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Research

Do Histopathological Findings of Kidney Biopsies Performed in Patients with Acute Kidney Injury Differ with Age?

Akut Böbrek Hasarı Nedeniyle Yapılan Böbrek Biyopsilerinin Histopatolojik Bulguları Yaşla Değişir Mi?

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ABSTRACT

Objective: Acute kidney injury (AKI) occurs in various conditions with different clinical presentations. Kidney biopsy (KB) is recommended when pre-renal and post-renal causes have been excluded, and the cause of AKI is unclear. We aimed to determine the histopathological features in patients with AKI and compare the frequency of the underlying causes in patients with different age groups.

Methods: This retrospective study was performed on all patients who underwent KB for AKI at our institution between January 2006 and April 2021. Demographic, clinical, and laboratory data and histopathological results were retrieved from the patients' files. Patients aged 60 years and older were regarded as elderly. The distribution of renal diseases was compared between the age groups.

Results: Overall, 767 kidney biopsies were performed at our institution for 15 years. Of these, 171 (22.2%) had unexplained AKI, of whom 35% were elderly. Males were predominated in both groups. The most common diagnosis was glomerular diseases (71.9%), followed by tubulointerstitial diseases (21.7%) and vascular lesions (5.3%). Immunoglobulin A nephropathy was the most frequent diagnosis in adults, whereas pauci-immune glomerulonephritis was the most frequent cause of AKI in the elderly.

Conclusion: Our data documents the different patterns of biopsy-confirmed causes of AKI according to the age groups and points the value of biopsy since most of the pathologic diagnoses are entities that are both difficult to diagnose without biopsy and are treatable.

Keywords: Acute kidney injury, histopathology, kidney biopsy

ÖZ

Amaç: Akut böbrek hasarı (ABH), farklı klinik bulgular ve farklı nedenler ile ortaya çıkabilir. ABH'ye yol açabilecek prerenal ve postrenal nedenler dışlandığında ve ABH'nin nedeni saptanamadığında böbrek biyopsisi (BB) önerilir. Bu çalışmada, ABH ile başvuran hastalarda histopatolojik özelliklerin belirlenmesi ve farklı yaş gruplarındaki hastalarda altta yatan nedenlerin sıklığının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Ocak 2006 ve Nisan 2021 tarihleri arasında ABH nedeniyle BB yaptığımız tüm hastalar geriye dönük olarak tarandı. Demografik, klinik ve laboratuvar verileri ile histopatolojik sonuçlar hasta dosyalarından kaydedildi. Altmış yaş ve üzeri hastalar yaşlı olarak kabul edildi. Böbrek hastalıklarının dağılımı yaş grupları arasında karşılaştırıldı.

Bulgular: On beş yılda yapılan 767 BB değerlendirildi. Yüz yetmiş birinde (%22,2) açıklanamayan ABH vardı ve bunların %35'i yaşlıydı. Her iki grupta da erkekler baskındı. En sık tanı glomerüler hastalıklar (%71,9) iken, bunu tubulointerstisyel hastalıklar (%21,7) ve vasküler lezyonlar (%5,3) izledi. Erişkinlerde en sık karşılaşılan patolojik tanı immünoglobulin A nefropatisi iken yaşlılarda pauci-immün glomerulonefrit idi.

Sonuç: Verilerimiz; ABH'de BB sonuçlarının yaşa göre değiştiğini ve BB tanı ve tedavinin yönlendirilmesindeki değerini göstermektedir.

Anahtar Kelimeler: Akut böbrek hasarı, histopatoloji, böbrek biyopsisi

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INTRODUCTION

Acute kidney injury (AKI) is a heterogeneous disorder, manifested by an increase in serum creatinine level with or without reduced urine output for hours to days (1,2). Injury ranges from mild to severe kidney failure, sometimes requiring dialysis. Moreover, AKI is associated with an increased risk of mortality and development of chronic kidney disease (3). The diagnostic evaluation can be used to classify AKI as pre-renal AKI, which results from inadequate perfusion of the kidneys, and post-renal AKI, which results from obstruction to the flow of urine and renal AKI, which can be due to injury or dysfunction of the renal glomeruli, tubules, interstitium, or blood vessels. The majority of AKI cases can be diagnosed by clinical history, physical examination, and investigations of urine, blood, and radiology tests. Kidney biopsy (KB) is a crucial diagnostic tool when pre-renal and post-renal causes have been excluded and the intrinsic cause of AKI is unclear (4). Further, KB is critical for correct treatment and predicting prognosis. Patients undergoing KB for evaluation of AKI had a higher risk for complications due to lower pre-biopsy hemoglobin and higher baseline serum creatinine (5). Therefore, clinicians must consider diagnostic uncertainty and potential therapeutic relevance when deciding to perform a diagnostic KB in patients with AKI and take all precautions to prevent complications. This study aimed to determine the histopathological features in patients presenting with AKI and to compare the frequency of the different causes in patients with different age groups.

METHODS

Our study was retrospective, including all patients who underwent native KB for AKI. All native kidney biopsies performed at University of Health Sciences Turkey Bakırköy Dr. Sadi Konuk Training and Research Hospital between January 2006 and April 2021 were screened. Indications for kidney biopsies are as follows:

1. AKI: Abrupt decrease in renal function, with or without oligoanuria or rapidly progressive renal failure, including worsening of chronic kidney disease

2. Nephrotic syndrome: Proteinuria >3.5 g/24 h, with hypoalbuminemia (serum albumin <3.5 g/L) and edema

3. Nephritic syndrome: Proteinuria (1.5-3.5 g/24 h), hematuria with or without high blood pressure, and edema

4. Urinary abnormalities: Proteinuria <1.5 g/day or hematuria, without impaired kidney function

The renal specimens were collected by biopsy needle guidance technique under ultrasonography. The same pathologist examined the KB specimens and processed them for standard analysis, including light microscopy with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, and periodic acid-methenamine silver staining and immunofluorescence. Patients were eligible if aged ≥16 years and submitted to KB for AKI. The exclusion criteria were incomplete records, inadequate biopsies (<8 glomeruli), and transplant kidney biopsies.

For all cases in which the indication for biopsy was AKI, we reviewed the patient's files, including the renal biopsy report. We recorded the following information: Age, sex, comorbidities, laboratory findings at the time of biopsy (serum creatinine, serum albumin, urine microscopy, 24-hour urine protein or spot urine protein/creatinine ratio, ANCA serological results), and histopathological diagnosis. Renal diseases were classified into three major categories: glomerular diseases, tubulointerstitial nephropathies, and vascular lesions. Patients aged 60 years and older were regarded as elderly.

Statistical Analysis

The 2007 NCSS (Number Cruncher Statistical System; Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used for study data evaluation. The suitability of quantitative data to normal distribution was tested by Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. Student's t-test was used to determine the significance of differences between normally distributed variables and Mann-Whitney U test for non-normally distributed variables. Pearson chi-square test, Fisher-Freeman-Halton Exact test, and Fisher's Exact test were used to compare qualitative data, where appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Of the 767 kidney biopsies performed at our institution for 15 years, 171 (22.2%) were conducted on patients with unexplained AKI (Table 1). The frequency of biopsy-confirmed AKI in adult patients was 18.5%, increasing to 36% in the elderly ($p=0.001$). As shown in Table 2, no statistically significant differences was observed in sex, serum creatinine, serum albumin, and proteinuria level between the age groups ($p>0.05$).

Table 3 lists the histological lesions encountered in the patients with AKI, subclassified according to age and primary site of involvement within the kidney. Glomerular disease was the most common type of disease observed in both groups [81 (72.9%) in the adults vs 42 (70%) in the elderly group]. The distribution of glomerular lesions

differed between the age groups. Immunoglobulin A nephropathy was the most common cause (36%) in adults, whereas pauci-immune glomerulonephritis (GN) was the most frequent pathology (33.3%) in the elderly (p=0.001 and p=0.001, respectively). Fifty-six (32.7%) patients presented with rapidly progressive GN: 18 had crescentic immunoglobulin A nephropathy, 32 had pauci-immune GN, 4 had anti-glomerular basement membrane disease, 1 had lupus nephritis class IV, and 1 had shunt nephritis. In detail, immunosuppressive treatment was applied to all of these patients, and seven patients with pauci-immune GN who had hemoptysis and/or radiologic evidence of pulmonary involvement were treated with plasmapheresis.

Table 1. Clinical presentations at the time of biopsy according to age

	Total n=767 (100%)	Adult (<60 years) n=603 (78.6%)	Elderly (≥60 years) n=164 (21.4%)	p
Acute kidney injury (n,%)	171 (22.2)	114 (18.9)	57 (34.7)	[d]0.001**
Nephrotic syndrome (n,%)	309 (40.2)	234 (38.8)	75 (45.7)	
Nephritic syndrome (n,%)	113 (14.7)	97 (16.1)	16 (9.7)	
Abnormal urine analysis (n,%)	174 (22.6)	158 (26.2)	16 (9.7)	

[d]Fisher-Freeman-Halton test, **p<0.01

Tubulointerstitial disease (TID) was noted approximately in 20% of the cases in both age groups. The most commonTID was tubulointerstitial nephritis (TIN) in two groups.

Vascular disease was the least common cause of AKI (5.3%). Noticeably, the most common vascular disease was hypertensive nephrosclerosis. All patients diagnosed with hemolytic uremic syndrome (HUS) were adults, and the frequency of renal cortical necrosis (RCN) was similar in the age groups.

About 49.1% of the patients required hemodialysis. Indications of hemodialysis included uremia, oligoanuria, metabolic acidosis, and hyperkalemia. Although we had incomplete data to quantify complications of KB, no major complications such as death and nephrectomy were reported.

DISCUSSION

Several registries have described clinicopathological spectrums of kidney biopsies in adults; however, a limited number of these studies analyzed the primary clinical syndromes that indicate KB in detail. This observational study describes the histopathological profiles of the patients undergoing a KB for AKI and highlights the difference in age prevalence of the different causes.

The incidence of AKI as a clinical syndrome in the study of kidney biopsies ranges from 10% to 25% (6-12). Our data collected over 15 years showed that AKI constitutes 22.2% of all KB; however, this percentage was lower in adult patients than in the elderly. It is crucial to say that structural and functional changes occurring with age make

Table 2. Demographic and biochemical characteristics of the patients with AKI at presentation according to age

	Total n=171 (100%)	Adults n=111 (64.9%)	Elderly n=60 (35%)	p
Age (years) (mean ± SD)	49.39±16.22	40.41±11.61	67.37±5.85	-
Male	47.35±16.75	38.60±11.27	67.77±6.27	-
Female	52.28±15.00	43.30±11.69 (16-59)	66.93±5.42 (60-81)	
Sex (n,%)	-	-	-	[b]**0.272**
Male	100 (58.4)	67 (67)	33 (33)	-
Female	71 (41.5)	44 (62)	27 (38)	
Laboratory on admission (mean ± SD)	-	-	-	-
Creatinine (mg/dL)	4.86±2.76	5.08±2.82	4.42±2.62	[c]**0.107**
Total protein (g/dL)	6.16±0.90	6.20±1.01	6.07±0.73	[a]**0.501**
Albumin (g/dL)	3.27±0.69	3.31±0.72	3.20±0.59	[a]**0.430**
Proteinuria (mg/g)	3148±2847	3274.35±2906.61	2897.86±2734.79	[c]**0.268**

[a]Student's t-test, [b]Pearson chi-square, [c]Mann-Whitney U test, SD: Standart deviation

Table 3. The results of renal pathology according to age

	Total n=171 (100%)	Adults n=111 (64.9%)	Elderly n=60 (35.1%)	p
Glomerular diseases	**123 (71.9)**	**81(72.9)**	**42 (70.0)**	**0.680**
Anti-GBM nephritis	4 (2.3)	3 (2.7)	1 (1.6)	[d]**1.000**
Amyloidosis (AA/AL)	6/3 (5.2)	4/1(4.5)	2/2 (6.6)	[d]**0.697**
Chronic glomerulonephritis	4 (2.3)	3 (2.7)	1 (1.6)	[d]**0.553**
Diabetic nephropathy	6 (3.6)	1 (0.9)	5 (8.3)	[d]**0.186**
Focal segmental GS	8 (4.6)	7 (6.3)	1 (1.6)	[d]**0.263**
IgA nephropathy	49 (28.6)	40 (36)	9 (15)	**0.001***
Lupus nephritis	3 (1.7)	3 (2.7)	0	[d]**0.553**
Membranoproliferative GN	7 (4.1)	6 (5.4)	1 (1.6)	[d]**0.424**
Pauci-immune crescentic GN	32 (18.7)	12 (10.8)	20 (33.3)	**0.001****
Shunt nephritis.	1 (0.5)	1 (0.9)	0	[d]**1.000**
Tubulointerstitial diseases	**37 (21.7)**	**23 (20.7)**	**14 (23.3)**	**0.701**
Tubulointerstitial nephritis	24 (14)	16 (14.4)	8 (13.3)	**1.000**
Acute tubular necrosis	13 (7.6)	7 (6.3)	6 (10)	[d]**0.383**
Vascular diseases	**9 (5.3)**	**6 (5.4)**	**3 (5)**	[d]**1.000**
Hemolytic uremic nephropathy	3 (1.7)	3 (2.7)	0	[d]**0.553**
Hypertensive nephrosclerosis	4 (2.3)	2 (1.8)	2 (3.3)	[d]**0.613**
Acute cortical necrosis	2 (1.1)	1 (0.9)	1 (1.6)	[d]**1.000**
Unclassified	**2 (1.1)**	**1 (0.9)**	**1 (1.6)**	[d]**1.000**
Oxalate nephropathy	1 (0.5)	1 (0.9)	0	[d]**1.000**
Phosphate nephropathy	1 (0.5)	0	1 (1.6)	[d]**1.000**

[b]Pearson chi-square, [d]Fisher-Freeman-Halton test, **p<0.01

GN: Glomerulonephritis, GS: Glomerulosclerosis, IgA: Immunoglobulin A, GBM: Glomerular basement membrane

the elderly more vulnerable to AKI, and once it happened, renal function did not recover fast after the induction of treatment in the older age group.

In both age groups, glomerular diseases accounted for 70% of all diagnoses, similar to the previous studies, in which GN was the primary finding in ≥50% of cases undergoing KB for AKI (8,11,12). The most common diagnosis was immunoglobulin A nephropathy in adults, which accounted for nearly one-third of the cases, and it causes AKI probably by hematuria and/or crescentic proliferation. Consistent with the previous report (8), the most common glomerular disease in elderly patients was pauci-immune GN in our cases. In the current study, 32.7% of the patients showed crescentic proliferation, and approximately 57.1% had pauci-immune GN. Regarding the higher prevalence of crescentic GN among AKI patients, early diagnosis is necessary to prevent irreversible kidney injury by initiating immunosuppressive treatment and plasmapheresis when appropriate.

TID includes TIN and ATN, both of which cause a rapid decline in kidney function. TIN is characterized by interstitial inflammatory infiltrates, edema, and tubulitis in histopathological examination and is usually caused by drugs, infection, and systemic and autoimmune disease and may be idiopathic in origin. It accounts for 2% of all native kidney biopsies and 15-27% of adult cases undergoing KB for unexplained AKI (8,13,14). TIN was the most common type of TID observed in our cohort and accounted for 14% of all biopsy cases. Clinical suspicion, particular attention to extrarenal manifestations, and review of potential risk factors are usually enough for accurate diagnosis of TIN. However, KB should be performed in cases with severe renal dysfunction, lack of an identifiable offending agent, and lack of renal recovery before initiation of immunosuppressive treatment.

ATN is a common etiology of AKI in hospitalized patients and is diagnosed by exclusion of pre-renal and post-renal causes of AKI, examination of urinary sediment, and analysis of urine measures such as fractional excretion of sodium. ATN prevalence in our cohort is low because most cases were diagnosed based on clinical data, and KB was performed only in patients with prolonged or atypical AKI. In fact, histopathological findings of ATN are only diagnostic and do not alter therapy, and its role in predicting renal outcome is unknown.

Vascular diseases are the least common cause of AKI in the present study. Hypertensive nephrosclerosis was present in 2.3% of our cases, which was similar to the findings of a report from Japan (1.3%) (15). HUS characterized by non-immune microangiopathic hemolytic anemia, thrombocytopenia, and AKI was detected in three patients and all were treated with eculizumab. RCN secondary to ischemic necrosis of the renal cortex is a rare disease, accounting for only 2% of all cases of AKI in Western countries and 3.8%-7.1% in patients dialyzed for AKI in developing countries (16,17). In line with the literature, we reported RCN in 1.1% of the cases, and none was associated with obstetrical complications.

Study Limitations

This study had a few limitations. Our study did not include follow-up or outcome data, and these entities must be studied in future studies.

CONCLUSION

The present study provides information about renal histopathology in patients with AKI and reveals the significance of KB for accurate diagnosis of underlying diseases as most of the histopathological diagnoses are entities that are both difficult to recognize without biopsy and are treatable.

ETHICS

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital of Local Ethics Committee (approval no: 214/2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ö., F.S.K.Y., K.G.E., M.Y., Concept: A.Ö., M.Y., Design: A.Ö., F.S.K.Y., M.Y., Data Collection or Processing: A.Ö., F.S.K.Y., K.G.E., Analysis or Interpretation: A.Ö., F.S.K.Y., K.G.E., Literature Search: A.Ö., Writing: A.Ö.

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