Clinical characteristics, causes and outcomes of acute interstitial nephritis in the elderly

Angela K. Muriithi[1], Nelson Leung[1], Anthony M. Valeri[2], Lynn D. Cornell[3], Sanjeev Sethi[3], Mary E. Fidler[3] and Samih H. Nasr[3]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [2]Division of Nephrology, Columbia University, College of Physicians and Surgeons, New York, New York, USA and [3]Division of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota, USA

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury (AKI), and its prevalence in the elderly may be increasing. It is largely unknown whether AIN in the elderly is similar to that in younger adults; therefore, we investigated the causes and characteristics of AIN in 45 elderly patients (65 years and older) and in 88 younger adults (18–64 years old). Compared with younger patients, the elderly had significantly more drug-induced AIN (87 vs. 64%), proton pump inhibitor–induced AIN (18 vs. 6%), but significantly less AIN due to autoimmune or systemic causes (7 vs. 27%). The two most common culprit drugs in the elderly were penicillin and omeprazole. Compared with younger patients, the elderly had higher prevalence of baseline CKD, higher peak creatinine, and more need for dialysis, all of which were significant. Among the elderly, 86% showed partial or complete recovery within 6 months. Significantly shorter delays in initiation of steroids correlated with recovery at 6 months. Lack of early recovery tended to correlate with progressive CKD. Compared with antibiotic-induced AIN, proton pump inhibitor–induced AIN had less severe AKI, but a longer duration of drug exposure, and was less likely to recover by 6 months, all significant. Thus, the vast majority of AIN cases in the elderly are due to drugs, primarily owing to proton pump inhibitors and antibiotics, while AIN of autoimmune or systemic origin is uncommon.

Kidney International advance online publication, 3 September 2014; doi:10.1038/ki.2014.294

KEYWORDS: acute kidney injury; kidney biopsy; nephritis

Correspondence: *Angela K. Muriithi, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street, Rochester, Minnesota 55905, USA. E-mail: muriithi.angela@mayo.edu or kagwiria76@yahoo.com*

Received 4 November 2013; revised 3 June 2014; accepted 26 June 2014

Acute kidney injury (AKI) in the elderly is of particular interest, as this growing population has the highest incidence of AKI.[1,2] Furthermore, the elderly appear to have a higher risk of development of chronic kidney disease (CKD) or end-stage renal disease (ESRD) after an episode of AKI than younger patients, and they have the highest mortality risk when they develop AKI during hospitalization.[1–5] In this population, AKI remains the most common indication for kidney biopsy,[6–8] and studies have shown that the performance of biopsies in this population is both safe and as likely to yield useful findings as in younger patients.[8,9]

Acute interstitial nephritis (AIN) is an important and common cause of AKI. The prevalence of AIN has been found to occur in 15–27% of patients in whom kidney biopsy is performed for AKI.[6,10] Since AIN from drugs was first described,[11,12] the prevalence of drug-induced AIN (DI-AIN) continues to rise, likely because of the widespread use of antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and other drugs.[13] The use of these drugs has increased especially in elderly patients (over 65 years of age),[1] and the prevalence of AIN in this population has been reported to be higher than in younger patients.[14] Furthermore, there appears to be a higher risk of AIN in elderly patients from certain drugs such as NSAIDs.[15] A recent Spanish biopsy registry study[16] showed the prevalence of AIN to have increased about threefold in all patients from 1994 to 2009, but in elderly patients specifically this increase was a marked eightfold. This increase was postulated to be due to the increasing biopsy rate in the elderly, as well as increasing use of the drugs that are most commonly implicated in DI-AIN such as antibiotics and NSAIDs. A biopsy study of 259 elderly patients with AKI in 2000 by Haas *et al.* found a prevalence of AIN of 19%.[6]

Since the introduction of proton pump inhibitors (PPIs) in 1989,[17] their high efficacy and low side effect profile has led to their becoming one of the most widely prescribed drugs in the world.[18] PPIs are emerging as a significant cause of AIN, and elderly patients appear to have greater susceptibility to them.[19–21]

Although the high and increasing incidence and impact of AKI in the elderly has been well elucidated, as has the high incidence of AIN in this population,[16] the causes of AIN in this population are not well described. The goal of this study

is to describe the causes, clinical presentation, and outcome of AIN in the elderly and to compare this with younger patients.

RESULTS

Characteristics of elderly versus non-elderly patients

One hundred thirty-three adult Mayo patients with biopsy-proven AIN were identified from 1993 to 2011, 45 (34%) of whom were ⩾65 years of age (Table 1). The total number of adult Mayo patients with native kidney biopsy during the same period was 7575, indicating that the prevalence of adult AIN in our medical center is 1.8%, which is comparable to prior studies that reported 1–3% prevalence.[16] The median age of the elderly was 73 years and 49 years in those aged <65 years. The elderly patients were more likely to present with pyuria ($P=0.04$), but tended to be less likely to have fever ($P=0.09$). There was otherwise no difference in clinical symptoms (Table 1). In both groups, the AKI was predominantly nonoliguric in nature. The elderly patients had lower estimated glomerular filtration rate (eGFR) at baseline—55 ml/min per 1.73 m^2 compared with 69 ml/min per 1.73 m^2 in the younger patients ($P=0.0018$)—and they were more likely to have CKD at baseline—69% compared with 28% ($P<0.0001$). During the episode of AKI, the elderly patients had higher creatinine levels at the time of biopsy, 4.0 vs. 3.3 mg/dl ($P=0.021$), and higher peak creatinine, 4.7 vs. 3.4 mg/dl ($P=0.012$). Of the 45 elderly patients, 15 patients (33%) required dialysis during the episode of AKI compared with 14 (16%) non-elderly patients ($P=0.0213$). Younger patients had a lower prevalence of DI-AIN (64%) compared with the elderly (87%; $P=0.0054$). A majority of patients were treated with steroids: 93% in the elderly patients and 83% in the non-elderly patients ($P=0.09$). Histologically, the elderly had a higher percentage of sclerotic glomeruli ($P=0.0004$) and more interstitial fibrosis and tubular atrophy ($P=0.01$). No difference was found between the presence of moderate/severe interstitial fibrosis and tubular atrophy and progressive disease ($P=0.39$). There was no difference in the occurrence of granulomatous AIN on biopsy: 22% compared with 28% ($P=0.44$).

By the end of the first 6 months after the diagnostic biopsy, the majority of patients achieved either complete (CR) or partial recovery (PR) at 47 and 38%, respectively, with only 14% having a status of no recovery (NR); there was no difference between the elderly or non-elderly patients as regards this status (CR: 39%, PR: 47%, NR: 14% compared with CR: 52%, PR: 34%, NR: 14%; $P=0.36$). At the end of follow-up (median 73 months), four patients had ESRD, three of whom were elderly.

Table 1 | Demographic, clinical, laboratory, treatment, and outcome characteristics of patients with AIN ($N=133$)

Characteristics	⩾65 years ($N=45$)	<65 years ($N=88$)	*P*-value
Age, years	73 (70,78.5)	49 (35,58)	<0.001
Male sex	20 (44)	44 (50)	0.54
Race-White	41/42 (98)	80/84 (95)	0.60
Rash	7/45 (16)	15/88 (17)	0.83
Fever	4/45 (9)	18/88 (20)	0.09
Oliguria	8/45 (16)	11/88 (13)	0.41
Leukocytosis	11 (24)	27 (31)	0.45
Eosinophilia	11/40 (28)	11/80 (14)	0.07
Triad: fever + rash + eosinophilia	2/40 (5)	7/81 (9)	0.47
Pyuria	26/44 (59)	35/87 (40)	0.04
Hematuria	13/44 (30)	26/86 (30)	0.94
Eosinophiluria	14/31 (45)	14/51 (27)	0.10
Proteinuria	41/44 (93)	81/88 (92)	0.82
Nephrotic-range proteinuria	7/44 (16)	12/88 (14)	0.73
White cell casts	2/44 (5)	2/88 (2)	0.47
Baseline serum creatinine (mg/dl)	1.1 (1.0,1.4)	1.1 (0.9,1.2)	0.27
Baseline estimated GFR	55 (47,65)	69 (53,85)	0.0018
CKD at baseline	29/42 (69)	19/67 (28)	<0.0001
Serum creatinine at time of biopsy (mg/dl)	4.0 (2.7,5.9)	3.3 (1.9,5.1)	0.021
AKIN stage			
Stage 1	6/42 (14)	15/64 (23)	0.26
Stage 2	11/42 (26)	17/64 (27)	—
Stage 3	25/42 (60)	32/64 (50)	—
Peak serum creatinine (mg/dl)	4.7 (3.2,8.6)	3.4 (2.4,6.4)	0.012
Comorbid conditions	41/44 (93)	70/87 (80)	0.056
Drug-induced AIN	39 (87)	56 (64)	0.0054
Dialysis	15 (33)	14 (16)	0.0213
Interstitial fibrosis/tubular atrophy			
None	7 (16)	33 (37)	—
Mild	29 (64)	38 (43)	—
Moderate	9 (20)	12 (14)	—
Severe	0 (0)	5 (6)	0.01
% Globally sclerotic glomeruli	18.0 (6.5,33)	0 (0,17)	0.0004
Granuloma present	10 (22)	25 (28)	0.44
Recovery within 6 months			0.36
Complete	14/36 (39)	33/63 (52)	—
Partial	17/36 (47)	21/63 (34)	—
None	5/36 (14)	9/63 (14)	—
Latest serum creatinine (mg/dl)	1.6 (1.2,2.2)	1.3 (1,2)	0.15
Ultimate outcome	—	—	0.21
Normal	15/32 (47)	33/57 (58)	—
Progressive CKD	14/32 (44)	23/57 (40)	—
ESRD	3/32 (9)	1/57 (2)	—

Abbreviation: AIN, acute interstitial nephritis; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate.
Continuous variables are reported as median (interquartile range) and categorical as number (percentage).

Causes of AIN by age group

Of all the 133 patients in the study, 95 had DI-AIN, of whom 39 patients (41%) were elderly and 56 (59%) were not (Table 2; Figure 1). The elderly patients were more likely to have drugs as the cause of AIN (87 vs. 64%, $P=0.005$), as detailed in Table 2, and they had more DI-AIN (87 vs. 64%, $P=0.005$), including more PPI–induced AIN (18 vs. 6%, $P=0.03$), and less AIN associated with autoimmune/systemic diseases (7 vs. 27%, $P<0.01$). In the younger patients, half of the cases of AIN associated with autoimmune/systemic diseases were due to sarcoidosis.

Overall, in elderly patients, antibiotics were the most common culprit (47%), followed by PPIs at 18%. In 13% of