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ORIGINAL ARTICLE

Drug-induced Acute Kidney Injury/Acute Tubulointerstitial Nephritis: A Clinico-etiological Study from a Single Center in North-east India

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ABSTRACT

Introduction: Drug-induced acute kidney injury (AKI)/acute tubule-interstitial nephritis (ATIN) is an important cause of AKI. There is little information about drug-induced AKI in our part of the world (north-east India).

Aim: To determine the clinico-etiological profile of drug-induced AKI and their outcome in our part of the world and correlation with the histological pattern.

Materials and methods: This is a retrospective observational study of patients who developed AKI following intake of some medications. AKI was defined as per risk' injury faiure less and end-stage kidney (RIFLE) criteria. On ultrasonography, kidney size was normal without any evidence of obstruction. Kidney biopsy was done in patients who didn't improve or had a history of multiple drugs or unknown drugs. Patients' clinical data were correlated with offending drug and histopathology findings

Results: A total of 97 patients were included in this study, 60% were males and 40% were females. Mean age of patients was 45 ± 12.09 years. Herbal medication (29%) was the most common cause of drug-induced AKI, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (26%). Renal biopsy was done in 54 patients, 59.6% had acute tubulointerstitial nephritis (ATIN), 35% of patients had acute on the chronic TIN. Renal replacement therapy was required in 57.7% patients. Full renal recovery occurred in 38% patients while as, partial recovery occurred in 30% patients. Out of 29 patients with herbal medication intake,17% had full recovery compared to 56% in NSAID group.

Conclusion: Drug-induced AKI is an important cause of renal dysfunction and can be under-diagnosed. AKI may occur with many drugs. Herbal medications were the most common cause of drug-induced AKI and had poor renal outcome compared to NSAIDs.

Clinical significance: In our study, herbal medications intake was a common cause of AKI and was associated with poor renal recovery. Early suspicion and withdrawal of the offending drug are needed to prevent renal damage.

Keywords: Acute kidney injury, Acute tubulointerstitial nephritis, Drug-induced AKI, Kidney biopsy.

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INTRODUCTION

Acute kidney injury is a growing problem worldwide with a lot of economic and medical burden.[1] Various prospective studies have documented the frequency of drugs as a cause of AKI in 14–26%.[2-4] The kidney is the main route of excretion for most of the drugs; many of which may cause kidney damage. Drug-induced acute kidney injury is an important cause of AKI. There are two mechanisms of kidney injury; hypersensitivity to a particular drug and direct drug toxicity. Nephrotoxicity can take several forms, which can lead to renal vasoconstriction and reduced glomerular filtration rate (GFR). The defective renal tubular function is a frequent event as proximal tubular cells are susceptible to injury because of the high capacity of transporting substances from urine to blood. Aminoglycosides have been the leading cause of antibiotic-induced nephrotoxicity for a few decades now.[5] Nephrotoxicity due to NSAIDS is now common, especially when used with multiple drugs.[6] Other common drugs implicated to cause tubulointerstitial nephritis (TIN) and AKI are Rifampicin,[7] contrast agents,[8] penicillin,[9] beta-lactams, and cloxacillin.[10]

There is an increased prevalence of use of herbal drugs in our part of the world.[11] Herbal medications have been known to cause TIN, which usually is difficult to identify.[12] Prevalence of biopsy-proven ATIN has been seen to be similar all over the world, between 0.5 and 2.6% of all renal biopsies, however, some retrospective registries have found higher (5–18%) prevalence of TIN.[13] TIN is broadly characterized by the primary involvement of tubulointerstitium with almost normal glomeruli. Injury to the renal tubule cells leads to the presentation of neoantigens on the cells, infiltration of the inflammatory cells and activation of cytokines; both proinflammatory and chemokines. The tubular damage leads to tubular dysfunction and AKI due to tubular obstruction, tubuloglomerular disconnection, and vasoconstriction. Usually acute TIN regardless of damage is reversible.[14]

Drug-induced renal dysfunction usually is reversible and renal function returns to the baseline if the offending drug is discontinued at earliest. Chronic renal injury can, however, be induced by some medications, leading to chronic tubulointerstitial inflammation, papillary necrosis or prolonged proteinuria.[15,16]

AIM

The aim of this study was to determine the clinico-etiological profile of drug-induced AKI and their outcome in our part of the world and correlation with the histological pattern.

MATERIALS AND METHODS

This is a retrospective study based on a cohort of 99 patients admitted in nephrology department of Gauhati Medical College and Hospital (GMCH) from 2012–2016 with the development of AKI following intake of some medications. Out of which two patients were lost to follow up and were excluded from the study. AKI was diagnosed using the RIFLE criteria.[17] Patients with underlying diabetes or pre-existing kidney disease were excluded.

History of the patient was ascertained for the drug intake before developing AKI and the name, duration and time since the intake of the drug was noted. Most of the patients were taking these drugs as a treatment either given by the practitioner or self-medication (especially NSAIDS and herbal medications). Patients' history of fever, rash and decreased urine output was noted. On the day of admission to hospital following tests were done in all patients; complete blood count (CBC) with differential count, serum urea, serum creatinine, serum electrolytes, liver function test, uric acid, blood sugar fasting and urine analysis including eosinophils in urine. Urine was checked for eosinophils by microscopy examination of slide stained with Leishman stain. Antinuclear antigen (ANA) and serum LDH were done in selected patients. Ultrasonographic (USG) examination of kidneys was done in all patients, and all had normal size non obstructed kidneys.

The offending drug was stopped and patients who persisted with renal dysfunction after stopping drugs were treated with a pulse of methylprednisolone 500mg daily for three days followed by oral steroids for 4 to 6 weeks. Renal biopsy was done in 54 cases which were evaluated by light microscopy (LM) and immunofluorescence (IF). All patients were followed till recovery, development of chronic kidney disease (CKD) and death.

Table 1: Medications causing acute tubulointerstitial nephritis and AKI

Medications used	*No. of patients*	*Percent*
Herbal/alt. medicine	29	29
NSAIDS	25	26
Antibiotics	13	13.5
Multiple drugs	11	11
Aminoglycosides	9	9.2
ATT	8	8.3
Chemotherapeutics	2	2

Statistics

Statistical analysis was done on the Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics of mean ± standard deviation (SD) were used for continuous variables and numbers (percentages) for categorical variables. $p < 0.05$ was taken as the significant level.

RESULTS

A total of 97 patients with AKI secondary to drug intake were registered in our department during the study period. There were 58 (60%) males and 39 (40%) females with a mean age of 45 ± 12.09 years. Herbal medications (29%) were the most common cause of drug-induced AKI, followed by NSAIDs (26%). The frequency of different drugs used in our study population is given in Table 1. Average time from insult to clinical symptoms was 15 ± 9.5 days. Around 59% of patients had oliguria on presentation; fever was present in 12(12.4%) patients and rash in3 patients. Laboratory values on the day of admission are given in Table 2. Urine analysis revealed 1+protein in 41 patients, 2+ in 7 and 3+ in 2 patients. Microscopic hematuria was seen in 23% of cases. Eosinophiluria was seen in 7 patients.

Renal biopsy was done in 54 patients (Table 3) whose renal function didn't improve after stopping the offending drug, or had delayed improvement, or had multiple or unknown medication intakes. In patients with TIN,

Table 2: Clinical features and laboratory parameters of the study population

Parameters	*Values*
Age (mean ± SD)	45 ± 12.09
Day of insult (mean ± SD)	15 ± 9.5
Fever, n (%)	12 (12.3%)
Rash, n (%)	03 (3.1%)
Oliguria, n (%)	57 (58.7%)
Hemoglobin g/dL (mean ± SD)	9.8 ± 1.2
Blood Urea mg/dL (mean ± SD)	180 ± 85
Serum Creatinine mg/dL (mean ± SD)	7.3 ± 4.0
Serum sodium mEq/L (mean ± SD)	132 ± 4.5
Serum potassium mEq/L (mean ± SD)	4.5 ± 0.89
Eosinophils in urine, n (%)	7 (7.2%)
Urine protein, n (%)	
Nil	51 (52.5%)
1+	40 (41.2)
>2+	06 (6.2%)
Microscopic hematuria (%)	23 (23.7%)
Serum Bilirubin mg/dL (mean ± SD)	0.8 ± 0.4
Alanine transaminase U/L (mean ± SD)	35 ± 12
Aspartate transaminase U/L (mean ± SD)	32 ± 15
Serum Albumin g/dL (mean ± SD)	3.6 ± 0.9
Dialysis (no.)	56

glomeruli were normal with interstitial mononuclear infiltrate and edema (Fig. 1). Thirty-two patients (59.6%) had acute tubulointerstitial nephritis (ATIN), 19 patients (35%) had acute on the chronic TIN, two patients (3.7%) had granulomatous infiltrate and one patient (1.8%) had thrombotic microangiopathy (TMA).

Eighty-five (87.6%) patients were treated with methylprednisolone pulse followed by steroids. Renal replacement therapy was required in 56 patients (57.7%). Full renal recovery occurred in 37 patients (38%) while as, partial recovery occurred in 29 patients (29.8%); no recovery was seen in 28 patients (28.8%), and three patients (3.1%) died during the acute phase of illness as shown in Table 4. Out of three patients who died, two had sepsis and one patient had bacterial endocarditis. Table 5 shows an association between renal outcomes with respect to the drug intake. Five patients had full recovery out of 29 patients with herbal medication intake while as, 12 had partial recovery and 12 had no recovery. On the other hand, out of 25 patients with NSAID intake 14 had a full recovery while as, 6 had partial recovery and 5 had no recovery. Patients with herbal medication and multiple drug intake had poor renal outcome compared to NSAID and single drug intake ($p = 0.007312$).

DISCUSSION

Any drug can cause AKI and damage to the kidney but most commonly reported are aminoglycosides (AG), penicillin, NSAIDs, rifampicin, contrast dyes, chemotherapeutic agents and herbal medications.[5-12] There is a decline in AG induced AKI with the development of less nephrotoxic drugs. In our study, AG toxicity was found in 12 patients. Leading causative agents of kidney dysfunction were herbal and complementary medicines in our study. These accounted for 29 of 97 (29%) patients. In our part of the world, phytotherapy is used as an alternative medicine for many chronic ailments. People take herbs for many reasons, such as losing weight, arthralgia, chronic illnesses, cancer, liver, kidney, and gynecological problems. There is a perception of many patients that these botanical remedies are inherently safe. A strong association has been seen between herbal medications and interstitial nephritis in the Chinese population.[18-22] Herbal medications contain undisclosed drugs, such as heavy metals, vasoconstrictors, hormones, and other undeclared drugs.[23] Chinese herb contains aristocholic acid which is nephrotoxic and carcinogenic.[24]

The clinical presentations of drug-induced kidney dysfunction are quite variable and have limitations for diagnosis by noninvasive methods. Symptoms and signs may be mild and nonspecific. The classical triad of rash, fever, and eosinophilia commonly used to suspect TIN occurs in less than 30% of the patients.[25] Typically they present with nonoliguric renal failure.[26] Diagnosis is based on clinical and laboratory suspicion, but renal biopsy is needed for definite diagnosis. In our study, classical symptoms of fever and rash were 12% and 3%, and most patients presented with oliguria (58.7%). A higher number of patients presented with oliguria in our patients, which can be because of late presentation to hospital with advanced kidney failure. Kidney biopsy was done in 54 patients, 35% of patients had acute on chronic tubulointerstitial changes on biopsy. These chronic changes probably also represent the late presentation of our patients to the hospital. This also emphasizes the need for early detection and stoppage of the offending drug to prevent the development of permanent damage.

Table 3: Histopathology of the patients who underwent kidney biopsy

Biopsy (n 54)	*Values n (%)*
Acute TIN	32 (59)
Acute on Chronic TIN	19 (35)
Granulomatous infiltrate	2 (3.7)
TMA	1 (1.8)

Table 4: Patients outcome of the study population

Outcome	*Values (%)*
Full recovery	37 (38)
Partial recovery	29 (29.9)
No recovery	28 (28.9)
Death	3 (3.1)

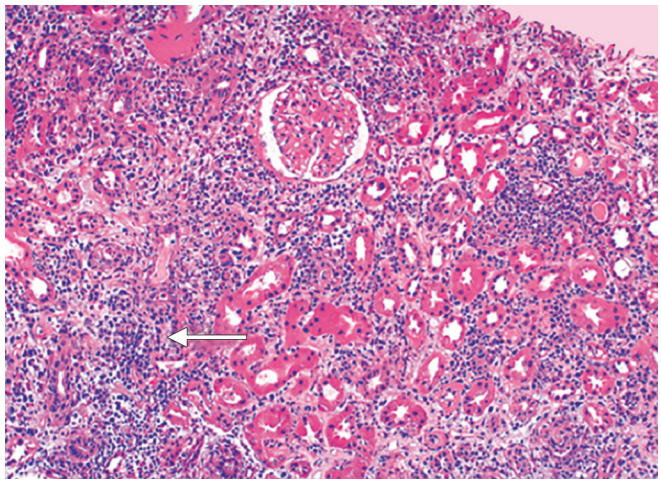

Fig. 1. Acute interstitial nephritis. There is a diffuse interstitial infiltrate with evidence of interstitial edema (arrow). Glomerulus is relatively well preserved (hematoxylin and eosin, × High power)

Table 5: kidney function outcome (full, partial and no recovery) compared with the offending drug

Drugs	*Full recovery (n = 37)*	*Partial recovery (n = 29)*	*No recovery (n = 28)*
Herbal/ alt medicine[29]	5	12	12
NSAIDS[25]	14	6	5
Antibiotics[21]	10	7	4
Multiple drugs[10]	1	3	6
ATT[9]	7	1	1

The course of acute TIN is usually reversible but can be variable depending upon the pre-existing kidney damage, nature, and duration of intake of offending drug, and the severity of kidney injury.[13] In this study, there was a full recovery of renal function in 38% of patients, while as in 58% of patients, renal function failed to reach baseline. Herbal and multiple drug use were the risk factors in our study of permanent kidney dysfunction (Table 5). Some of our cases needed permanent renal replacement therapy. Many people in our part of the world buy medicines and botanical remedies through the media or from street vendors. Inappropriate use and poor quality control in the manufacture of complementary medicines may result in the development of TIN, which may result in an increased incidence of end-stage renal disease.

CONCLUSION

Drug-induced AKI is an important cause of AKI. Most of our patients presented with oliguric AKI. ATIN is an important cause of renal dysfunction and can be underdiagnosed. Herbal drugs were the most common cause of TIN in our study. Full recovery of kidney function was seen in less than 40% of patients.

CLINICAL SIGNIFICANCE

In our study, herbal medications intake was a common cause of AKI and was associated with poor renal recovery. Early suspicion and withdrawal of the offending drug are needed to prevent renal damage.

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