Histomorphologic analysis in adult nephrotic syndrome: Changing scenario

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ABSTRACT

Background: Nephrotic syndrome (NS) is the manifestation of a wide variety of underlying disease processes. The spectrum of diseases causing NS is changing globally in the last few decades. In this context, renal biopsy findings in adult nephrotics studied during 1996-1998 are revisited.

Materials and Methods: The cross-sectional analytical study was conducted during the period May 1996-July 1998 at a medical college in Western India. Renal biopsies were performed on 72 adult nephrotic patients. Histopathology reports along with clinical data were reviewed and analyzed.

Results: Primary glomerular diseases accounted for 70% of cases, while amyloidosis was the most common secondary glomerular disease. Mesangiocapillary glomerulonephritis was the most common cause of primary NS followed by minimal change disease (MCD) and membranous glomerulonephritis (MGN). Previous studies showed that MGN was the most common cause of adult NS. More recent studies have shown that focal segmental glomerulosclerosis (FSGS) is increasing significantly with reduction in diffuse proliferative glomerulonephritis while there was no major change in incidence of other diseases. FSGS is the most common cause of NS in adult in other studies accounted for only 8.5% in our study. Immunofluorescence and electron microscopy was not done in these cases resulting in more cases of MCD and less number of IgA nephropathy and FSGS.

Conclusion: In view of changing spectrum of renal diseases, evaluation of adult NS should be done on a regular basis for the correct diagnosis.

Keywords: Adult, glomerulonephritis, nephrotic syndrome, renal biopsy

Introduction

Nephrotic syndrome (NS) may be caused by primary (idiopathic) renal disease or by a variety of secondary causes. Most cases of NS appear to be caused by primary renal diseases. There is wide variation in epidemiology, etiology, and natural history of glomerular diseases in tropical countries and in temperate countries. Prevalence of NS varies according to socioeconomic conditions, race, and age. Previous studies showed membranous glomerulonephritis (MGN) is the most common cause of adult NS in the United States (US) and Europe. However, focal segmental glomerulosclerosis (FSGS) is increasing significantly and has become the most common glomerular disease.[1] Studies from India also showed an increased incidence of FSGS with declining incidence of mesangiocapillary glomerulonephritis (MPGN) while such trend was not observed by others.[2,3]

In this publication, we first described the histological spectrum of renal biopsy in adult NS analyzed during 1996-1998. This study was conducted to ascertain the histological spectrum of NS in adults at our institute and to

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note the change in the spectrum of these diseases over the last five decades.

**Materials and Methods**

The study of evaluation of renal biopsy in adult onset NS was carried out in Nephrology Unit of Medical College in Western India during 1996-1998. Renal biopsy was done in seventy-two adult patients with NS diagnosed by proteinurea >3.5 g/day, serum albumin <2.5 g/dl and evidence of fluid retention. Of these 72 patients, renal tissue was included in the renal biopsy in 50 cases, and these were analyzed clinically and histologically. All these patients were evaluated with routine and microscopic examination of urine, blood sugar level, blood urea, serum creatinine, urinary total protein, serum cholesterol, serum total protein and albumin, along with serological tests to detect syphilis, hepatitis B and human immunodeficiency virus infection. Antinuclear antibody and anti-ds-DNA were done in patients with suspected systemic lupus erythematosus (SLE).

Ultrasound (USG) of the abdomen was done to locate the kidney and to know the size and position. USG guided point was marked on abdomen to take renal biopsy. Before performing renal biopsies, apart from radiological investigations bleeding time and clotting time were assessed in an attempt to obviate the possibility of any abnormality in coagulation and to detect hemorrhagic diathesis if any.

After explaining the procedure to the patient, the biopsy was performed under USG guidance and local anesthesia using 22 gauge tru-cut needle. The patients were watched for 24 h for complications such as hematuria, perinephric hematoma infection and ileus. The biopsy was fixed in 10% formalin and processed routinely for paraffin embedding. The sections were cut into 3-4 µ in thickness and stained with hematoxylin and eosin, periodic acid Schiff stain (PAS), and silver methanamine (SM). Congo red was done wherever amyloid was suspected. Tissue was sent to other institute for electron microscopy (EM) whenever possible.

The morphological diagnosis offered by us during the study period 1996-1998 at Department of Pathology based on light microscopy and special stains for these renal biopsies are considered for this study.

**Results**

Renal biopsies from 72 patients aged 14 and onward who presented with NS were studied with their clinical features, hematological, biochemical and serological tests. Of 72 cases, no renal tissue was obtained in 17 cases and was inadequate in five cases. The age range of the nephrotic patients varied from 14 years to 75 years. There were 26 males and 24 females, and no sex preference was seen. Maximum numbers of patients were in the second decade of life. Clinically, all patients presented with edema. Oliguria and hypertension were present in 20% and 46%, respectively.

Histological spectrum of renal biopsies in these 50 adult nephrotic patients is listed in Table 1. Idiopathic NS was detected in 70% cases, and NS secondary to systemic diseases was found in 30% cases. Among the array of systemic diseases, SLE, amyloidosis, diabetes, and Alport’s syndrome were encountered.

MPGN was the most common type of lesion seen in 50 cases of adult patients biopsied who presented with NS. Of 12 cases of MPGN, four showed typical tram track on SM staining. At places, glomerular capillary wall showed subepithelial projections, i.e., spikes on PAS and SM staining which is seen in MPGN III. Segmental ribbon like thickening of basement membrane which is the unique light microscopic appearance of MPGN II was also seen in few cases. For precise classification of MPGN into I, II, and III requires sophisticated techniques like complement assay, immunofluorescent study coupled with EM. Such typing was not done in our study.

In the present study, we encountered 20% cases of MGN. There was no clinical and radiological evidence of malignancy in these cases.

Two cases showed epithelial crescent formation in 70-80% of glomeruli and hyalinization of tubules was also evident. Only three cases (8.6%) showed FSGS.

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Number of cases</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary glomerular disease</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>MPGN</td>
<td>12</td>
<td>34.3</td>
</tr>
<tr>
<td>MCD</td>
<td>10</td>
<td>28.6</td>
</tr>
<tr>
<td>MGN</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>FSGS</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>DPGN</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>ESRD</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>Secondary glomerular disease</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>LN</td>
<td>5</td>
<td>33.3</td>
</tr>
<tr>
<td>DN</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Alport's syndrome</td>
<td>1</td>
<td>6.3</td>
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</table>

Table 2: Age wise distribution of adult nephrotic patients

<table>
<thead>
<tr>
<th>Age group</th>
<th>MPGN</th>
<th>MCD</th>
<th>Primary or idiopathic</th>
<th>FSGS</th>
<th>ESRD</th>
<th>Secondary</th>
</tr>
</thead>
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<tr>
<td>14-20</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>21-30</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>31-40</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>41-50</td>
<td>—</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>51-60</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;61</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>


Table 3: Incidences of primary and secondary NS in various countries

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Number of cases</th>
<th>Primary NS percentage</th>
<th>Secondary NS percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td></td>
<td>50</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Rathi et al.</td>
<td>India</td>
<td>1811</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>1980-1998</td>
<td></td>
<td>2947</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>2002-2007</td>
<td></td>
<td>361</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>Tarik et al.</td>
<td>Bangladesh</td>
<td>100</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>China</td>
<td>493</td>
<td>89.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Said et al.</td>
<td>Jordan</td>
<td>260</td>
<td>72.2</td>
<td>27.8</td>
</tr>
<tr>
<td>1997-1999</td>
<td></td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal and Dash</td>
<td>India</td>
<td>2250</td>
<td>58.5</td>
<td>41.5</td>
</tr>
<tr>
<td>1996-2000</td>
<td></td>
<td>404</td>
<td>78.71</td>
<td>21.82</td>
</tr>
</tbody>
</table>

NS: Nephrotic syndrome

Table shows age distribution of adult nephrotic patients. MPGN was seen in all the age groups and incidence of MCD decreased with age, and that of membranous GN increased with age.

**Discussion**

This study encompasses the study of 72 adult nephrotic patients. Adequate renal tissue was obtained in 50 cases. For evaluation of a glomerular lesion, a biopsy should contain at least five glomeruli. Oberhozer and others pointed that for tubulointerstitial lesion a biopsy size of 6-10 glomeruli is necessary. Although this criterion is not absolute but depends on the underlying disease and if the disease is diffuse even a single glomerulus may be sufficient for diagnosis. However, other associated interstitial and vascular changes or the degree of glomerular obsolescence cannot be assessed when the lesion is directly proportional to the number of glomeruli. The accuracy of biopsy in these conditions can be quantitatively assessed considering the actual number of glomeruli and the size of the specimen as observed by Corwin et al. NS is of multiple etiologies and is mostly due to intrinsic renal diseases. In the present study, idiopathic NS was seen in 70% cases while NS secondary to systemic diseases accounted for 30% of total cases. The frequency of idiopathic NS and NS secondary to systemic diseases varies widely in different series as shown in Table 3.

It is noted from the above table that incidence of idiopathic (primary) NS varied from 69% to 90% and that of secondary NS from 10% to 30%. In the present study, incidences of both primary and secondary NS are well within the range documented in the literature.

The prevalence of biopsy-proven renal disease varies according to geographic areas, socioeconomic conditions, race, age, and indications for renal biopsy. Table 4 shows the spectrum of primary glomerular diseases as a cause of NS.

Minimal change disease (MCD) is the most common cause of the NS in children. It is also an important cause of primary NS in adults of all ages, accounting for 10-15% of cases. While the earlier studies found MCD to be the most common cause of adult onset NS in study done by Beaufils et al. and others. Incidence of MPGN and MCD was somewhat equal in previous studies. From Table 4, it's evident that incidence of MPGN remained the same in recent and previous studies, but that of MCD is reduced in recent studies. This reduction may be due to using of more advanced technology like EM. In our study, incidence of MPGN and MCD is 33.3% and 28.5%, respectively. While no such change in incidences of MPGN and MCD was observed by Rathi et al. in their previous and recent studies.
Postinfectious glomerulonephritis (PIGN) is an immunologic response of the kidney to infection, commonly triggered by streptococci, although many other organisms can cause the condition. In recent decades, the prevalence of PIGN has tended to decline in most industrialized countries, but high rates persist in some developing communities.[22]

In recent years, patients affected by DPGN (PIGN) in the developed world, especially Europe and the US, tend to be adults. Individuals with comorbidities such as diabetes and alcoholism are at an increased risk of developing the disease; one-third of individuals with acute PIGN (APIGN) have one or two of these comorbidities.[23] This finding is in contrast to reports published between 1960 and 1980, in which most of the affected patients had no such history.[24,25]

In our study, DPGN/PIGN was seen in 5.7% cases during our study period 1996–1998. The highest incidence of DPGN (36.6%) is reported by Rath[7] (1964–1980). The same author reported least incidence of DPGN (2.8%) in his study done during 2002–2007 period emphasizing the declining trend of DPGN.

In the present study, incidence of MGN is 20%. The highest incidence of MGN of 42.3% is seen in the study by Aryal G. and Kaffe[19] done during 2001–2007. The lowest incidence of 7.5% is reported by Rath[7] in their study done during 1964–1980.

There is an association between malignancy and MGN. Brueggemeyer and Ramirez[26] proved a relation between malignancy and MGN in their study. In addition, the study indicates that malignancy will become detectable within a relatively short period after the diagnosis of MGN, and that the malignancy rate is five times greater than the incidence in a baseline population. This risk is also highest in the elderly.

In the present study, the elderly patients comprise only 42.2% of total cases, and the follow-up was also not extensive. Hence, we did not get any case of MGN associated with malignancy. In the present study, MGN secondary to HIV and hepatitis was seen in two cases. In Africa, China, Korea and Greece, hepatitis B is a significant factor in the etiology of MGN. Chang et al.[27] reported a total of 128 hepatitis B surface antigen positive patients in Korea, with 30.5% of them having MGN.

FSGS is the most common lesion reported from Saudi Arabia.[28] The prevalence of FSGS appears to be increasing as reported from New York, where the prevalence is increased from 2.5% to 18.7% over 20-years period.[29] Studies by Johnson et al. have shown the association of FSGS with the hepatitis C virus.[30]

Among adults undergoing biopsy for evaluation of idiopathic NS, FSGS is now the most common lesion, being seen in up to 35% of patients overall and in up to 80% of African American patients.[7,16] FSGS has become an increasingly important cause of renal disease and end-stage renal disease in adult patients in the US and in African Americans.[31] However, studies done from European countries do not show such increased trend of FSGS in adult nephrotics, and MGN is the most common cause of adult NS in Italy and Spain.[32,33]
In India, a study done at Vellore also found that incidence of FSGS is increased in adult patients presenting with NS from 15% to 19%. We encountered only six cases of FSGS in our study. In few studies, low incidence of FSGS is explained on the basis of sampling problem and the juxtamedullary distribution of the involved glomeruli. Studies from Pakistan and Nepal have shown that IgA nephropathy (IgAN) is an infrequent cause of NS with figures of around 2% while IgAN is the second most common cause of NS in China and Korea. We did not find any case of IgAN in our study. The incidence of IgAN was only 2% in study by Rathi et al. as compared to 4-14% in other studies from India probably since the majority of those with IgAN do not have a NS.

Table 5 shows the percentage of NS cases associated with systemic diseases. NS is the most common manifestation of renal involvement by amyloidosis. The least incidence of amyloidosis as 3% has been reported by Kark et al. and highest as 74.4% by Aggarwal HK et al.

In our study, we encountered 40% cases of amyloidosis. In the present study, all cases showed secondary amyloidosis. Tuberculosis (66.6%) was the most common cause of secondary amyloidosis followed by a chronic suppurative lung disease (25%), rheumatoid arthritis, and chronic osteomyelitis (4.68%) in the study by Aggarwal et al.

In the present study, amyloidosis was secondary to tuberculosis in five cases (83.3%) and rheumatoid arthritis was the underlying cause of secondary amyloidosis in one case (16.7%).

Renal involvement is a major complication of SLE and occurs in 30-70% of patients with SLE. Lupus nephritis (LN) was the most common secondary cause in the study by Rathi et al. accounting for 62.5%. In our study, SLE accounts for 33.3% which is comparable with the one seen by Said et al. While in study by Tarik et al., out of 10 cases, nine cases showed NS secondary to SLE.

The main limitation of the present study is the small sample size and EM examination, and immunofluorescence study was done in only few cases. This may be the reason we could not diagnose IgAN in our study and LN accounted for only 33.3% cases.

**Conclusion**

There is wide variation in the histologic spectrum of the NS. Incidence of FSGS is increasing worldwide so also in Indian Population. Incidence of DPGN (PIGN) causing NS is declining while that of MPGN is not changed over a period of time. MPGN is the most common cause of adult NS in our study.

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**Conflicts of interest**
There are no conflicts of interest.

**References**