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Clinical Study

Acute Kidney Injury in ADPKD Patients with Pneumonia

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Background. In animal models, polycystic kidneys are susceptible to acute kidney injury (AKI). We examined the occurrence of AKI in a cohort of autosomal dominant polycystic kidney disease (ADPKD) and non-ADPKD patients with acute pneumonia. *Design*. All ADPKD patients admitted to Mayo Clinic Rochester for pneumonia from January 1990 to April 2010 were examined. Sixty-three patients had lobar infiltration and consolidation on chest X-ray. After excluding patients on dialysis, with organ transplantation, and on chronic immunosuppression, 24 remaining ADPKD patients were enrolled. Twenty-three of the 24 were matched with 92 (1 : 4 ratio) non-ADPKD pneumonia patients based on their baseline eGFR. AKI was defined as serum creatinine elevation ≥0.3 mg/dL. *Results*. Sixteen of the 23 ADPKD patients (69.6%) and 36 of the 92 (39.1%) non-ADPKD patients developed AKI, $P = 0.008$. In both groups, those who developed AKI had a lower baseline eGFR (41.1 ± 5.00 versus 58.7 ± 11.8 in ADPKD and 40.2 ± 3.65 versus 51.8 ± 2.24 mL/min/1.73 m^2 in the non-ADPKD group), more intensive care unit admissions, and longer hospital stays. AKI was associated with a reduced survival in both groups. *Conclusions*. Patients with ADPKD admitted for acute pneumonia had more frequent episodes of AKI than non-ADPKD patients with comparable kidney function.

1. Introduction

Acute kidney injury (AKI) occurs in 7–18% of all hospitalized patients [1] and is an independent predictor of mortality [2]. Risk factors for the development of AKI include infection, sepsis, medication toxicity, intravenous contrast administration, and major surgeries. Patients with underlying kidney disease are more susceptible to AKI in the setting of infection [3].

Autosomal dominant polycystic kidney disease (ADPKD) is a common, inherited disease, characterized by formation of kidney cysts due to renal tubular dilatation, leading to cystic kidney enlargement and kidney failure in more than half of the affected patients by age 50–70 [4]. Kidney tubules in ADPKD exhibit features of dedifferentiation with elevated rates of proliferation and apoptosis at baseline [5, 6]. In orthologous polycystic kidney mouse models, cystic kidneys exhibit an increased susceptibility to AKI induced by ischemic-reperfusion injury, with changes seen as early as 48 hours after the insult [7–9]. Whether humans with ADPKD have the same increased susceptibility to AKI as the animal models of ADPKD is unknown.

Acute pneumonia, mild or severe, has been shown to cause AKI in a fraction of patients, leading to an increased in-hospital and one-year mortality [10, 11]. In this study, we examined the incidence, severity, and associated mortality of AKI in a cohort of patients with and without ADPKD who were hospitalized for pneumonia.

2. Subjects and Methods

2.1. Study Protocol and Data Collection. The study was approved by the Institutional Review Board. A total of 345 patients with ADPKD who were cared for at Mayo Clinic Rochester for acute pneumonia from January 1990

to April 2010 were identified through the institutional radiology database. Sixty-three of the 345 patients were admitted to the hospital for treatment. The 63 patients were enrolled for analysis. Non-ADPKD patients admitted for pneumonia with a comparable estimated glomerular filtration rate (eGFR; within ± 10 mL/min/1.73 m^2) during the same time period were enrolled as the control group. All patients were treated in the general internal medicine ward or medical intensive care unit (ICU). Estimated GFR was determined from serum creatinine concentration using the 4-variable Modification of Diet in Renal Disease (MDRD) Equation [12]. Patients with the following conditions were excluded: age younger than 18, end-stage kidney failure on renal replacement therapy, any organ transplantation, on chronic immunosuppressive therapy, systemic vasculitis, or incomplete medical information.

Pneumonia was defined as clinical evidence of infection with an accompanying chest X-ray showing new infiltration and/or consolidative process, not due to atelectasis. Radiological evidence of pneumonia was reconfirmed by a radiologist (RPH). For patients with several admissions for pneumonia during the study period, only the most recent pneumonia episode was studied. The severity of pneumonia was graded upon admission using a five-point scoring system (CURB-65 score) with one point assigned for each of the following: confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic blood pressure (<90 mmHg), low diastolic blood pressure (≤60 mmHg), and age ≥65 years. This scoring system was validated with a higher score being associated with higher risk of mortality [13].

Baseline serum creatinine (mg/dL) was defined as the creatinine concentration on admission and was confirmed by reviewing prior creatinine values within six months of admission. AKI was considered present if peak serum creatinine concentration during the hospital stay increased by ≥0.3 mg/dL over the baseline, with or without oliguria. The severity of AKI was determined using creatinine definitions of the RIFLE criteria [14]. The RIFLE criteria classifies AKI into the following: stage I (Risk) is defined as serum creatinine elevation ≥1.5-times the baseline creatinine; stage II (Injury) ≥2-times the baseline; stage III (Failure) ≥3-times the baseline or creatinine ≥4.0 mg/dL; complete loss of kidney function requiring renal replacement therapy. Patient comorbidity was determined by the number of chronic diseases that required maintenance treatment.

2.2. Statistical Analysis. Fisher's exact test (for categorical data) and Student's t-test (for continuous variables) were used for comparisons between two different groups. Each value is reported as percentage frequencies or means ± standard error (SEM). Survival curves were generated using the Kaplan-Meier method. Survival was defined as the time between the hospital admission and death. Survival was censored up to patients' last followup. Cox proportional hazards regression modeling was used to examine long-term survival in ADPKD and non-ADPKD adjusted for age difference. Logistic regression analysis was also conducted controlling for several known risk factors for AKI. A two-tailed P value of <0.05 was considered significant. All the analyses were performed using JMP version 8 and GraphPad statistical software.

3. Results

3.1. Patient Characteristics. Of the 63 patients admitted for acute pneumonia, all of them had chest X-ray evidence of lobar infiltrative and/or consolidative processes consistent with pneumonia. Thirty-nine of the 63 were excluded because of end-stage renal failure on dialysis (19 cases), after kidney transplantation (14 cases), incomplete clinical information (4 cases), and on immunosuppressive therapy for other reasons, systemic vasculitis, and rheumatoid arthritis (2 cases). The remaining 23 of the 24 ADPKD patients were matched with 92 (1 : 4 ratio) non-ADPKD patients with comparable baseline eGFR who were admitted for pneumonia (with chest X-rays showing lobar infiltration and/or consolidation) during the same time period. One of the 24 ADPKD patients had eGFR of 7 mL/min/1.73 m^2 and was not on dialysis. We were unable to identify any non-ADPKD patient with similar eGFR not on dialysis.

As shown in Table 1, the baseline characteristics of ADPKD and non-ADPKD patients were similar except for non-ADPKD patients being significantly older and showing a higher number of comorbidities. Comorbid conditions seen more often in non-ADPKD patients were atrial fibrillation on anticoagulation, congestive heart failure, severe valvular heart diseases, and hypothyroidism. There was no difference in the incidence of nephrotoxic medication exposure, including NSAIDs, intravenous contrast, diuretic therapy, angiotensin converting enzyme inhibitor, and angiotensin receptor blocker between ADPKD and non-ADPKD patients. For ADPKD patients, there was a tendency towards male predominance.

3.2. Incidence and Severity of AKI in Patients with Pneumonia. Of the 23 ADPKD patients, 16 (69.6%) developed AKI. Of the 92 non-ADPKD patients, 36 (39.1%) developed AKI. The frequency of AKI was significantly higher in patients with ADPKD, $P = 0.008$. This difference occurred despite the age advantage and lesser comorbidity in ADPKD patients, suggesting a predilection among ADPKD patients for developing AKI.

To characterize AKI severity, patients with AKI were stratified based on the magnitude of their serum creatinine elevation, according to the RIFLE criteria. As shown in Table 2, the distribution of AKI severity was not statistically different in this cohort, although five of 16 (31.3%) ADPKD patients were in the category of failure whereas two of 36 (5.56%) non-ADPKD patients were in the same category.

3.3. Characteristics and Hospital Course of Patients with and without AKI. We further compared ADPKD and non-ADPKD patients with and without AKI (Table 3). The baseline eGFR was lower in patients with AKI in both ADPKD and non-ADPKD groups, with statistical significance in

Table 1: Baseline characteristics of patients with and without ADPKD.

	ADPKD	Non-ADPKD	*P*
N, pneumonia episodes	23	92	
Baseline eGFR mL/min/1.73 m^2 (mean, SEM)	46.4 ± 5.13	47.3 ± 2.05	0.88
Age (mean, range), years	59.7 (31–88)	81.9 (99–25)	<0.0001
Male/female	17/6	49/43	0.07
Pneumonia severity score (mean, SEM[1])	1.95 ± 0.22	2.26 ± 0.08	0.21
Smoking (%)	12 (54.5%)	56 (60.87%)	0.73
Diabetes (%)	5 (21.7)	21 (22.8)	0.91
Hypertension (%)	20 (87.0)	74 (80.4)	0.46
Coronary artery disease (%)	10 (43.5)	50 (54.4)	0.35
N of disease diagnosis (mean, SEM)	5.26 ± 0.56	8.96 ± 0.33	<0.0001

[1] SEM: standard error of the mean.

Table 2: AKI in pneumonia patients with and without ADPKD.

	ADPKD ($n = 23$)	Non-ADPKD ($n = 92$)	[1]*P*
AKI episode, number (%)	16 (69.6)	36 (39.1)	0.008
AKI severity			
Cr elevation ≥0.3 and <1.5-fold (%)	5 (31.3)	9 (25.0)	0.73
[2]Risk, number (%)	3 (18.8)	17 (47.2)	0.06
[3]Injury, number (%)	1 (6.25)	2 (5.56)	1
[4]Failure, number (%)	5 (31.3)	2 (5.56)	0.02
Dialysis, number (%)	2 (12.5)	6 (16.7)	1

[1]*P* value adjusted for age. [2]Risk: serum creatinine (Cr) increase ≥1.5 fold. [3]Injury: serum Cr increase ≥2 fold. [4]Failure: serum Cr increase ≥3 fold or serum Cr >4 mg/dL.

Table 3: Patient characteristics and clinical course in ADPKD and non-ADPKD patients with and without AKI.

Patient characteristics	ADPKD			Non-ADPKD		
	− AKI ($n = 7$)	+ AKI ($n = 16$)	*P* value	− AKI ($n = 56$)	+ AKI ($n = 36$)	*P* value
Age, year mean (range)	58.7 (34–82)	60.2 (31–88)	0.87	83.1 (62–99)	80.1 (25–99)	0.54
Gender (male), *N* (%)	3 (42.9)	14 (87.5)	0.02	29 (51.8)	20 (55.6)	0.72
Baseline eGFR Mean ± SEM (mL/min/1.73 m^2)	58.7 ± 11.8	41.1 ± 5.00	0.20	51.8 ± 2.24	40.2 ± 3.65	0.009
Comorbidity, number of diagnosis	5.28 ± 1.42	5.25 ± 0.55	0.98	8.89 ± 0.49	9.08 ± 0.57	0.80
Clinical course						
Hospital stay (days) mean ± SEM	3.28 ± 0.91	16.3 ± 4.23	0.008	5.32 ± 0.73	20.1 ± 7.28	0.05
ICU admission, patient number (%)	0	8 (50)	0.02	8 (14.29)	16 (44.44)	0.001
Vasopressor use, patient number (%)	0	3 (18.75)	0.21	1 (1.79)	8 (22.22)	0.001
Mechanical ventilation (number)	0	5 (31.25)	0.09	1 (1.79)	7 (19.44)	0.003

the non-ADPKD group. This is consistent with preexisting kidney dysfunction as a risk factor for AKI. The number of medical comorbidities was not different in patients with or without AKI. We also compared the clinical course of those with and without AKI. In both groups, patients with AKI required a longer hospital stay than those without AKI (Table 3, clinical course). Similarly, patients with AKI required more ICU admissions, inotropic administration, and mechanical ventilation compared to patients without AKI.

To investigate the contribution of known risk factors of AKI in this patient cohort, logistic regression analysis was performed. As shown in Table 4, baseline eGFR, CURB65, diabetes, and pressor administration were independent risk factors for AKI. Notably, after adjusting for all confounding variables, ADPKD remained an independent risk factor for AKI.

3.4. Survival Analysis in ADPKD and Non-ADPKD Patients with AKI. Hospital mortality was more common in patients with AKI in both groups, two versus zero in ADPKD and seven versus three in non-ADPKD group. We further examined survival rates in AKI patients with and without

Table 4: Multivariate analysis for AKI risk factors in the entire cohort ($N = 115$).

Variable	Odds ratio	CI 95%	P value
Baseline eGFR	0.95	0.92, 0.98	0.005
CURB65 score	1.86	1.02, 3.59	0.05
CAD	1.13	0.68, 1.87	0.63
HTN	0.62	0.33, 1.12	0.12
DM	1.94	1.10, 3.55	0.02
Hypotension requiring pressors	5.91	2.11, 29.5	0.005
ADPKD	2.42	1.33, 4.81	0.006

Table 5: Cox proportional hazards model showing the effect of age, AKI, and ADPKD on mortality.

Variable	Hazard ratio	95% CI	P value
ADPKD	0.75	0.43, 1.18	0.17
AKI	1.40	1.08, 1.08	0.01
Age	1.05	1.02, 1.08	<0.0001

ADPKD. The 30-day mortality rate for the ADPKD group was 12.5% in AKI and 0% in non-AKI patients, and for the non-ADPKD group 19.5% in AKI and 10.9% in non-AKI patients although the absolute patient number was small. When using Kaplan Meier analysis, as shown in Figures 1(a) and 1(b), there was higher number of deaths in patients with AKI in the ADPKD group, but statistical significance was not reached likely due to the small patient number; in non-ADPKD patients, there was a statistically significant increase in mortality in patients with AKI.

We also performed Cox proportional hazards model, correcting for the age difference between the non-ADPKD and ADPKD groups. AKI and older age were significantly associated with higher mortality. ADPKD status did not influence the AKI-associated mortality in this analysis (Table 5).

4. Discussion

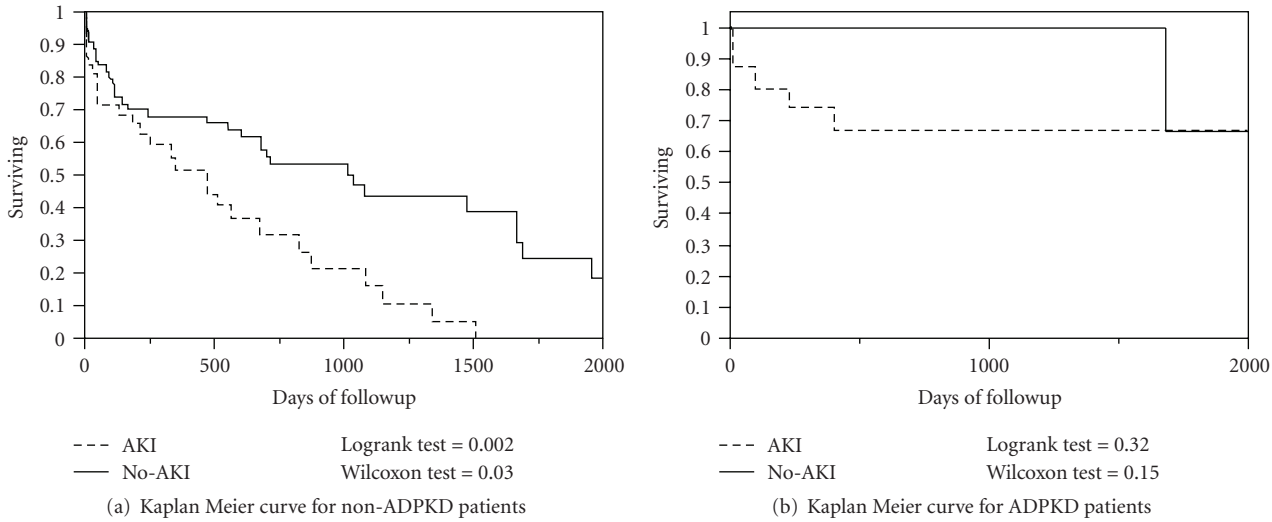
To our knowledge, this study represents the first investigation of AKI in patients with ADPKD in the setting of an infectious process. It shows that in the context of pneumonia, ADPKD patients exhibit a significantly higher occurrence of AKI than non-ADPKD patients with a comparable baseline eGFR.

ADPKD is the most common monogenic kidney disease, affecting 1 in 400 to 1 : 1000 livebirths. Mutations in the PKD1 or PKD2 gene, encoding polycystin-1 and polycystin-2, respectively, are responsible for the disease manifestations [4]. Considerable data indicate that polycystins may form a macromolecular signaling structure, the polycystin complex, that regulates fundamental aspects of renal epithelial function, including cell cycle progression and cell survival [15]. PKD mutations in animal models have been shown to cause dysregulation in polycystin-mediated signaling, leading to abnormal proliferation and apoptosis. Abnormal elevations in cellular proliferation and apoptosis have been demonstrated in both cystic and noncystic renal tubular cells in human ADPKD [5, 6].

Several recent studies by independent groups have shown that othologous PKD mutant mice are more susceptible to kidney ischemic reperfusion injury resulting in more extensive renal tubular destruction [7–9]. Moreover, repair mechanisms are defective with evidence of dysregulated proliferation in tubular cells and higher levels of interstitial inflammation and fibrosis, leading to permanent loss of kidney function [7–9]. These observations suggest that *PKD* gene products, polycystins, exert key roles in regulating tubular maintenance, susceptibility to injury, and mechanisms of repair. Although these animal studies have shed light on the pathways of kidney injury and repair in relation to *PKD* mutations, the susceptibility of human ADPKD kidneys to AKI and the severity of AKI have not been previously examined. Our observed increase in AKI occurrence, albeit in a different setting (pneumonia), is consistent with studies generated from animal models of ADPKD.

The occurrence of AKI in the context of pneumonia has been reported recently by Murugan et al. [10]. In that study, AKI occurrence rate ranged between 16 and 30% depending on the pneumonia severity. In our cohort, the non-ADPKD patients showed a higher occurrence of AKI (39.1%). This increased rate could have potentially been related to the age difference between the two studies, as patients in our non-ADPKD cohort were older (mean age of 80.1 years in AKI and 83.1 years in non-AKI) compared to mean ages of 73.4 in AKI and 65.2 in non-AKI patients in the study by Murugan et al.

Older age is a known risk factor for AKI [1]. Age-related changes in the kidney and renal vasculature are thought to account for the increased risk [1, 16]. Moreover, decreased renal perfusion has been shown to be among the most important causes of AKI [1]. Further, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) [17] has shown that ADPKD kidneys display a significant reduction in renal perfusion earlier in age with preserved kidney function (eGFR >70 mL/min/BSA). Such ADPKD-related renal hemodynamic changes could render ADPKD kidneys vulnerable for developing AKI. It is



(a) Kaplan Meier curve for non-ADPKD patients

(b) Kaplan Meier curve for ADPKD patients

Figure 1: Survival analysis of non-ADPKD patients (a) and ADPKD patients (b) with no AKI versus AKI.

therefore possible that, in addition to inherent renal tubular defects, reduction in renal perfusion in ADPKD kidneys plays an important role in the genesis of AKI, offsetting the effects of age. In our study, ADPKD itself appeared to be a risk factor for AKI, but not for mortality.

Several limitations in this study are worth noting. First, the retrospective nature of the study limited the consistency of blood sampling which could influence the levels of peak and discharge creatinine concentrations. However, this would be expected to affect both ADPKD and non-ADPKD patients in the same fashion. Second, the GFR used in this study was estimated from converting serum creatinine to eGFR using the MDRD equation, which is not as precise as measured GFR, that is, iothalamate clearance. However, the eGFR generated by this method is generally accepted as a surrogate marker for kidney function. Third, this study enrolled patients over a 20-year time-span. The level of intensity in the clinical observation and documentation could vary; brief changes in respiratory rates and changes in blood pressure might have gone unrecorded, leading to a potential underestimation of the pneumonia score. Fortunately, our study subjects were from a single medical center, where care protocol has not changed qualitatively, especially in the initial admission evaluation for patients with signs of infection (the time for establishing the pneumonia score). Moreover, any differences in routine care would have applied to both ADPKD and non-ADPKD groups and standardized diagnostic criteria for pneumonia were applied to all study subjects. Fourth, the sample size for ADPKD is relatively small. This could be explained by the following (1) only a small fraction of pneumonia cases was hospitalized, (2) patients admitted were local residents; without referral, the relatively low prevalence of ADPKD limited the number of cases, and (3) more than 50% of ADPKD patients with pneumonia and admitted to hospital were excluded due to end-stage renal disease on dialysis and renal transplant. Finally, this study was limited by older age and a higher level of comorbidity in non-ADPKD patients (Table 1). Such differences could have introduced bias to the AKI occurrence and, possibly, severity. However, because aging and medical comorbidity are risk factors for AKI, such bias introduced here would be towards worse kidney outcome in the non-ADPKD group. The fact that AKI occurrence was higher despite the age advantage and less comorbidity in the ADPKD group, made the study results even more compelling. Taken together, limitations inherent in this study would not change the study results. Conclusion

5. Conclusion

To our knowledge, this study represents the first investigation of AKI in patients with ADPKD in the setting of an infectious process. The results show that ADPKD patients are more vulnerable to the development of AKI in the context of pneumonia, suggesting that ADPKD itself is a risk factor for AKI. Further studies are needed to confirm our findings.

Conflict of Interests

The authors report no conflict of interests.

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C. F. Palacios, M. T. Keddis, R. P. Hartman contributed equally to this work.

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