrotic syndrome is recognized as an independent entity of renal disease for over half a century.¹ Causes of nephrotic syndrome varies with age, time period, geographical location and race. In children, minimal change nephrotic syndrome is the commonest²; however, membranous nephropathy is most frequent in adults.³ As it commonly affects the younger age group and is associated with high morbidity and mortality, there is a need to understand and diagnose the disease at an early stage. Hence, this study has been done to identify the clinical presentation, biochemical parameters and histopathology associated with nephrotic syndrome in adults and its subtypes. OBJECTIVE: To study the clinical, biochemical and histopathological profile of patients with Adult Nephrotic Syndrome admitted in our tertiary care hospital. METHODS: Prospective study of 100 patients with Adult Nephrotic Syndrome admitted in our tertiary care hospital were screened with facial puffiness and pedal edema. They were tested for urine proteinuria, urine protein creatinine ratio or 24 hour urine protein estimation. Later renal biopsy was done for all patients to stratify the subtypes. RESULTS: In this study, males were predominantly affected. Most common presenting complaints were facial puffiness and pedal edema. Systolic BP was increased in 96% of patients and diastolic BP was elevated in 50% of patients. Serum LDL and TGL were elevated in nephrotic syndrome. In young patients less than 40 years Focal Segmental Glomerulosclerosis (FSGS) is the commonest type, then Membrano Proliferative Glomerulo Nephritis (MPGN) and Minimal Change Disease (MCD). In individuals more than 40 years, membranous nephropathy was predominantly seen followed by FSGS. CONCLUSION: There is a changing trend in primary nephrotic syndrome and FSGS was found to be the commonest subtype. Male preponderance was noticed and also FSGS was found to be more common in younger adults. Most patients in this study were found to have high BP at presentation. Serum creatinine was markedly elevated in patients with IgA Nephropathy and FSGS subtype. Most patients with FSGS who had elevated creatinine were found to have significant protein loss in urine. Lipids were observed to be elevated in all the subtypes, most significantly in the IGA nephropathy type. KEYWORDS: Focal Segmental Glomerulosclerosis, Nephrotic Syndrome, Membranous Nephropathy, Renal Biopsy.

INTRODUCTION: The nephrotic syndrome is defined by heavy proteinuria due to abnormal increase in glomerular permeability and following that hypoalbuminemia, hyperlipidemia and oedema.⁴ In a study conducted in the United States, during the 1976 to 1979 period, the relative frequencies of membranous (36%), minimal-change (23%) nephropathies and of FSGS (15%) as causes of unexplained nephrotic syndrome. In contrast to the previous study, changing trends from 1995 to 1997 shows FSGS to be the most common cause of this syndrome, accounting for 35% of cases.
compared with 33% for membranous nephropathy. During the 1995 to 1997 period, FSGS accounted for more than 50% of cases and for 67% of cases in adults younger than 45 years.  

Diagnostic Criteria for Nephrotic Syndrome: Proteinuria greater than 3-3.5g/24 hour or spot urine protein: creatinine ratio of >0.3 or Serum albumin <25g/l with clinical evidence of peripheral oedema and severe hyperlipidaemia. The issues important in the pathogenesis of nephrotic syndrome are proteinuria and the mechanism of glomerular injury.

Nephrotic syndrome has many causes and may either be the result of a disease limited to the kidney, called primary nephrotic syndrome, or a condition that affects the kidney and other parts of the body, called secondary nephrotic syndrome. The predominant cause of the nephrotic syndrome in children is minimal change disease. Approximately 30 percent of adults with the nephrotic syndrome have a systemic disease such as diabetes mellitus, amyloidosis, or systemic lupus erythematosus; the remaining cases are usually due to primary disorders including minimal change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy. Heavy proteinuria in patients without edema or hypoalbuminemia is more likely to be due to secondary FSGS. Primary causes of nephrotic syndrome are usually described by the histology. Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children, and focal segmental glomerulosclerosis, is the most common cause of nephrotic syndrome in adults. Secondary causes of nephrotic syndrome have the same histologic patterns as the primary causes, though it may exhibit some differences suggesting a secondary cause. They are usually described by the underlying cause as follows: Diabetic nephropathy, Amyloidosis, Systemic lupus erythematus, Multiple myeloma, Lymphoma, HIV, Hepatits B and C, Filariosis, Malaria, Syphilis, Alport’s syndrome, Pierson’s syndrome and Nail-patella syndrome.

Complications of nephrotic syndrome include. (1) Infections: bacterial infections-pneumonia, cellulitis, peritonitis &Viral infections in immunocompromised patients. (2) Venous thrombosis: Deep vein thrombosis or renal vein thrombosis, which can lead to pulmonary thromboembolism. Arterial thrombosis is rare. (3) Acute Renal Failure: is a rare spontaneous complication of nephrotic syndrome. It can also be caused by excessive diuresis, interstitial nephritis related to the use of diuretics or non-steroidal anti-inflammatory drugs, sepsis, or renal vein thrombosis. Reviews of case reports suggest that older patients, young children, and those with heavy protein loss are at most risk. Patients may need dialysis for recovery. (4) End Stage Renal Disease: primary FSGS is a risk factor for developing ESRD.

Regarding the diagnosis, today most nephrologists use Trucut biopsy needle or biopsy gun and they perform the biopsy under ultrasound or CT-guided renal biopsy for better yield.

Indications of Renal Biopsy: 1. Features suggesting a diagnosis other than minimal change nephropathy. 2. NS presenting in first year of life. 3. NS presenting after six years. 4. Failure to respond to adequate dose of steroid therapy in 28 days. 5. Frequently relapsing NS. 6. Steroid dependent NS. 7. Development of Steroid resistance. 8. Change in clinical course. 9. Before starting immunosuppressive therapy.

Treatment includes the administration of an angiotensin-converting enzyme (ACE) inhibitor or Angiotensin receptor blockers (ARBs) to lower intraglomerular pressure, dietary sodium restriction and loop diuretics to reduce edema. The lipid abnormalities induced by the nephrotic syndrome usually reverse with resolution of the disease, but most patients are initially treated with an HMG CoA reductase inhibitor (statin). ACE inhibitors or ARBs and statin together are considered as non-immunosuppressive therapy for nephrotic syndrome. Arterial and venous
thromboemboli are typically treated with heparin followed by warfarin as long as the patient remains nephrotic. Patients with minimal change disease often require only steroids whereas FSGS and membranous type require steroids plus immunosuppressive therapy like cyclosporine, cyclophosphamide, tacrolimus depending on the renal biopsy. In resistant cases, Rituximab (anti CD20) has been recommended.

MATERIALS AND METHODS: Prospective study of 100 consecutive patients with Adult Nephrotic Syndrome admitted in our hospital between December 2010-August 2012 were included.

Inclusion Criteria:
Clinical Criteria:
1. Pedal edema.
2. Facial Puffiness.
Laboratory Criteria:
1. Proteinuria greater than 3-3.5 g/24 hour or spot urine protein: creatinine ratio of >0.3.
2. Dyslipidemia.

Exclusion Criteria:
1. Type 2 Diabetes Mellitus.
2. Systemic Hypertension.
3. Decompensated Liver Disease (Child-Pugh score: B and C).
4. Congestive Cardiac Failure (LVEF: <40%).
5. Sepsis.
6. Documented Chronic Kidney Disease.
7. Age <18 yrs.

METHODS: Blood Pressure: Blood pressure was measured in right arm with the patient in supine position using sphygmomanometer using appropriate size cuff, recorded in mmHg to the precision of 2mmHg/second. 2 readings were recorded. Higher reading among systolic and diastolic blood pressure was taken for analysis. Patient was asked for previously diagnosed hypertension and response recorded. Hypertension is defined as clinical history of documented elevated blood pressure or persistent systolic blood pressure >140mmHg and diastolic blood pressure >90 mmHg.

Serum Creatinine: Serum creatinine was done by modified kinetic Jaffe’s method.

Albuminuria: Two nonconsecutive early morning urine samples were taken and assessed by Immunoturbidometric method.

Urine Protein Creatinine Ratio: Urine protein and urine creatinine were analysed individually. Urine protein was analysed by the Immunoturbididity method. Urine creatinine was measured by the modified Jaffe’s method. Later urine protein creatinine ratio was calculated.

Fasting Lipid Profile: Blood samples for fasting lipid profile were taken after twelve hours overnight fast. TGL was analyzed by the enzymatic method. LDL was measured by direct measurement.
Renal Biopsy: USG guided renal biopsy was done for all the patients using trucut biopsy needle.

Ethical Committee Approval: The present study was approved by the Ethical committee of our hospital.

Statistical Analysis: Statistical Analysis of data was done by using the software statistical percentage for social science for Windows (Ver-17).

Frequencies, Percentages, Range, Median, Mean, S.D. and 'p' values were calculated using this package.

RESULTS: A total of 100 patients were selected after excluding the patients using the exclusion criteria mentioned above.

A total of 100 patients were studied, of which 60 % were males and 40% were females. (Figure 1)
The mean age of the patients in this study was 44.35, the youngest being 20 and oldest being 70. (Table 1)

On dividing the patients into two groups according to age, in the age group less than 40 years, the commonly seen subtypes of Nephrotic syndrome was FSGS (61.4%), followed in sequence by MPGN(18.2%), MCD(9.1%) and as age increases (> 40 years), Membranous Nephropathy was seen predominantly (50 %), followed by FSGS (32.1%) and MPGN(14.3%) (Table 1).

Table 1. Age distribution in relation to the subtypes

|                | AGE RANGE |          |          |
|----------------|-----------|----------|----------|
|                | < 40      | > 40     |
| RenalBX FSGS   | 27        | 18       |
| % within RenalBX | 61.4%    | 32.1%    |
| MEMBRANOUS NPHRO| 2         | 28       |
| % within RenalBX | 4.5%     | 50%      |
| MEMBRANO PRO GLO| 8        | 8        |
| % within RenalBX | 18.2%    | 14.3%    |
| MINIMAL CHANGE DISEASE | 4 | 1 |
| % within RenalBX | 9.1% | 1.8% |
| IGA NPHRO | 3 | 1 |
| % within RenalBX | 6.8% | 1.8% |
| Total | 44 | 56 |

Figure 2. Relative frequency of chief complaints

- Pallor: 79%
- Pedal Edema: 73%
- Facial Puffiness: 65%
The most common presenting complaints of the patients were found to be facial puffiness and pedal oedema. In this study group 79% of the patients had facial puffiness, 65% had pedal oedema and 73% had pallor (Fig 2).

Over all in this study, the commonest subtype of adult nephrotic syndrome was found to be Focal Segmental Glomerulosclerosis (45%) followed by Membranous Nephropathy (30%), Membrano Proliferative Glomerulonephritis (16%) Minimal Change Disease (5%) and IgA Nephropathy (4%) respectively. (Fig 3).

Table 2. Systolic Blood Pressure values in various subtypes
Table 3. Diastolic Blood Pressure values in various subtypes

| Blood Pressure (in mmHg) | DIASTOLIC RANGE | < 90 | ≥ 90 |
|--------------------------|-----------------|------|------|
| RenalBX FSGS             | Count % within RenalBX | 23 | 22 |
|                          |                 | 51.11% | 48.89% |
| Membranous Nephro        | Count % within RenalBX | 16 | 14 |
|                          |                 | 53.33% | 46.67% |
| Membrano Pro Glo         | Count % within RenalBX | 5  | 11 |
|                          |                 | 31.25% | 68.75% |
| Minimal Change Disease   | Count % within RenalBX | 2  | 3 |
|                          |                 | 40.00% | 60.00% |
| IGA Nephro               | Count % within RenalBX | 0  | 4 |
|                          |                 | 0.00% | 100.00% |
| Total                    |                 | 46 | 54 |

Fig 4. Elevation of SBP & DBP in study group
The mean systolic blood pressure of the patients in this study was 149.56mmHg, and diastolic blood pressure was 89.12mmHg. Systolic BP, ≥ 140mmHg was found in 96% of the patients and Diastolic BP ≥ 90mmHg was found in 54% of total patients. (Table 2 and 3; Fig 4)

Anemia with hemoglobin <12gm/dl was observed only in 50% of the patients. (Fig 5)

| URINE ROUTINE RBC/mm3 | URINE ROUTINE RBC/mm3 | Total |
|-----------------------|-----------------------|-------|
|                       | 0         | 3-4   | 5-6  |       |
| RenalBX               | Count     | % within RenalBX |
| FSGS                  | 23        | 4      | 18    | 45    |
| % within RenalBX      | 51.1%     | 8.9%   | 40.0% | 100.0%|
| MEMBRANOUS            | Count     | % within RenalBX |
| NPHRO                 | 15        | 4      | 11    | 30    |
| % within RenalBX      | 50.0%     | 13.3%  | 36.7% | 100.0%|
| MEMBRANO              | Count     | % within RenalBX |
| PRO GLO               | 7         | 1      | 8     | 16    |
| % within RenalBX      | 43.8%     | 6.3%   | 50.0% | 100.0%|
| MINIMAL               | Count     | % within RenalBX |
| CHANGE DISEASE        | 3         | 0      | 2     | 5     |
| % within RenalBX      | 60.0%     | 0.0%   | 40.0% | 100.0%|
| IGA NEPHRO            | Count     | % within RenalBX |
|                       | 2         | 0      | 2     | 4     |
| % within RenalBX      | 50.0%     | 0.0%   | 50.0% | 100.0%|

Table 4. Urine RBCs in various subtypes
Urine routine showed proteinuria which was later quantified by urine protein creatinine ratio, urine routine also showed hematuria which was significantly observed in IgA nephropathy and MPGN (50%); followed by FSGS and MCD (40%); MN at 36.7% (Table 4; Fig 6)

| Protein Creat Ratio | FSGS | MN | MPGN | MCD | IGA Neph |
|---------------------|------|----|------|-----|----------|
| 3.4 – 4.5           | 7    | 22 | 16   | 5   | 4        |
| 4.6 – 5.5           | 9    | 7  | 0    | 0   | 0        |
| 5.6 – 7.5           | 29   | 1  | 0    | 0   | 0        |
| TOTAL               | 45   | 30 | 16   | 5   | 4        |

Table 5. Urine PCR in various subtypes
Proteinuria was quantified using urine protein creatinine ratio, and it was observed that a significant amount of protein loss was present in the FSGS subtype of nephrotic syndrome (64.4%) at 5.6–7.5, the other types were found to have lesser Urine protein creatinine ratio compared with FSGS. All Patients who had MPGN, IgA Nephropathy and MCD and 73.3% of MN had protein creatinine ratio between 3.4–4.5. (Table 5, Fig 7).

**Figure 7.** Urine PCR in various subtypes

**Figure 8.** Blood urea nitrogen values in various subtypes.
Blood urea nitrogen analysis (BUN) showed that many patients had a BUN less than 20, but in FSGS, the BUN value was more. (Fig 8)

![Figure 9. Serum creatinine values in various subtypes](image)

Serum Creatinine analysis revealed that higher creatinine values were observed in the IgA Nephropathy and FSGS group, 50% and 48.8 % respectively, and lower values were seen in MN (63.3%), MCD (60%) and MPGN (56.25%) (Fig: 9)

![Fig 10. Serum Triglyceride values in various subtypes](image)
Serum Triglyceride level were found to be elevated in all the patients but significant elevation (>250mg/dl) was observed in IgA Nephropathy (100%), followed by MN (56.6%), MPGN (50%), FSGS (48.8%), lastly MCD (40%) (Fig 10).

![Fig 10. Serum LDL values in various subtypes](image)

Serum Low density lipoprotein was observed to be elevated significantly (>160mg/dl) in patients with IgA Nephropathy (75%), MN (60%), FSGS (57.7%), MPGN (56.25%), lastly MCD (40 %) (Fig 11).

**DISCUSSION:** In this study of 100 patients the commonest cause of Adult Nephrotic syndrome was FSGS (45%). In the age group less than 40 years, the commonly seen subtype was FSGS (61.4%), followed in sequence by MPGN(18.2%), MCD (9.1%) .As age increases (>40years) Membranous Nephropathy was seen predominantly at 50%, followed by FSGS (32.1%) and MPGN (14.3%).The mean systolic blood pressure of the patients in this study was 149.56mmHg, and diastolic blood pressure was 89.12mmHg. It was observed that 60 % of the patients were males and 40% were females.

Features that increased the risk for progressive renal disease include elevated serum creatinine at the time of diagnosis, hypertension, age at time of diagnosis, and male gender.

- A male preponderance was noticed.\(^{18}\)
- For a 10 unit increase in Diastolic BP the risk for kidney failure increased by an average of 34% and could increase up to 80%.\(^{19}\)
- With advancing age FSGS becomes less common.
- In a study done in Spain, of 35.5% patients with NS were studied a male preponderance was noticed at 3:2.
• Studies in Iran done in children with Nephrotic syndrome also showed, focal segmental glomerulosclerosis was the most common pathologic finding (41%).

**PREVALENCE OF SUBTYPES:** In this study, the commonest cause of Adult Nephrotic Syndrome was found to be Focal Segmental Glomerulosclerosis (FSGS), (45%) followed by Membranous Nephropathy (MN) (30%), Membrano Proliferative Glomerulo Nephritis (MPGN) (16%), Minimal Change Disease (MCD) (5%) and IgA Nephropathy (4%) of the total number of patients.

A study done in USA during 1995-1997 compared the aetiologies of NS in 1000 native kidney biopsy patients, showed that FSGS was the most common aetiology of nephrotic syndrome, accounting for 35% of cases and membranous nephropathy in 33% of patients. This article also said that FSGS accounted for more than 50% of NS in black adults and for 67% of such cases in black adults younger than 45 years.

**SERUM CREATININE:** In this study it was observed that higher creatinine values were observed in the IgA Nephropathy and FSGS group, 50% and 48.8 % respectively. Of the 22(48.8%) patients with significantly elevated Creatinine (>2.0), 17(37.7%) patients had significantly elevated Protein Creatinine Ratio (5.6-7.5).

**PROTEIN CREATININE RATIO:** In this study, it was observed that a significant amount of protein loss was present in the FSGS subtype of nephrotic syndrome (64.4%) at 5.6–7.5.

• In nephrotic syndrome (proteinuria ≥3.0 or 3.5 g/day and low plasma albumin concentration) have five-year renal survival rates of 60 to 90 percent, and 10-year renal survival rates of 30 to 55 percent.\textsuperscript{20}
• Moderate severity of proteinuria has minimal utility in kidney failure risk profile.
• Heavy proteinuria, either at the time of biopsy but particularly following treatment, portends a poor long-term outcome.
• Massive proteinuria (>10g/day), when unresponsive to treatment, is associated with an even worse prognosis, with most patients progressing to ESRD within five years.
• The most compelling predictor for progression of FSGS appears to be the response of proteinuria after treatment is initiated.

**SERUM TGL AND LDL:** Lipids were observed to be elevated in all the patients in this study, TGL was seen to be elevated predominantly in the IgA Nephropathy, followed by MN, MPGN, FSGS group and elevated LDL was predominantly seen in the IGA Nephropathy patient, followed in sequence by MN, FSGS.

**CONCLUSION:**

• This study shows the changing trends in the prevalence of subtypes in primary nephrotic syndrome.
• FSGS was found to be the commonest subtype. Male preponderance was noticed.
• FSGS was found to be more common in younger adults.
• The clinical presentation was not varied among the subtypes, pedal edema, facial puffiness and pallor was present significantly in most patients.
• Most patients in this study were found to have high BP at presentation.
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- Serum creatinine was markedly elevated in the patients with IGA Nephropathy and FSGS subtype.
- Most patients with FSGS who had elevated creatinine were found to have significant protein loss in urine.
- Lipids were observed to be elevated in all the subtypes, most significantly in the IgA nephropathy group.

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FINANCIAL OR OTHER COMPETING INTERESTS: None

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Date of Submission: 27/08/2015.
Date of Peer Review: 28/08/2015.
Date of Acceptance: 31/08/2015.
Date of Publishing: 02/09/2015.