ORIGINAL ARTICLE

A Clinical and Pathological Analysis of 3722 Renal Biopsy Specimens from Adults with Primary Glomerular Disease in Shandong Province, China

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ABSTRACT

Objectives: *To determine the pattern of disease in adults with primary glomerular diseases (PGD) in the Shandong Province of China, to identify the clinical and renal pathology and to assess the relationship between these two factors.*

Methods: *This was a retrospective analysis of renal biopsies performed during the period January 2008 to June 2013. All biopsy specimens were evaluated according to the clinical data available and standard histological methods; the results were analysed according to age and clinical findings.*

Results: *A total of 3722 renal biopsies from adults with PGD were analysed. Nephrotic syndrome and nephritic syndrome were the two most common indications for biopsy among all PGD cases. The most common form of primary glomerulonephritis was due to immunoglobulin A (IgA) nephropathy (37.72%), followed by membranous glomerulonephritis (27.57%), minimal change disease (16.42%), focal segmental glomerulosclerosis [FSGS] (8.79%) and mesangioproliferative glomerulonephritis [Non IgA] (5.05%). The most common cause of nephrotic syndrome was membranous nephropathy (44.00%). Immunoglobulin A nephropathy was the leading cause of nephritic syndrome, asymptomatic urinary abnormalities and chronic renal failure. Crescentic glomerulonephritis was the pathological type associated with an older age group, whereas minimal change disease was the pathological type associated with a younger age group. Over the six years analysed, membranous glomerulonephritis showed a significant per cent increase, minimal change disease did not significantly vary and FSGS decreased slightly.*

Conclusions: *Nephrotic syndrome was the most common indications for biopsy among all PGD cases. The most common form of primary glomerulonephritis was due to IgA nephropathy. Minimal change disease was the pathological type associated with a younger age group. Membranous nephropathy showed a significant per cent increase during the six years.*

Keywords: Immunoglobulin A (IgA) nephropathy, membranous glomerulonephritis, nephrotic syndrome, primary glomerular disease, retrospective analysis

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INTRODUCTION

The proteinuria and elevated serum creatinine levels that result from glomerular disease are associated with cardiovascular morbidity and renal failure. Glomerular disease continues to be the leading cause of end-stage renal disease (ESRD) and is associated with a high morbidity and mortality, as well as with an increase in the financial costs to the healthcare system (1, 2) worldwide. Primary glomerular diseases (PGD), diagnosed by renal biopsy, have been the predominant form of renal disease reported in many studies from China (3), the Kingdom of Bahrain (4) and Senegal (5). This might be explained by the low rate of renal biopsy for secondary glomerular disease. Many doctors believe that once a diagnosis of secondary glomerular disease is established as the clinical diagnosis, treatment can be implemented. However, it is well known that a renal biopsy plays a fundamental role not only in establishing an accurate diagnosis but also in deciding the appropriate treatment and

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prognosis. A number of cases have been diagnosed based only on clinical findings at basic-level hospitals in China; at these institutions, some renal physicians do not perform renal biopsies and some patients might decline such procedures.

The prevalence of biopsy proven glomerulonephritis varies according to race, age, geographic regions, socio-economic conditions and the indications for a renal biopsy. However, there is no valid data on the epidemiology of glomerulonephritis in Shandong, China, to date. Therefore, in order to determine the relationship between the clinical findings and renal pathology of PGD, we collected renal biopsy data from 22 basic-level hospitals in Shandong, China.

SUBJECTS AND METHODS

Native Chinese patients from 22 basic-level hospitals in Shandong, China, were included in this study from January 2008 to June 2013. The indications for renal biopsy included proteinuria, unexplained microscopic or macroscopic haematuria and systemic disease with evidence of renal involvement, and mild-to-moderate renal impairment. All samples were obtained by percutaneous methods using a Tru-Cut® biopsy needle under ultrasound guidance. Patients' age and clinical findings were systematically collected at the time of the renal biopsy. Primary glomerular diseases include the following: nephrotic syndrome, nephritic syndrome, asymptomatic urinary abnormalities, acute renal failure and chronic renal failure. Nephrotic syndrome was diagnosed in patients with proteinuria greater than 3.5 g/24 hours and a serum albumin less than 30 g/L with or without oedema. Nephritic syndrome was diagnosed in patients with haematuria, proteinuria (less than 3.5 g/24 hours) and oedema with or without hypertension (systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg). Asymptomatic urinary abnormalities included patients with persistent proteinuria less than 3.0 g/24 hours with or without microscopic haematuria. Acute renal failure was defined as a rapid decline in renal function and chronic renal failure was considered in patients with serum creatinine levels above 115 μmol/L that persisted for more than six months.

Three renal biopsy specimens were taken from each patient and evaluated by the same pathologist. Sections were made from formalin fixed paraffin embedded tissue and stained by haematoxylin-eosin (HE), periodic-acid Schiff, periodic acid-methenamine silver and Masson's trichrome stains. All biopsies were conventionally processed for light microscopy and immunofluorescence. Immunofluorescence microscopy panels included staining for: IgA, IgM, IgG, C3, C1q and fibrinogen. Electron microscopy was not systematically performed.

Statistical analysis

Data were stored in a database file (Excel 2003). All statistical calculations were carried out with the statistical package SPSS for Windows 17.0. Age is reported as the mean ± standard error (SE). The analysis of variance was used to test the significance of differences. Frequency counts were compared using the Chi-squared test. *P*-values < 0.05 were considered significant.

RESULTS

Among 5115 cases, PGD was the most common finding (n = 3817; 74.93%). In addition to 95 paediatric cases, there were 3722 adult cases of primary glomerulonephritis analysed. Table 1 shows the clinical presentation and the distribution of the various types of primary glomerulonephritis. There was a statistically significant association between the clinical and pathological types of primary glomerulonephritis (X^2 = 2439.77, p = 0.003). Among the 3722 adult renal biopsies, nephrotic and nephritic syndromes were the two most com-

Table 1: Distribution of clinical and pathological correlations of primary glomerular diseases in adults

Pathological type	NS	NiS	AUA	CRF	ARF	Total	Percentage
IgAN	318	718	297	64	7	1404	37.72
MN	795	174	45	10	2	1026	27.57
MCD	456	95	58	1	1	611	16.42
FSGS	116	145	40	26	0	327	8.79
MesPGN	67	81	37	2	1	188	5.05
MPGN	43	16	1	3	1	64	1.72
FGN	5	23	0	22	0	50	1.34
Crescentic GN	6	6	3	8	23	46	1.24
EnPGN	1	5	0	0	0	6	0.16
Total	**1807**	**1263**	**481**	**136**	**35**	**3722**	**100**

X^2 = 2439.77, p = 0.003

NS: nephrotic syndrome; NiS: nephritic syndrome; AUA: asymptomatic urinary abnormalities; CRF: chronic renal failure; ARF: acute renal failure; IgAN: immunoglobulin A nephropathy; MN: membranous glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangioproliferative glomerulonephritis; MPGN: membrano-proliferative glomerulonephritis; FGN: fibrous glomerulonephritis; Crescentic GN: crescentic glomerulonephritis; EnPGN: endocapillary proliferative glomerulonephritis

mon indications for renal biopsies, accounting for 48.55% and 33.93% of all cases, respectively, followed by asymptomatic urinary abnormalities (12.92%), chronic renal failure (3.65%) and acute renal failure (0.94%). The most common histopathological diagnosis for PGD was immunoglobulin A (IgA) nephropathy (n = 1404; 37.72%), followed by membranous glomerulonephritis [MN] (n = 1026; 27.57%), minimal change disease [MCD] (n = 611; 16.42%), focal segmental glomerulosclerosis [FSGS] (n = 327; 8.79%), and mesangioproliferative glomerulonephritis [Non IgA] (n = 188; 5.05%). Diagnoses of membranoproliferative glomerulonephritis (MPGN), fibrous glomerulonephritis, crescentic glomerulonephritis and endocapillary proliferative glomerulonephritis (EnPGN) accounted for less than 5% cases.

The most common cause of nephrotic syndrome was MN (n = 795; 44%), followed by MCD (n = 456, 25.24%) and IgA nephropathy (n = 318, 17.60%). Immunoglobulin A nephropathy was the leading cause of nephritic syndrome, asymptomatic urinary abnormalities and chronic renal failure, accounting for 56.85% (n = 718), 61.75% (n = 297) and 47.06% (n = 64), respectively. The most common cause of acute renal failure was crescentic glomerulonephritis (n = 23; 65.71%).

Table 2 shows the age distribution of the histopathological lesions. There was a statistically significant association between the nine pathological types (F = 21.03, p = 0.001). At the time of the renal biopsies, the mean age of the patients with PGD was 38.50 years (SD 14.159) with a range of 14 to 84 years. Patients with MPGN were the oldest (mean age 46.13 years), followed by those with crescentic glomerulonephritis (mean age 44.59 years) and MN (mean age 42.82 years). The patients with MCD were the youngest (mean age 34.07 years). Table 3 shows a statistically significant association between the four age groups (X^2 = 403.85, p = 0.003). There were 191, 1848, 1353 and 330 patients with PGD in the 14–18-year (teenagers), 19–39-year (youths), 40–59-year (middle-aged people) and the ≥ 60-year (older age) age groups, respectively. Patients 19–59 years of age accounted for 86% of the cases (3201/3722). In the 14–18-year old group, a high incidence of IgA nephropathy was identified (35.60%, 68/191), followed by MCD (28.80%, 55/191), MN (20.42%, 39/191) and MesPGN (6.8%, 13/191), with a much lower incidence of the other PGD cases. In the 19–39-year old group, there was a larger proportion of IgA nephropathy (42.32%, 782/1848), MN (20.35%, 376/1848), MCD (18.61%, 344/1848) and FSGS (10.01%, 185/1848). In the 40–59-year-old group, IgA nephropathy accounted for 35.77% (484/1353), MN for

Table 2: Age distribution of primary glomerular diseases in adults

Pathological type	Case	Age (years) Mean	SD	Min	Max
IgAN	1404	36.95	12.464	14	77
MN	1026	42.82	15.276	14	84
MCD	611	34.07	14.393	14	82
FSGS	327	37.97	12.565	16	76
MesPGN	188	38.05	13.362	14	72
MPGN	64	46.13	16.810	15	78
FGN	50	38.20	14.216	16	81
Crescentic GN	46	44.59	16.094	18	74
EnPGN	6	36.50	21.980	16	64
Total	**3722**	**38.50**	**14.159**	**14**	**84**

F = 21.03, p = 0.001
IgAN: immunoglobulin A nephropathy; MN: membranous glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangioproliferative glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; FGN: fibrous glomerulonephritis; Crescentic GN: crescentic glomerulonephritis; EnPGN: endocapillary proliferative glomerulonephritis.

Table 3: Distribution of primary glomerular diseases according to age group

Pathological type	Age group 14–18 years	19–39 years	40–59 years	≥ 60 years	Total
IgAN	68	782	484	70	1404
MN	39	376	451	160	1026
MCD	55	344	178	34	611
FSGS	7	185	113	22	327
MesPGN	13	94	65	16	188
MPGN	4	20	26	14	64
FGN	2	28	16	4	50
Crescentic GN	1	17	20	8	46
EnPGN	2	2	0	2	6
Total (%)	**191 (5.13)**	**1848 (49.65)**	**1353 (36.35)**	**330 (8.87)**	**3722 (100)**

X^2 = 403.85, p = 0.003
IgAN: immunoglobulin A nephropathy; MN: membranous glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangioproliferative glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; FGN: fibrous glomerulonephritis; Crescentic GN: crescentic glomerulonephritis; EnPGN: endocapillary proliferative glomerulonephritis

33.33% (451/1353), MCD for 13.16% (178/1353), FSGS for 8.35% (113/1353) and MesPGN for 4.80% (65/1353) of the PGD cases. Finally, in the ≥ 60-year old group, MN was the most common form of PGD in 48.48% of the patients (160/330), followed by IgA nephropathy in 21.21% (70/330) and MCD 10.30% (34/330); there were smaller proportions of the other types.

Table 4 shows the annual distribution of the various types of primary glomerulonephritis. There was a statistically significant association among the analysed data for six years [2008–2012 and first half of 2013] (X^2 = 637.85, p = 0.001). The Figure shows the annual percentage change among the pathological types as well as the trend for the changes observed among the nine types over six years. Membranous glomerulonephritis showed a significant percentage increase over six years, IgA nephropathy dramatically increased during the period of study, MCD did not show significant variation, MesPGN dramatically decreased from 2008 to 2013, while there was a slight decrease in FSGS. There was no significant variation in the other types.

Table 4: Annual distribution of primary glomerular diseases in adults

Pathological type	2008	2009	2010	2011	2012	2013	Total
IgAN	207	321	194	234	305	143	1404
MN	70	247	177	170	218	144	1026
MCD	112	137	114	77	117	54	611
FSGS	63	139	49	24	39	13	327
MesPGN	126	49	8	4	0	1	188
MPGN	20	17	9	5	11	2	64
FGN	18	19	8	3	1	1	50
Crescentic GN	18	16	5	0	6	1	46
EnPGN	0	2	2	0	1	1	6
Total (%)	**634 (17.03)**	**947 (25.44)**	**566 (15.21)**	**517 (13.89)**	**698 (18.75)**	**360 (9.67)**	**3722 (100)**

X^2 = 637.85, p = 0.001

IgAN: immunoglobulin A nephropathy; MN: membranous glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangioproliferative glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; FGN: fibrous glomerulonephritis; Crescentic GN: crescentic glomerulonephritis; EnPGN: endocapillary proliferative glomerulonephritis

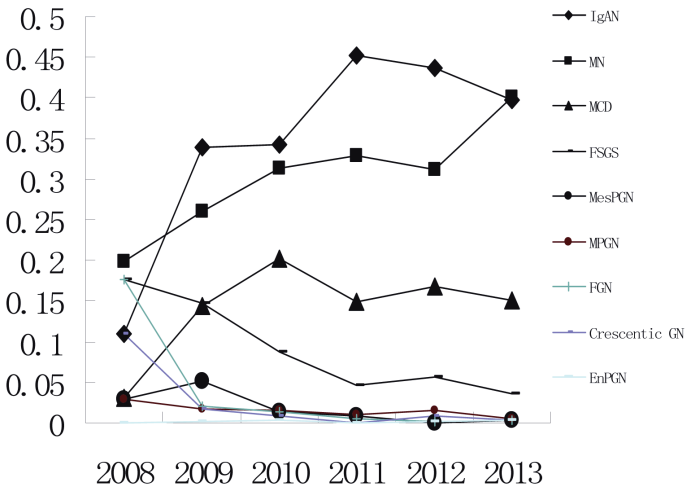

Figure: Annual percentage of primary glomerular diseases in adults. IgAN: immunoglobulin A nephropathy; MN: membranous glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MesPGN: mesangioproliferative glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; FGN: fibrous glomerulonephritis; Crescentic GN: crescentic glomerulonephritis; EnPGN: endocapillary proliferative glomerulonephritis

DISCUSSION

A renal biopsy registry has not yet been established in China. The current study included hospitals such as Jinling Hospital of Nanjing Medical University (3), Peking University First Hospital (6) and the First Clinical Medical College at Harbin Medical University (7). Renal biopsy has been performed on a large scale in the basic-level hospitals of Shandong province since 2006; however, a centralized collection of clinical data, and follow-up of patients after renal biopsy, has not been developed. There has been no single study with a large sample size to demonstrate statistical conclusions in Shandong province. It is well known that a review of renal biopsy data might provide insights into the spectrum of clinically significant renal disease in a given community. Because the diagnosis of secondary glomerular disease mainly depends on clinical as well as renal biopsy pathology examination, data from these evaluations are very meaningful to the diagnosis of primary glomerular nephritis. This study reports on the results of 3722 renal biopsies collected from adults over a period of six years and analysed retrospectively.

Among the primary glomerular diseases, the various conditions differ in incidence among different studies. This survey showed that IgA nephropathy was the most common cause of PGD (37.72%). The high incidence of IgA nephropathy was in accordance with previously published studies from east Asia (8–11), Hungary (12) and western Europe (13). This is in contrast to the results of studies performed in southwestern Asia and northern Africa that have reported a high incidence of FSGS (14–16); a high prevalence of MCD has also been reported from southeastern Asia (17, 18). The criteria used for selecting patients for renal biopsy, as well as geographic and ethnic factors, may account for these variations. Racial differences may explain geographic differences in the frequency of IgA nephropathy; east Asians may be more susceptible to this disease.

The results of this study show that the mean age of patients with IgA nephropathy was 36.95 years, 1.55 years less than the mean age of 38.50 years for the total group. It is well known that IgA nephropathy is more frequent in younger patients and most commonly presents with asymptomatic abnormalities in the urine with normal renal function. On the other hand, a minority of patients have presented with clinical/histological evidence of rapidly progressive glomerulonephritis (19) with rapid progression to ESRD. Therefore, the clinical presentation and prognosis for patients with IgA nephropathy is highly variable (20, 21), which suggests that it may encompass multiple subsets of disease that are not distinguishable by the clinical tools currently available. In other words, immunoglobulin A is not likely pathogenic, but is an important factor. Further studies are needed to improve understanding of the pathophysiology of this disease as well as the precipitating factors; such improvements will likely result in better treatment and improved health status among people living in China.

The primary indication for a renal biopsy in the group studied here was nephrotic syndrome (48.55%). Two possible explanations for this are severe oedema which alerted patients to seek help, and that most patients with nephrotic syndrome had no contraindications to a renal biopsy. Membranous glomerulonephritis was the leading cause of nephrotic syndrome in adults; it was present in 44% of the study patients. Similar observations were reported from Beijing (22) and Spain (23). One possible reason is that children were excluded from the data analysis; the pathology in children was mostly MCD.

The results of this study showed that the young (19–39 years) and middle-aged (40–59 years) patients accounted for most of the cases of PGD (86%) that underwent renal biopsy; older men and teenagers were less likely to have this procedure, as determined by the incidence of PGD and their tolerance for a renal biopsy. Immunoglobulin A nephropathy was the most common pathological type in teenagers, the young and the middle-aged, while MN was more common in older men. According to the data on mean age, as noted in Table 2, crescentic glomerulonephritis was the pathological type associated with the oldest age group, MN came next and MCD was the most common pathological type in the youngest age group. These findings are consistent with a prior study from northeastern China (7). It is well known that patients with crescentic glomerulonephritis and MN are difficult to cure and their prognosis is poor; however, for MCD, the prognosis is good. These findings suggest that an older age of onset is associated with a poorer prognosis.

An important finding of this study, of data collected over six years, was that MN had a significant percentage increase and MesPGN significantly decreased. The same trend has also been observed in Korea (8), Singapore (9), Brazil (24) and Estonia (25). Primary glomerulonephritis was divided into inflammatory glomerulopathies and non-inflammatory glomerulopathies, the former included MesPGN, IgA nephropathy and MPGN, and the latter included MN, MCD and FSGS. The decreased prevalence of inflammatory glomerulopathies is probably associated with better control of chronic persistent viral and bacterial infections. Non-inflammatory glomerulopathies that increased in frequency might be explained by the improvement of living standards and an increase in the average lifespan. This trend has been reported in studies over a long period of time (10–30 years). Whether the changes observed in this study are related to environmental factors or the frequency of infections remains unknown. However, the availability of electron microscopy and technical improvements for diagnosis likely played a major role.

There are several limitations to this study. Firstly, the diagnosis in certain cases, such as in MCD and FSGS, could not be diagnosed with certainty without an electron microscope. Secondly, not all patients with glomerular disease were biopsied so the true prevalence of primary glomerular disease was underestimated. Thirdly, the time span of six years used in this study is relatively short.

In summary, the pattern identified in the data from patients analysed in this study tended to reflect less severe glomerular lesions, mainly due to the criteria used for selection of patients to undergo renal biopsy. To obtain more precise epidemiological data, it will be necessary to establish a National Renal Biopsy Registry with a unified biopsy policy and standardized collection of clinical data as well as follow-up of patients after renal biopsies.

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