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CLINICAL STUDY

Differences in new-onset IgA nephropathy between young adults and the elderly

Yao-Ko Wen[1] and Mei-Ling Chen[2]

[1] *Division of Nephrology, Changhua Christian Medical Center, Changhua, Taiwan*
[2] *Department of Pathology, Changhua Christian Medical Center, Changhua, Taiwan*

ABSTRACT

Background: The goal of this study was to define the clinical and histological differences in new-onset IgA nephropathy between young adults and the elderly. Methods: We retrospectively examined renal biopsy findings, clinical features at presentation and outcomes in 82 young adults (mean age 30.3 ± 10.2 years) and 17 elderly patients (mean age 71.9 ± 4.5 years) with IgA nephropathy whose renal biopsies were taken within 1 year from the onset of renal manifestations. Results: The elderly group more frequently had hypertension ($p < 0.001$), acute renal failure ($p < 0.001$), and nephrotic range proteinuria ($p = 0.001$) at presentation than the young adults group. On histology, a higher percentage of globally sclerotic glomeruli ($p < 0.001$) was present in the elderly group. In patients presenting with acute renal failure, the elderly group more frequently had an intercurrent disease ($p = 0.02$), mostly infection, and a higher mortality rate ($p = 0.033$). On histology, the young adults group had a higher percentage of glomeruli affected by crescents ($p = 0.027$); in contrast, the elderly group more commonly had acute tubular injury ($p = 0.02$). Conclusions: The elderly patients affected by IgA nephropathy had more severe renal manifestations at presentation (acute renal failure in 52.9% and nephrotic syndrome in 41.2% of patients). In cases of acute renal failure, the elderly patients had more predominant tubular rather than glomerular injury. Moreover, the considerable mortality rate (44.4%) might be associated with the intercurrent disease, mostly infection, which was more commonly present in the elderly patients.

Keywords: aged; acute renal failure; IgA nephropathy; renal biopsy; renal disease

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Correspondence: Yao-Ko Wen, Division of Nephrology, Changhua Christian Medical Center, Changhua, Taiwan; fax: +886 4 7228289; E-mail: wensnake1100@yahoo.com.tw

INTRODUCTION

IgA nephropathy may present at any age, but there is a peak incidence in the second and third decades of life, with less commonly occurring in elderly population. Because of a shorter patient life span and a lower disease prevalence, very limited information is available on the nature of elderly IgA nephropathy and the differences from what are described in the young are not known. Improvements in sanitation and health care have led to a worldwide increase in human life expectancies. Simultaneously, lower growth rates in the developed world have contributed to the relative increase in the elderly population. Moreover, with improvement in techniques, the number of renal biopsies has increased annually, even among aged population. As a result, the disease prevalence in the elderly may increase and there may be a longer time to observe the disease course. There are many medical reasons to believe that renal diseases in the elderly are different from that in the young. First, age is associated with many structural and functional changes that lead to diminished renal reserve.[1] Second, increased long-term life expectancy may result in larger numbers of people with chronic diseases such as hypertension, diabetes mellitus, and cardiovascular diseases that may cause renal damage. Third, the elderly people may be prescribed many medications, including nephrotoxic agents. In this study, we have tried to determine the clinical and histological differences in new-onset IgA nephropathy between young adults and the elderly.

METHODS

A total of 136 patients with a biopsy diagnosis of IgA nephropathy from 2000 to 2009 at a medical center in Taiwan were reviewed. The diagnosis of IgA nephropathy was based on the demonstration by direct immunofluorescence of IgA as the dominant or co-dominant

immunoglobulin in a predominantly mesangial distribution. An additional criterion for inclusion in the study was biopsy-proven IgA nephropathy identified within 1 year of the first detection of renal abnormalities and no treatment during this period. We excluded patients with clinical or serological evidence for systemic lupus erythematosus, Henoch–Schönlein purpura, chronic liver disease, or human immunodeficiency virus infection.

We subdivided the patients enrolled in the study into two groups: young adults group (under age 50 years) and elderly group (over age 60 years). The renal manifestations as indications for renal biopsy in elderly and non-elderly groups were summarized in Table 1. For each patient, the following clinical data were compiled from review of written and/or electronic patient records: age at the time of the biopsy, gender, degree of hematuria, serum creatinine (mg/dl), and urinary protein excretion (g/24 hr or protein/creatinine ratio) at the approximate time of the biopsy, presence or absence of hypertension (defines as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg in three consecutive measurements) prior to or at the time of the biopsy, and patient and renal outcomes at the last follow-up. Scoring of hematuria was on the number of red blood cells per high-power field in sediment, and was graded as 0 if 0–5, 1 if 6–20, 2 if 21–50, 3 if 51–100, and 4 if >100. Histological parameters were scored as 0 if none, 1+ if involving <25%, 2+ if involving 25–50%, and 3+ if involving ≥50%. The intensity of immunofluorescence staining was also graded on a scale of 0 to 3+.

For outcome analysis, complete remission of acute renal failure was defined as normalization of serum creatinine to baseline levels or to ≤1.2 mg/dL for those patients in whom baseline levels of creatinine were unavailable; and partial remission was defined by elevation of serum creatinine above baseline levels or follow-up creatinine >1.2 mg/dL for those patients in whom baseline levels of creatinine were unavailable.

TABLE 1. Reasons for renal biopsy in young adults and the elderly with IgA nephropathy.

	Young adults group (n = 82)	Elderly group (n = 17)
Acute renal failure + hematuria + proteinuria	10 (12.2%)	9 (52.9%)
Hematuria + nephrotic range proteinuria	19 (23.2%)	7 (41.2%)
Hematuria + non-nephrotic range proteinuria	44 (53.7%)	0 (0%)
Isolated hematuria	9 (11.0%)	1 (5.9%)

End-stage renal disease was defined as requiring maintenance dialysis therapy.

Statistical analyses were performed using SPSS version 12 (SPSS Inc., Chicago, IL, USA) for Windows and produced by simple nonparametric test (Mann–Whitney U-test and Fisher's exact test). A p-value <0.05 was considered significant.

RESULTS

There were 82 patients with mean age of 30.3 ± 10.2 years in young adults group and 17 patients with mean age of 71.9 ± 4.5 years in elderly group. The comparison of clinical and histological parameters between the two groups was summarized in Table 2. The mean time from last normal urinalysis to the presence of abnormal findings was 41.7 ± 12.4 weeks in the young adults group and 40.5 ± 11.1 weeks in the elderly group. The elderly group had a shorter time from clinical presentation to renal biopsy than the young adults group although there was no statistically significant difference (6.3 ± 5.6 vs. 10.8 ± 9.5 weeks, $p = 0.079$). In comparison to clinical parameters, the elderly group more frequently had hypertension (88.2 vs. 30.5%, $p < 0.001$), nephrotic range proteinuria (70.6 vs. 26.8%, $p = 0.001$), and acute renal failure (52.9 vs. 12.2%, $p < 0.001$) at presentation. The elderly group also had a greater urinary protein excretion (5.1 ± 4.2 vs. 2.6 ± 4.0 g/24 hr, $p = 0.009$) than young adults group. In contrast, the most common renal manifestation in young adults group was hematuria with non-nephrotic range proteinuria (53.7%). On histology, there was no significant difference in the degree of mesangial hypercellularity, the prevalence of endocapillary proliferation, segmental glomerular sclerosis, and glomerular crescents, and the severity of interstitial fibrosis and tubular atrophy between the two groups, but the elderly group had a higher percentage of globally sclerotic glomeruli than the young adults group (20.9 ± 14.8 vs. 9.3 ± 11.1%, $p < 0.001$).

We compared the clinical and histological features between young adults and the elderly patients presenting with acute renal failure (Table 3). In comparison of clinical parameters, there were no significant differences in the severity of hematuria, proteinuria, and renal failure at the time of renal biopsy between the two groups. However, the elderly group more frequently had an intercurrent disease (88.9 vs. 30.0%, $p = 0.02$). Table 4 summarized the intercurrent diseases in patients presenting with acute renal failure. Outstandingly, the majority of patients (77.8%) in the elderly group had a bacterial infection. On histology, the elderly group more commonly had acute tubular injury (acute tubular necrosis and/or tubulointerstitial nephritis) than the

TABLE 2. Comparison of clinical and histological parameters of IgA nephropathy between young adults and the elderly.

Variables	Young adults group (n = 82)[c]	Elderly group (n = 17)[c]	p-Value
Clinical parameters			
Age (years)	30.3 ± 10.2	71.9 ± 4.5	
Gender (male/female)	40/42	11/6	0.291[b]
Hypertension	25 (30.5)	15 (88.2)	<0.001[b]*
Hematuria (score)	2.3 ± 1.5	2.1 ± 1.8	0.571[a]
Macroscopic hematuria	16 (19.5)	3 (17.6)	1.000[b]
Proteinuria (g/24 h)	2.6 ± 4.0	5.1 ± 4.2	0.009[a]*
Proteinuria ≥3 g/24 h	22 (26.8)	12 (70.6)	0.001[b]*
Acute renal failure	10 (12.2)	9 (52.9)	<0.001[b]*
Histological parameters			
Mesangial hypercellularity (score)	1.5 ± 0.8	1.6 ± 0.8	0.711[a]
Globally sclerotic glomeruli (%)	9.3 ± 11.1	20.9 ± 14.8	<0.001[a]*
Segmental glomerular sclerosis	14 (17.1)	1 (5.9)	0.457[b]
Endocapillary proliferation	1 (1.2)	0 (0)	1.000[b]
Glomerular neutrophil infiltration	1 (1.2)	2 (11.8)	0.075[b]
Glomerular crescents	18 (22.0)	4 (23.5)	1.000[b]
Tubular atrophy (score)	0.9 ± 0.4	0.9 ± 0.2	0.562[a]
Interstitial fibrosis (score)	0.3 ± 0.5	0.5 ± 0.5	0.224[a]
Interstitial infiltration (score)	0.7 ± 0.8	1.1 ± 0.8	0.112[a]
IgA intensity (score)	1.6 ± 0.5	1.7 ± 0.5	0.455[a]
IgG positive staining	45 (54.9)	13 (76.0)	0.114[b]
IgM positive staining	47 (57.3)	11 (64.7)	0.787[b]
C3 positive staining	63 (76.8)	12 (70.6)	0.551[b]
C1q positive staining	5 (6.1)	3 (18.0)	0.136[b]

Notes: *p-Value < 0.05.
[a]Data were analyzed by Mann–Whitney U-test.
[b]Data were analyzed by Fisher's exact test.
[c]Mean ± SD or number (%).

TABLE 3. Comparison of clinical and histological parameters of acute renal failure in IgA nephropathy between young adults and the elderly.

Variables	Young adults group (n = 10)[c]	Elderly group (n = 9)[c]	p-Value
Clinical parameters			
Age (years)	38.2 ± 11.0	74.0 ± 4.8	
Gender (male/female)	6/4	8/1	0.303[b]
Hematuria (score)	3.1 ± 1.5	3.2 ± 1.4	0.930[a]
Proteinuria (g/24 h)	4.0 ± 6.5	3.1 ± 2.6	0.659[a]
Serum creatinine at biopsy (mg/dl)	5.4 ± 3.2	7.8 ± 5.2	0.310[a]
Dialysis support requirement	5 (50.0)	5 (55.6)	1.000[b]
Intercurrent disease	3 (30.0)	8 (88.9)	0.020[b]*
Histological parameters			
Globally sclerotic glomeruli (%)	9.5 ± 8.8	22.3 ± 15.7	0.077[a]
Glomeruli with crescents	9 (90.0)	4 (44.4)	0.057[b]
Crescents in >30% of glomeruli	9 (90.0)	3 (33.3)	0.020[b]*
Crescents in >50% of glomeruli	5 (50.0)	2 (22.2)	0.350[b]
% Glomeruli affected by crescent	48.9 ± 25.5	18.2 ± 27.2	0.027[a]*
Acute tubular injury	1 (11.1)	6 (66.7)	0.020[b]*
Interstitial infiltration (2+ or 3+)	3 (30.0)	2 (22.2)	1.000[b]
Outcome			
Follow-up (months)	18.8 ± 8.5	8.6 ± 5.5	
Death	0 (0)	4 (44.4)	0.033[b]*
Complete remission	3 (30.0)	2 (22.2)	1.000[b]
Partial remission	2 (20.0)	1 (11.1)	1.000[b]
End-stage renal disease	5 (50.0)	2 (22.2)	0.350[b]

Notes: *p-Value < 0.05.
[a]Data were analyzed by Mann–Whitney U-test.
[b]Data were analyzed by Fisher's exact test.
[c]Mean ± SD or number (%).

young adults group (66.7 vs. 11.1%, p = 0.02). In contrast, the young adults group had a higher percentage of glomeruli affected by crescents than the elderly group (48.9 ± 25.5 vs. 18.2 ± 27.2%, p = 0.027). As to the outcome, there were no differences in renal survival between the two groups, however, the elderly group had a significant higher mortality rate than the young adults group (44.4 vs. 0%, p = 0.033).

We also summarized the clinical and histological differences between young adults and elderly patients presenting with nephrotic syndrome in Table 5. There were no significant differences in the clinical and histological parameters and outcome between the two groups except that the elderly group had a higher percentage

TABLE 4. Intercurrent diseases in cases of IgA nephropathy with acute renal failure.

Young adults group (n = 3)	Elderly group (n = 8)
Bacteremia (2)	Bacteremia (4)
MRSA (infected surgical wound)	MRSA (central line infection)
MSSA (septic arthritis of hip)	MSSA (osteomyelitis of spine)
Autoimmune hemolysis (1)	*Klebsiella pneumoniae* (septic arthritis of knee)
	Acinetobacter baumannii (unknown origin)
	Pneumonia (3)
	Klebsiella ozaenae
	Pseudomonas aeruginosa
	MRSA
	Malignancy (1)
	Small cell carcinoma of lung

Notes: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

of globally sclerotic glomeruli than the non-elderly group (21.3 ± 14.5 vs. 7.0 ± 11.6%, p = 0.009).

DISCUSSION

The major objective of this study is to determine whether there were differences in IgA nephropathy presenting in the elderly compared with that in young adults. The first striking finding was that most elderly patients with IgA nephropathy had more severe renal manifestations; and acute renal failure (52.9%) and nephrotic syndrome (41.2%) were the two most common reasons for renal biopsy. In contrast, hematuria with mild proteinuria was the most common presentation in the young adult patients (53.7%). Since the relative frequency of renal manifestations depends in large part on screening for renal disease and renal biopsy practices, prevalence of mild renal manifestations may therefore appear to be higher with an active urine-testing program and a low threshold for the performance of renal biopsy in the elderly. In Taiwan, urine testing is routinely performed in schools and in the workplace, but not in retired aged population which may lead to decreased discovery of asymptomatic cases. On the other hand, the clinicians' reluctance to subject the elderly patients with isolated hematuria or mild proteinuria to such invasive procedures as renal biopsy results in an apparently lower disease prevalence in this age group; and it is therefore not surprising that the elderly group had more severe manifestations at the time of renal biopsy. Our data showed a slightly higher prevalence rate of IgA nephropathy (11%) in aging renal biopsies compared with previous studies (1–7%).[2–4]

On histology, there were no significant differences in the majority of parameters between young adults group and elderly group except that a higher percentage of globally sclerotic glomeruli were observed in the elderly group. Interpretation of renal biopsy in the

TABLE 5. Comparison of clinical and histological parameters of nephrotic IgA nephropathy between young adults and the elderly.

Variables	Young adults group (n = 19)[c]	Elderly group (n = 7)[c]	p-Value
Clinical parameters			
Age (years)	26.9 ± 10.3	70.1 ± 2.6	
Gender (male/female)	7/12	3/4	1.000[b]
Hypertension	13 (68.4)	6 (85.7)	0.629[b]
Hematuria (score)	2.1 ± 1.6	1.0 ± 1.4	0.148[a]
Proteinuria (g/24 h)	6.5 ± 5.0	8.5 ± 3.7	0.099[a]
Serum creatinine at biopsy (mg/dL)	1.0 ± 0.2	1.0 ± 0.3	0.817[a]
Histological parameters			
Globally sclerotic glomeruli (%)	7.0 ± 11.6	21.3 ± 14.5	0.009[a]*
Mesangial cellularity (score)	1.6 ± 0.8	1.4 ± 0.5	0.603[a]
Segmental glomerulosclerosis	5 (26.3)	1 (14.3)	1.000[b]
Outcome			
	(n = 13)	(n = 6)	
Follow-up (months)	33.3 ± 9.1	20.1 ± 8.6	
Complete remission	5 (38.5)	3 (50.0)	1.000[b]
Partial remission	2 (15.4)	1 (16.7)	1.000[b]
Not remission with preserved renal function	2 (15.4)	1 (16.7)	1.000[b]
Renal insufficiency	2 (15.4)	0 (0)	1.000[b]
End-stage renal disease	2 (15.4)	1 (16.7)	1.000[b]

Notes: *p-Value < 0.05.
[a]Data were analyzed by Mann–Whitney U-test.
[b]Data were analyzed by Fisher's exact test.
[c]Mean ± SD or number (%).

elderly may be complex because of changes associated with aging. It is well known that the percentage of globally sclerotic glomeruli increases with age.[5] It may be difficult to judge whether glomerular sclerosis results from previously healed proliferative glomerulonephritis or just aging. In general, sclerotic glomeruli with breaks in the glomerular basement membrane may be a sequela of severe glomerular inflammation and crescent formation and favors underlying glomerulonephritis. In addition, it has been suggested that "pathological" glomerulosclerosis should be seriously considered when the number of globally sclerotic glomeruli exceeds the number calculated by the formula: (patient's age/2) – 10.[6] As a result, the globally sclerotic glomeruli of a mean 20.9 ± 14.8% in the elderly group could be related to the structure changes of the aging kidney.

Another outstanding finding from this study was that in cases of acute renal failure the elderly patients had more predominant tubular rather than glomerular injury. It has been suggested that acute kidney injury in IgA nephropathy develops mainly by two mechanisms: One is immune-mediated glomerular injury presenting as proliferative glomerulonephritis with crescent formation and the other is macroscopic hematuria-associated acute tubular injury that is induced by intratubular obstruction by erythrocytic casts and a possible nephrotoxic effect of the hemoglobin released from the casts.[7,8] Our data showed that the young adult patients had a higher percentage of glomeruli affected by crescents, and half of them had diffuse crescentic glomerulonephritis (crescents in >50% of glomeruli). In contrast, the elderly patients had a less degree of glomerular destruction by crescents, but most patients had acute tubular injury presenting with luminal ectasia, epithelial flattening and simplification, and loss of brush border; and two of the nine patients had acute tubulointerstitial nephritis. In our patients, the acute tubular injury did not seem to be associated with macroscopic hematuria since the characteristic histological finding of widespread tubules filled by red blood cells was present in only one of the nine biopsies. On the other hand, the glomerular lesions present were themselves rarely if ever a cause of acute renal failure. In these cases acute renal failure appeared related to the acute tubular necrosis, and which was most likely secondary to renal hemodynamic disturbances and/or exposure of nephrotoxic agents such as antibiotics and nonsteroidal anti-inflammatory drugs. Since most patients had current infectious diseases, we proposed another possible explanation, although unproved, that the glomerular IgA dominant or co-dominant deposits may be a peculiar pattern of infection-associated glomerulonephritis, which was increasingly identified over the past years.[9–12] It is speculated that enterotoxins produced by methicillin-resistant *Staphylococcus aureus* may serve as superantigens which contribute to this type of glomerulonephritis.[13] However, whether similar mechanism exists in other bacterial infection is not known. On histology, IgA-dominant postinfectious glomerulonephritis is difficult to differentiate from primary IgA nephropathy. However, these patients had clinical features that favor postinfectious glomerulonephritis over primary IgA nephropathy including older age, documented infection, and presentation of acute renal failure which is unusual in primary IgA nephropathy without extensive crescent formation.

Acute renal failure has been associated with a considerable mortality rate (28–43%) in the elderly.[14,15] In addition, renal recovery tends to be less frequent, slower, and less complete. Our results were in accordance with the previous reports of unfavorable outcomes. Furthermore, mortality in cases of acute renal failure was usually related to the intercurrent disease and was at most rarely attributable directly to renal disease.

In conclusion, IgA nephropathy, albeit less commonly, occurring in the elderly, had more severe renal manifestations at presentation. In cases of acute renal failure, the elderly patients had more predominant tubular injury rather than glomerular destruction by crescents and had a considerable mortality rate. Both acute tubular injury and high mortality rate might be associated with the intercurrent disease, mostly infection, which was more commonly present in the elderly patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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