The renal histopathological spectrum of patients with nephrotic syndrome: an analysis of 1523 patients in a single Chinese centre

Fu-de Zhou, Hai-yan Shen, Min Chen, Gang Liu, Wan-zhong Zou, Ming-hui Zhao and Hai-yan Wang

Renal Division, Department of Medicine; Peking University First Hospital; Institute of Nephrology, Peking University; Key Laboratory of Renal Disease, Ministry of Health of China; Beijing, People’s Republic of China

Correspondence and offprint requests to: Min Chen; E-mail: leimeng@public3.bta.net.cn

Abstract

Background. Nephrotic syndrome is caused by a variety of glomerulopathy. The current study investigated the renal histopathological spectrum of patients with nephrotic syndrome who received a renal biopsy in our department within the last 15 years.

Methods. One thousand five hundred and twenty-three consecutive patients (≥14 years old at renal biopsy) with nephrotic syndrome were recruited. Patients were divided into four groups according to age at the time of renal biopsy. The renal histopathological spectrum was also compared between nephrotic-range proteinuria patients with and without hypoalbuminaemia.

Results. Among the 1523 patients, the most common cause of nephrotic syndrome was idiopathic membranous nephropathy (IMN) (20.7%), followed by minimal change disease (MCD) (20.4%). Among the patients aged 14–24, 25–44, 45–59 and ≥60 years, the most common cause of nephrotic syndrome was MCD (33.0%), lupus nephritis (LN) (23.0%), IMN (37.9%) and IMN (42.3%), respectively. Among the female patients aged 14–24 and 25–44 years, LN was the leading cause of nephrotic syndrome (35.8 and 36.2%, respectively). The proportion of patients with renal amyloidosis increased in parallel with patient age. The comparison between nephrotic patients with and without hypoalbuminaemia suggests that patients with MCD, LN or renal amyloidosis were more likely to develop hypoalbuminaemia.

Conclusions. The renal histopathological spectrum of nephrotic syndrome differs between ages. MCD, LN and IMN were the main cause of nephrotic syndrome among younger patients, and IMN was the main cause of nephrotic syndrome among older patients. The proportion of patients with renal amyloidosis increased in parallel with patient age.

Keywords: histopathology; idiopathic membranous nephropathy; lupus nephritis; minimal change disease; nephrotic syndrome

Introduction

Heavy proteinuria is often associated with hypoalbuminaemia, hyperlipidaemia and/or oedema, and is, therefore, given the term nephrotic syndrome. As a result of the renal biopsy technique, it is now well-known that nephrotic syndrome is caused by a variety of pathological entities, i.e. primary glomerulopathy, including mainly IgA nephropathy (IgAN) [1], idiopathic membranous nephropathy (IMN) [2], minimal change disease (MCD) [3], focal segmental glomerulosclerosis (FSGS) [4], non-IgA mesangial proliferative glomerulonephritis (non-IgA MsPGN) [5] and idiopathic membranoproliferative glomerulonephritis (morphologically characterized by diffuse mesangial cell proliferation and the thickening of capillary walls due to subendothelial extension of the mesangium) [6, 7] and secondary glomerulopathy, such as lupus nephritis (LN) [8], Henoch–Schoenlein purpura glomerulonephritis (HSPGN) [9] and renal amyloidosis [10]. However, patients may have normal level of serum albumin in spite of nephrotic-range proteinuria [11]. Of note, our recent study found that among patients with primary glomerulopathy and nephrotic-range proteinuria, normoalbuminaemia was associated with IgAN [12].

The cause of nephrotic syndrome varies with ages and genders. The disease spectrum of nephrotic syndrome has rarely been studied in Chinese patients except for in a few studies [13, 14]. The current study investigated the renal histopathological spectrum of patients with nephrotic syndrome who received a renal biopsy in Renal Division, Peking University First Hospital, one of the largest clinical nephrology centres in Northern China, within the last 15 years. In addition, a brief comparison was made between nephrotic patients with and without hypoalbuminaemia.

Materials and methods

Patients

One thousand nine hundred and twenty-three consecutive patients (≥14 years old at renal biopsy) with nephrotic-range proteinuria, who received native renal biopsies in Renal Division, Peking University First Hospital from 1993 to 2007, were recruited in this retrospective study. Indications for
renal biopsy, which has been described previously [14], were as follows: (i) nephrotic syndrome or nephrotic-range proteinuria, (ii) acute nephritic syndrome, (iii) rapidly progressive glomerulonephritis syndrome, (iv) chronic nephritic syndrome, (v) asymptomatic haematuria with proteinuria and (vi) acute renal failure without confirmed diagnosis. The indication of renal biopsy remained unchanged during the whole observation period. For diabetic patients, renal biopsy was performed in those who were suspected to have renal diseases other than diabetic nephropathy, since renal histology rarely provided further information for the treatment decision in diabetic nephropathy. Incomplete records, inadequate biopsies (<10 glomeruli in the specimen for light microscopy when there were no typical findings in immunofluorescence or electron microscopy or absence of a glomerulus in immunofluorescence) and repeat biopsies were excluded. Clinical and pathological data were collected.

Among these 1920 patients, 1523 (79.3%) had hypoalbuminaemia (defined as serum albumin <30 g/L), oedema and/or hyperlipidaemia, and therefore, termed as nephrotic syndrome; 397 (20.7%) did not have hypoalbuminaemia. Further analysis was performed by dividing patients into four groups arbitrarily according to age at the time of renal biopsy (14–24, 25–44, 45–59 and ≥60 years, respectively).

Renal histology

Renal biopsy specimens were forwarded to two pathologists. They were examined by light immunofluorescence and electron microscopy. In light microscopy, they were fixed in 10% buffered formaldehyde, embedded in paraffin, and 2- to 3-μm sections were stained with haematoxylin and eosin, PAS and periodic acid-silver methenamine. The methods for immunofluorescence and electron microscopy were described previously [14]. The pathologic diagnostic criteria have been stable during the 15 study-years. When new entities were recognized or new diagnostic criteria appeared, we updated the previous diagnoses one by one according to the new criteria. For example, when fibrillary glomerulonephritis, immunotactoid glomerulopathy, fibroectin glomerulopathy and collagen III glomerulopathy were first recognized in China in 1998, we retrospectively reviewed and updated the diagnoses of our renal biopsies obtained between January 1993 and December 1998. We also updated diagnoses of FSGS in patients admitted between January 1993 and December 2002, according to new classification criteria for FSGS [15]. Differences in results between the two pathologists were resolved by re-reviewing the biopsy slides and coming to a consensus.

Statistical analysis

The percentage and mean ± SE of the mean were used to describe categorical and continuous variables, respectively. The χ² and Fisher’s exact test were used to compare qualitative variables. P-values of <0.05 were considered to be statistically significant. All the statistics were done by SPSS software (SPSS11.0, Chicago, IL).

Results

General data

Among the 1523 patients with nephrotic syndrome, 847 (55.6%) were male, 676 (44.4%) were female, with an average age of 37.7 ± 16.0 (range 14–81) years at the time of renal biopsy. One thousand-and-five (66.0%), 509 (33.4%) and 9 (0.6%) patients were diagnosed as primary, secondary and hereditary glomerulonephritis, respectively. The urinary protein was 7.8 ± 4.5 (range 3.5–40.0) g/24 h. The level of albumin was 22.4 ± 4.8 g/L. The level of serum creatinine was 135.5 ± 93 μmol/L. Eight hundred and fifty-two of 1523 patients (55.9%) had microscopic or gross haematuria. Fifty-nine of 1523 (3.87%) patients had diabetes. The median interval between onset of the disease and renal biopsy was 3.0 (range 0.1–420) months. The average number of glomeruli was 25.2 ± 12.7 in each renal biopsy specimen. All the specimens were examined by light and immunofluorescence microscopy, and 1465 (96.2%) specimen were examined by electron microscopy.

The most common cause of nephrotic syndrome was IMN (20.7%), followed by MCD (20.4%), LN (16.0%), IgAN (10.5%), hepatitis B virus-associated glomerulonephritis (HBVGN, defined as membranous nephropathy with glomerular deposition of HBV-antigen-containing immune complexes [16]) (10.5%) and non-IgA MsPGN (7.88%) (Table 1). Among the 120 patients with non-IgA MsPGN, the profile of immunoglobulin depositions in immunofluorescence microscopy was as follows: on a scale of 0–4+, 84, 21, 12 and 3 were graded as 0, 1+, 2+ and 3+ of IgG staining; 98, 21 and 1 were graded as 0, 1+ and 2+ of IgA staining; 56, 27, 34 and 3 were graded as 0, 1+, 2+ and 3+ of IgM staining, respectively. Among the 1363 patients whose pathological diagnosis was not HBVGN, the prevalence of HBV infection was 3.67% (the prevalence of HBV infection in the general public in China is ~7.5% [17]).

The difference in the renal histopathological spectrum between nephrotic patients with and without hypoalbuminaemia is listed in Table 1. The proportion of IgAN in patients without hypoalbuminaemia was significantly higher than that in patients with hypoalbuminaemia (P < 0.001), which was consistent with our previous finding [12]. On the other hand, the proportion of MCD, LN and renal amyloidosis in patients without hypoalbuminaemia was significantly lower than that in patients with hypoalbuminaemia (P < 0.001, P < 0.001, P < 0.05, respectively).

The histopathological spectrum of patients with nephrotic syndrome at different ages

The spectrum of nephrotic syndrome in different age stratification groups was significantly different (P < 0.001). Among the patients between 14 and 24 years old, the most common cause of nephrotic syndrome was MCD (33.0%) (Table 2). Further analysis showed that there was also significant difference in the disease spectrum of nephrotic

### Table 1. Difference of renal histopathological spectrum between nephrotic syndrome and nephrotic-range proteinuria without hypoalbuminaemia

<table>
<thead>
<tr>
<th>Serum albumin</th>
<th>IgAN</th>
<th>Non-IgA MsPGN</th>
<th>FSNG</th>
<th>IMN</th>
<th>LN</th>
<th>HBVGN</th>
<th>HSPGN</th>
<th>Renal amyloidosisb</th>
<th>MPGN</th>
<th>DNG</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30 g/L, (n = 397)</td>
<td>142 (35.8%)</td>
<td>36 (9.1%)</td>
<td>14 (3.5%)</td>
<td>73 (18.4%)</td>
<td>36 (9.1%)</td>
<td>30 (7.6%)</td>
<td>9 (2.3%)</td>
<td>2 (0.5%)</td>
<td>3 (0.76%)</td>
<td>3 (0.76%)</td>
<td>20 (5.0%)</td>
</tr>
<tr>
<td>&lt; 30 g/L, (n = 1523)</td>
<td>160 (10.5%)</td>
<td>120 (7.9%)</td>
<td>63 (4.1%)</td>
<td>316 (20.7%)</td>
<td>244 (16.0%)</td>
<td>160 (10.5%)</td>
<td>29 (1.9%)</td>
<td>41 (2.7%)</td>
<td>16 (1.1%)</td>
<td>11 (0.72%)</td>
<td>52 (3.4%)</td>
</tr>
</tbody>
</table>

P < 0.001

MCD, IgAN, Non-IgA MsPGN, FSNG, IMN, LN, HBVGN, HSPGN, Renal amyloidosisb, MPGN, DNG, Others

aMPGN, membranoproliferative glomerulonephritis.
bAmong the 43 patients with renal amyloidosis, 42 were classified as light chain amyloidosis (AL amyloidosis) and 1 was classified as amyloid A (AA) amyloidosis.
mainly serving the following provinces (or cities): Beijing, clinical nephrology referral centre in Northern China, although this is a study from a single centre, it is the largest renal biopsy in our single centre during the last 15 years. A characteristic feature of the disease spectrum of nephrotic syndrome of different ages and genders who received a renal biopsy in our single centre during the last 15 years. This is a study from a single centre, it is the largest clinical nephrology referral centre in Northern China, mainly serving the following provinces (or cities): Beijing, Tianjin, Hebei, Henan, Shandong, Shanxi, Inner Mongolia, Liaoning, etc. More than 70% of the patients were referrals. Among the whole group of patients with nephrotic syndrome, the most common pathological type was IMN, followed by MCD. This is similar to results from some other countries including Spain [5], Italy [19] and United Arab Emirates [20], but different from Denmark [21] and Japan [22], where the most common cause of nephrotic syndrome was MCD, followed by IMN. One of the possible reasons is that the current study did not include patients <14 years old; therefore, the proportion of patients with MCD was underestimated. Another reason might be the different indication of renal biopsies. For example, in our centre, for young patients with primary nephrotic syndrome and without nephritis syndrome, corticosteroids are often employed before renal biopsy. In that circumstance, renal biopsy is only indicated for those who do not respond to corticosteroids. Therefore, the proportion of MCD, proven by renal biopsy, is lower than that in some other countries.

Another feature of the disease spectrum of nephrotic syndrome in the current study was that the proportion of IgAN was much higher in the current study than that in some other countries such as Spain [5] and Italy [19]. This was consistent with the result of our previous observations in that IgAN is the most common type of glomerulopathy in Chinese patients [14, 23]. As was expected, MCD and IMN was the main cause of nephrotic syndrome among patients aged 14–24 and ≥60 years old, respectively. However, it was somewhat unexpected that among patients of 25–44 years old, LN was the most common cause of nephrotic syndrome. Further analysis showed that the reason lay in the female patients of 25–44 years old, and thus, LN was the leading cause of nephrotic syndrome. It was also the case in the female patients aged 14–24 years old.

The proportion of patients with renal amyloidosis increased in parallel with patient age. Especially in older patients (≥60 years), renal amyloidosis constituted nearly one-tenth of patients with nephrotic syndrome. Since the treatment of renal amyloidosis is totally different from that of primary nephrotic syndrome, this finding highlighted the necessity of renal biopsy in older patients with nephrotic syndrome.

### Discussion

In China, glomerulopathy is still the leading cause of end-stage renal disease [18], and heavy proteinuria, if untreated, is an independent predictor for poor renal outcomes. The disease spectrum of nephrotic syndrome has rarely been studied in Chinese patients. The current study analysed the renal histopathological spectrum of patients with nephrotic syndrome of different ages and genders who received a renal biopsy in our single centre during the last 15 years. Although this is a study from a single centre, it is the largest clinical nephrology referral centre in Northern China, mainly serving the following provinces (or cities): Beijing, Tianjin, Hebei, Henan, Shandong, Shanxi, Inner Mongolia, Liaoning, etc. More than 70% of the patients were referrals.

### Table 2.

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>14–24 year, (n = 382), (number and %)</th>
<th>25–44 year, (n = 662), (number and %)</th>
<th>45–59 year, (n = 290), (number and %)</th>
<th>≥60 year, (n = 189), (number and %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCD</td>
<td>126 (33.0)</td>
<td>116 (17.5)</td>
<td>39 (13.4)</td>
<td>30 (15.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgAN</td>
<td>57 (14.9)</td>
<td>81 (12.2)</td>
<td>14 (4.8)</td>
<td>8 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-IgA MsPGN</td>
<td>34 (8.9)</td>
<td>70 (10.6)</td>
<td>12 (4.1)</td>
<td>4 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSGS</td>
<td>27 (7.1)</td>
<td>24 (3.6)</td>
<td>5 (1.7)</td>
<td>7 (3.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>IMN</td>
<td>12 (3.1)</td>
<td>114 (17.2)</td>
<td>110 (37.9)</td>
<td>80 (42.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LN</td>
<td>63 (16.5)</td>
<td>152 (23.0)</td>
<td>22 (7.6)</td>
<td>7 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBVGN</td>
<td>27 (7.1)</td>
<td>63 (9.5)</td>
<td>44 (15.2)</td>
<td>26 (13.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>HSPGN</td>
<td>18 (4.7)</td>
<td>6 (0.9)</td>
<td>5 (1.7)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal amyloidosis</td>
<td>0 (0)</td>
<td>7 (1.1)</td>
<td>19 (6.6)</td>
<td>15 (7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Others</td>
<td>18 (4.7)</td>
<td>29 (4.4)</td>
<td>20 (6.9)</td>
<td>12 (6.3)</td>
<td></td>
</tr>
</tbody>
</table>
The proportion of patients with HBVGN in the current study was much higher than that in reports from Nanjing, China [13,24]; in particular, Li et al. [13] reported that HBVGN constituted \(<1\%\) of patients with secondary glomerulonephritis. There were two possible reasons for this discrepancy. Firstly, the current study focussed on patients with nephrotic syndrome rather than patients with glomerulonephritis, and patients with HBVGN were likely to have heavy proteinuria [16]. So the proportion of patients with HBVGN in the current study was higher than the study from Nanjing. Secondly, as a referral centre, the area served by our hospital is less developed than that served by the hospital in Nanjing, which might contribute to the relatively ‘high’ proportion of patients with HBVGN in the current study.

In contrast to IgAN, nephrotic patients with MCD, LN and renal amyloidosis were more likely to have hypoalbuminaemia, indicating different mechanism for developing hypoalbuminaemia in different type of glomerulopathy [25].

There were some biases in the current study, mainly due to the indication of renal biopsy. Firstly, as stated above, the proportion of MCD especially in young people was underestimated. Secondly, in the current study, there were few patients with diabetic nephropathy, which is one of the most common causes of nephrotic-range proteinuria in the elderly [26]. This is because in our centre, patients with established diagnosis of diabetic nephropathy will not receive renal biopsy, since the renal histology will rarely provide further information for the treatment decision. In the current study, 59 diabetic patients received renal biopsy, and 45 (76.3\%) were diagnosed with non-diabetic nephropathy. Moreover, although the data of the current study were from a large referral centre, it is difficult to identify the true incidence or prevalence of nephrotic syndrome in this area.

In conclusion, the renal histopathological spectrum of nephrotic syndrome differs in varies ages. MCD, LN and IMN were the main cause of nephrotic syndrome among

The proportion of patients with HBVGN in the current study was much higher than that in reports from Nanjing, China [13,24]; in particular, Li et al. [13] reported that HBVGN constituted \(<1\%\) of patients with secondary glomerulonephritis. There were two possible reasons for this discrepancy. Firstly, the current study focussed on patients with nephrotic syndrome rather than patients with glomerulonephritis, and patients with HBVGN were likely to have heavy proteinuria [16]. So the proportion of patients with HBVGN in the current study was higher than the study from Nanjing. Secondly, as a referral centre, the area served by our hospital is less developed than that served by the hospital in Nanjing, which might contribute to the relatively ‘high’ proportion of patients with HBVGN in the current study.

In contrast to IgAN, nephrotic patients with MCD, LN and renal amyloidosis were more likely to have hypoalbuminaemia, indicating different mechanism for developing hypoalbuminaemia in different type of glomerulopathy [25].

There were some biases in the current study, mainly due to the indication of renal biopsy. Firstly, as stated above, the proportion of MCD especially in young people was underestimated. Secondly, in the current study, there were few patients with diabetic nephropathy, which is one of the most common causes of nephrotic-range proteinuria in the elderly [26]. This is because in our centre, patients with established diagnosis of diabetic nephropathy will not receive renal biopsy, since the renal histology will rarely provide further information for the treatment decision. In the current study, 59 diabetic patients received renal biopsy, and 45 (76.3\%) were diagnosed with non-diabetic nephropathy. Moreover, although the data of the current study were from a large referral centre, it is difficult to identify the true incidence or prevalence of nephrotic syndrome in this area.

In conclusion, the renal histopathological spectrum of nephrotic syndrome differs in varies ages. MCD, LN and IMN were the main cause of nephrotic syndrome among
younger patients, and IMN were the main cause of nephrotic syndrome among older patients. The proportion of patients with renal amyloidosis increased in parallel with patient age.

Acknowledgements. This study is supported by a grant of the National Natural Science Fund (No. 30972733).

Conflict of interest statement. None declared.

References


Received for publication: 5.9.10; Accepted in revised form: 6.3.11