The changing pattern of adult primary glomerular disease

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Abstract

Background. Published biopsy series have shown geographical and temporal variations in the patterns of primary glomerulonephritis (GN). IgA nephropathy is the most common type of GN in most European studies, but there is evidence suggesting that focal segmental glomerulosclerosis (FSGS) is increasingly common in the USA in all ethnic groups. We report the analysis of 30 years of native renal biopsies and the temporal pattern of primary glomerular disease in a single United Kingdom (UK) region.

Methods. All 1844 adult native kidney biopsies for 30 years (1976–2005 inclusive) were analysed. The data were divided into three 10-year time frames, and trends in the biopsy rate and diagnosis of primary glomerular disease were considered.

Results. Biopsy rates increased significantly from 2.02 to 7.08 per hundred thousand population per year (php/year) ($\chi^2 = 55.9, P < 0.001$), and the mean patient age at biopsy rose from 33 to 49 years over the study period ($F = 58, P < 0.001$). Primary GN was documented in 49% of biopsies; the most common diagnoses within this group were IgA nephropathy (38.8%), membranous nephropathy (29.4%), minimal change disease (9.8%), membranoproliferative GN type 1 (9.6%) and FSGS (5.7%). There was a significant increase in the proportion of IgA nephropathy ($\chi^2 = 9.6, P = 0.008$) and a decrease in membranous nephropathy ($\chi^2 = 7.2, P = 0.03$) over time. The population incidence of FSGS was low and unchanged at 0.18 php/year from 1986 to 2005.

Conclusions. Consistent with several other European studies, IgA nephropathy was the most common primary glomerular disease in this UK region. The diagnosis of FSGS was uncommon with no evidence of a rise in incidence.

Keywords: glomerular disease epidemiology; glomerulonephritis incidence; renal biopsy; renal pathology

Introduction

Publications from several renal biopsy databases have reported that a primary glomerular disorder is present in approximately half of all native renal biopsies; however, there is marked variation both geographically and temporally in the proportions of different glomerulopathies that comprise this group. Of particular note is the increasing incidence of focal segmental glomerulosclerosis (FSGS) reported in the USA, Brazil and India [1–7] making this the most common identified primary glomerulopathy in some centres. A higher incidence of FSGS in African Americans is well recognized, but some reports have documented a significant increase in this renal diagnosis in Caucasian individuals as well as in African American and Hispanic populations [3,4].

In most European studies, IgA nephropathy is the most common histologically diagnosed primary renal disease [8–12], although membranous nephropathy [13] or membranoproliferative glomerulonephritis (MPGN) [14] is reported as the most frequent primary glomerulopathy in some countries. However, direct comparisons between such studies are limited by different reporting methods both of the histological specimens and of the statistical analyses.

There are limited published data on biopsy-proven renal disease in the United Kingdom (UK). Northern Ireland is a geographically distinct region of the UK with a stable, almost entirely Caucasian, population of ~1.7 million and very low migration rates. All renal histological assessments are performed at a single centre. It is ideally suited for following trends in histologically determined renal disease. We report the analysis of 30 years of native renal biopsies and the temporal pattern of primary glomerular disease in this UK region.

Methods

Histological specimens

All adult native kidney biopsies performed in Northern Ireland from 1 January 1976 until the 31 December 2005 inclusive were analysed. Adults were defined as 16 years of age or older. Those biopsy reports
without an accompanying valid date of birth, to enable their age at the time of biopsy to be calculated were excluded.

**Histological assessment**
Renal services in Northern Ireland are delivered by a Regional Nephrology Unit in Belfast City Hospital and five sub-regional units. All renal biopsy specimens are analysed at a central pathology laboratory in the Department of Pathology, Belfast City Hospital. Over the study period (1976–2005), three consultant histopathologists with a special interest in renal pathology have provided the interpretation of all biopsy specimens. The reports are forwarded to a lead clinician who records them in a central database.

All biopsy specimens were analysed by light microscopy. Immunofluorescence has been used routinely in our institution since 1973 in the analysis of renal histology and was available for 97% of specimens in this study. Electron microscopy was not routinely performed. Overall, 43% of biopsy samples in this series were examined by electron microscopy.

**Histological diagnoses**
The histological findings were classified according to the European Dialysis and Transplant Association (EDTA) diagnostic codes. They were categorized for the purpose of this analysis as primary GN, secondary GN, tubulointerstitial disease, vascular disease, miscellaneous diagnoses and no defined histological diagnosis. Primary glomerulonephritis (GN) included IgA nephropathy, membranous nephropathy, FSGS, minimal change disease (MCD), MPGN type 1 and type 2 and unclassified GN. Secondary GN included vasculitis, Goodpasture’s disease, amyloid deposition, diabetic nephropathy, lupus nephritis, post-infectious GN and unspecified glomerulonephritis. Specimens with the pathological lesion of FSGS with proteinuria exceeding 1 g and no clear secondary cause were classified as primary FSGS. Those patients with less than 1 g proteinuria or an identified potential secondary cause of FSGS were categorized as ‘unspecified glomerulosclerosis’. Secondary causes of the other forms of GN were distinguished from primary disease on the basis of clinical and histological information. The interpreting pathologist had a clinical summary available at the time of biopsy. This strategy identified the majority of secondary causes of GN. It is accepted that some clinical features may not be initially apparent (for example, undetected malignancy associated with membranous nephropathy), but if such information was available at a later date then the lead clinician maintaining the renal biopsy database amended the designation of the glomerulopathy from primary to secondary. The number of ‘unrecognized’ secondary glomerulopathies is likely to be small and unlikely to negate the main findings of this study.

**Time periods**
The data were divided into three inclusive 10-year time frames: 1976–85, 1986–95 and 1996–2005. The population at the midpoint of each 10-year period (1981—1.54 million, 1991—1.69 million) [15] was used to determine the biopsy rates. These data were retrieved from the Northern Ireland Statistics and Research Agency [15]. The adult population aged 16 years or older was used to calculate the incidence of each primary glomerulopathy (1981: 1.10 million, 1991: 1.19 million, 2001: 1.29 million) [15].

**Statistics**
Numerical variables in descriptive analysis were reported as mean ± standard deviation, or median (interquartile range) as appropriate to their distribution.

Statistical analysis was performed using the chi-square test and Fisher’s exact test for categorical variables, and the one-way analysis of variance for continuous variables. P-values <0.05 were considered statistically significant.

SPSS for Windows® (SPSS® Inc., Chicago, IL, USA) version 15.0 was employed for all analyses.

**Results**

**Demographics**
A total of 2128 native renal biopsy results were recorded, of which 2111 (99.2%) had a recorded date of birth and 1844 were from persons at least 16 years old at the time of biopsy. In this adult cohort, there were 1126 (61%) men. The oldest person was 92 years at time of biopsy. In this adult cohort, there were 1126 (61%) men. The mean age was 49 ± 17.8 years.

**Trends in biopsy practice**

**Frequency of renal biopsy.** Overall biopsy rates increased significantly from 2.02 per hundred thousand population per year (php/year) in the decade 1976–85 to 3.86 php/year in the period 1986–95 and 7.08 php/year in the final era 1996–2005 (χ² = 55.9, P < 0.001).

**Age at time of biopsy.** The average age of adults who had a native renal biopsy increased progressively from 40 ± 16 years in the first decade to 47 ± 17 years in the second and 52 ± 17 years in the third. This was statistically significant (F = 58, P < 0.001). The percentage of patients older than 65 years rose from 5% in the years 1976–85 to 26% in the period 1996–2005.

**Diagnostic categories.** Overall 907/1844 (49%) of adult biopsies had a primary glomerular disease (Table 1) and this proportion was comparable across all three decades (χ² = 0.14, P = 0.94). There were fewer histological specimens that could not be defined into a diagnostic category in the final time period, a decrease from 17% in 1976–85 to 7% in 1996–2005 (χ² = 6.0, P = 0.05). The diagnosis of both tubulointerstitial disease (χ² = 8.9, P = 0.01) and vascular disease (χ² = 10.3, P = 0.006) rose significantly over the study period, whereas the proportion of specimens with secondary glomerular disease (χ² = 1.5, P = 0.48) and miscellaneous diagnoses (χ² = 2.2, P = 0.33) remained constant. The category of vascular disease primarily comprised hypertensive nephrosclerosis without evidence of an underlying glomerular or tubulointerstitial disease.

**Primary glomerular disease**

**Overall.** Overall IgA nephropathy was the most common primary GN histologically diagnosed accounting for 39% of cases (Table 2). Membranous nephropathy was the next most frequent GN diagnosis (29%), followed by minimal change nephropathy (10%), MPGN type 1 (10%), FSGS (6%) and MPGN type 2 (1%).

**Trends with time.** IgA nephropathy and membranous nephropathy combined have accounted for at least two-thirds of all primary GN in each of the time periods.
considered (Table 2). However, there was a significant decrease in the proportion with a diagnosis of membranous nephropathy ($\chi^2 = 7.2, P = 0.03$) and a corresponding increase in the proportion of IgA nephropathy ($\chi^2 = 9.6, P = 0.008$). Membranous disease was the most common primary GN in the era 1976–85, but IgA nephropathy gained parity in terms of proportion of histological diagnoses in the middle decade, and surpassed it to be the most frequent primary GN in the final study period. The proportion of MPGN type 1 increased marginally over the study period ($\chi^2 = 4.4, P = 0.11$), while that of type 2 significantly decreased ($\chi^2 = 16.5, P < 0.001$). There were no significant differences in the percentage of primary GN due to MCD ($\chi^2 = 2.3, P = 0.32$). The change in FSGS as a proportion of primary GN just reached statistical significance ($\chi^2 = 6.4, P = 0.04$) over the study period and this was analysed further.

### Trends in FSGS.

The incidence of biopsy-proven primary FSGS is low in our region and has remained so over the 30 years of this study. There was a higher proportion of histologically diagnosed primary GN due to FSGS in the period 1986–95. This period was significantly different from the final decade when the proportion of biopsy-proven FSGS decreased to 4% of all primary GN ($\chi^2 = 6.3, P = 0.01$). However, the population incidence was the same in these two eras at 0.18 cases per hundred thousand adult (aged 16 or over) population per year (Table 3). The numbers were too small to permit valid analyses of different histological subtypes of FSGS.

### Trends with age.

Data from this population are consistent with the reported differences in frequency of primary renal disease with patient age (Table 3). MCD was most commonly diagnosed in the youngest age group of 16–25 years (24/89, 27%); subsequently, there was a steady decline in incidence with 7/89 (8%) diagnosed in those >65 years. The peak incidence of IgA nephropathy was in the 26–35-year age category with more than a quarter of all cases (92/365, 26%). Membranous nephropathy was the most common diagnosis in those aged over 45 years and accounted for 56/96 (58%) of all primary GN in those >65 years. FSGS incidence peaked in middle-aged individuals with 15/52 (29%) of cases occurring between the ages of 46 and 55 years. Type 2 MPGN had the lowest mean age at the time of diagnosis of 25 years, although the numbers in this category were small.

### Discussion

Renal biopsy series from single regions or national databases have provided insights into the epidemiology of renal disease; there is evidence of geographical, racial and temporal variations in the diagnosis of primary GN [1–14,16–24].

In our region, over the 30-year period of the study, there were significant changes in the type of primary glomerular disease with a rise in the proportion of IgA nephropathy being mirrored by a fall in the proportion with membranous nephropathy. In the final period (1996–2005), IgA nephropathy accounted for 43% of all primary GN. This is consistent with other European countries, some Asian countries and Australia, most of which report IgA nephropathy as the most common GN [8–12,18,19,24]. In some regions of the USA, IgA nephropathy was documented most frequently [4] but not in others [2,3]. In India, IgA nephropathy made up >10% of the primary GN lesions [7]; in Thailand, the incidence of IgA nephropathy was almost 18%, but IgM nephropathy was more common [17]; in Korea, IgA nephropathy was recorded in 22% of primary GN biopsies, second in frequency to MCD [18]; while in China the proportion of IgA nephropathy was comparable to our region at just over 45% [19,24], and is increasing [24].

It is possible that the increased frequency of IgAN over time may be due in part to a greater willingness of nephrologists to biopsy patients with isolated haematuria. The procedure has become safer over time with improvements in technique such as the use of real-time ultrasound. However, we did not find an increase in the incidence rate of thin basement membrane disease (TBMD) over the 30-year period of this study, suggesting that the epidemiology of GN is not being appreciably altered by any change in physician practice resulting in higher biopsy rates of individuals with isolated microscopic haematuria and low-grade proteinuria. Nevertheless, the relatively limited use of electron microscopy analysis over the three decades may have

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<tr>
<td></td>
<td>n (%)</td>
<td>Incidence</td>
<td>n (%)</td>
<td>Incidence</td>
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<tr>
<td></td>
<td>php/year</td>
<td></td>
<td>php/year</td>
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<tr>
<td>IgA nephropathy</td>
<td>37 (32)</td>
<td>0.34</td>
<td>84 (33)</td>
<td>0.71</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>43 (37)</td>
<td>0.39</td>
<td>83 (33)</td>
<td>0.70</td>
</tr>
<tr>
<td>MCD</td>
<td>11 (9)</td>
<td>0.10</td>
<td>19 (8)</td>
<td>0.16</td>
</tr>
<tr>
<td>FSGS</td>
<td>7 (6)</td>
<td>0.06</td>
<td>22 (9)</td>
<td>0.18</td>
</tr>
<tr>
<td>MPGN type 1</td>
<td>5 (4)</td>
<td>0.05</td>
<td>26 (10)</td>
<td>0.22</td>
</tr>
<tr>
<td>MPGN type 2</td>
<td>5 (4)</td>
<td>0.05</td>
<td>3 (1)</td>
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<tr>
<td>Unclassified GN</td>
<td>9 (8)</td>
<td>0.15</td>
<td>15 (6)</td>
<td></td>
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</tbody>
</table>

php, per hundred thousand adult (aged 16 or over) population per year; MCD, minimal change disease; FSGS, focal and segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; GN, glomerulonephritis.
lead to an underestimate of TBMD especially in the category ‘no defined diagnosis’.

Interestingly, despite membranous nephropathy being the most common primary GN in older patients (>55 years) and the rising age of the population being biopsied in our region, the proportion of primary GN due to membranous disease fell significantly. The reason for this is unclear, but this trend has also been documented by others [2]. However, the literature is inconsistent as no significant change [4] and an increase in frequency of membranous nephropathy [8] have also been reported.

FSGS is of particular interest given the rise in incidence in the USA [2,3,4,20]. This has not been reported from Europe where the incidence of biopsy-proven primary FSGS remains low with no evidence of a temporal increase in the frequency of diagnosis. It has been well documented that the rates of FSGS are higher in the African American population [20]. More recent data have suggested that the incidence of FSGS within Caucasian populations in the USA is also increasing [1,2,4]. Swaminathan and colleagues reported that from 1974 to 2003, the proportion of FSGS increased from 2.9% to 20% in the Caucasian population in Minnesota. In contrast, our data from a Caucasian population in Northern Europe revealed a relatively low incidence of FSGS remaining unchanged over the past two decades at 0.18 php/year.

The reasons for the differing patterns in renal biopsy epidemiology are unclear. It seems improbable that there is any substantial difference in the diagnosis or differentiation of FSGS from other primary glomerular diseases. There has been consistency of both pathological procedure and consultant-led interpretation of biopsy specimens in our region over the study period, and a difference in detection rates was discounted by the authors of other reports that documented an increase in FSGS [2].

Undoubtedly, differing ethnic population proportions may contribute to some of the differences in incidence between Europe and the USA. Our population was over 99% Caucasian, and it is generally accepted that the African American population is at higher risk for FSGS development, presumably in part due to genetic risk factors. Other aetiological factors such as lower birth weights in this group leading to reduced nephron mass in addition to an increased predisposition to hypertension and diabetes mellitus may increase their risk of FSGS. However, the increase in incidence of FSGS reported in both Hispanic and White American populations suggests that there may be an unidentified environmental risk factor that is contributing to the changing epidemiology in the USA.

There are a number of well-documented causes of secondary FSGS including infections such as human immunodeficiency virus (HIV) and obesity. Interestingly, Northern Ireland has very low rates of human immunodeficiency virus infection (0.02% [25] versus 0.6% [26] in USA) and lower rates of obesity (17% [27] versus 30% [28]) than the USA. It is unlikely that the variation in proportion of primary FSGS can be explained by a failure to identify known causes of secondary FSGS. However, there is clear evidence of a higher incidence of known risk factors for secondary FSGS in the USA, and it is plausible that there are other, as yet unidentified, aetiological factors that are also more common in North America.

Comparing biopsy data between different centres and registries is complicated by factors such as biopsy rates, methods of disease classification and data analyses. There are substantial differences in biopsy rates between countries (Table 4). It could be argued that a fee-for-service funded health system may result in relatively higher biopsy rates, and in the USA, the rate of renal biopsy is indeed greater than in most European studies including this one. The renal biopsy rate has increased 3.5-fold in our region over the

### Table 3. Gender and age characteristics of primary glomerular diseases

<table>
<thead>
<tr>
<th>Gender</th>
<th>IgA</th>
<th>Mem</th>
<th>MCD</th>
<th>FSGS</th>
<th>MPGN type 1</th>
<th>MPGN type 2</th>
<th>MCD</th>
<th>FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Mean</td>
<td>39.6</td>
<td>52.6</td>
<td>40.1</td>
<td>48.0</td>
<td>43.8</td>
<td>24.9</td>
<td>64</td>
<td>48.0</td>
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<tr>
<td>16-25 n (%)</td>
<td>77 (54)</td>
<td>24 (17)</td>
<td>16 (10)</td>
<td>4 (3)</td>
<td>11 (7)</td>
<td>2 (1)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>26-35 n (%)</td>
<td>92 (57)</td>
<td>35 (22)</td>
<td>11 (7)</td>
<td>4 (3)</td>
<td>11 (7)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td></td>
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<tr>
<td>36-45 n (%)</td>
<td>64 (44)</td>
<td>40 (27)</td>
<td>15 (10)</td>
<td>11 (7)</td>
<td>11 (7)</td>
<td>1 (1)</td>
<td>14 (7)</td>
<td></td>
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<tr>
<td>46-55 n (%)</td>
<td>51 (34)</td>
<td>54 (36)</td>
<td>18 (12)</td>
<td>15 (10)</td>
<td>15 (10)</td>
<td>0 (0)</td>
<td>15 (7)</td>
<td></td>
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<tr>
<td>&gt;65 n (%)</td>
<td>48 (30)</td>
<td>69 (43)</td>
<td>13 (8)</td>
<td>10 (6)</td>
<td>13 (8)</td>
<td>0 (0)</td>
<td>15 (7)</td>
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</table>

Table 4. International biopsy rates per hundred thousand population per year

<table>
<thead>
<tr>
<th>Country</th>
<th>Biopsy rate</th>
<th>Years</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>8.2</td>
<td>1990–94</td>
<td>Stratta et al [12]</td>
</tr>
<tr>
<td>Italy</td>
<td>3.3</td>
<td>1987–93</td>
<td>Schena et al [9]</td>
</tr>
<tr>
<td>Spain</td>
<td>4.8</td>
<td>1994–99</td>
<td>Rivera et al [8]</td>
</tr>
<tr>
<td>Denmark</td>
<td>3.9</td>
<td>1985–97</td>
<td>Haff et al [25]</td>
</tr>
<tr>
<td>Romania</td>
<td>1.1</td>
<td>1995–2004</td>
<td>Covic et al [14]</td>
</tr>
</tbody>
</table>
study period; it is now comparable with other European centres.

While using the incidence per population as a measure of disease allows more useful comparison of data across different reports, this does not obviate the need to consider the variation in biopsy practices. All studies of biopsy-proven GN will underestimate the true incidence of disease, as not all patients with GN will have this invasive diagnostic procedure performed. Our data, as with other registry reports, would be enhanced if the clinical features of those with possible primary GN who were not biopsied were known. However, even without this information, it is reasonable to assume that in countries with lower rates of renal biopsy people with mild disease are less likely to have histological records and therefore the incidence per population reflects those with moderate or severe disease. While this may explain some of the variation across countries, it does not account for the changing trends noted within some countries; an increasing willingness over time to biopsy those with milder clinical features may be in part responsible for changing population incidence in certain glomerular diseases within a region.

The reporting of longitudinal renal biopsy data from single centres or national registries is a useful tool in assessing the changing pattern of renal disease. While often limited by a dearth of clinical details and variability in renal biopsy practices across countries, there is evidence to suggest a divergence in the pattern of primary GN even within comparable ethnic groups in different continents. This suggests the presence of an, as yet, unidentified environmental factor(s) that has a clinically significant impact on primary renal disease.

Acknowledgements. AEC is supported by a Northern Ireland Kidney Research Fund Clinical Fellowship. We thank Dr Claire Hill and Dr Moyra Gray for access to renal biopsy reports.

Conflict of interest statement. None declared.

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