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RETROSPECTIVE STUDY

Characteristics and clinical outcome of nonsteroidal anti-inflammatory drug-induced acute hepato-nephrotoxicity among Chinese patients

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Abstract

AIM: To determine the clinicopathological characteristics of nonsteroidal anti-inflammatory drug (NSAID)-induced acute hepato-nephrotoxicity among Chinese patients.

METHODS: We conducted a retrospective chart review of patients using the International Classification of Diseases, Ninth Revision diagnosis code for acute kidney injury (AKI) (584.5 or 584.9) and for acute liver injury (ALI) (570.0 or 573.3) from January 2004 to December 2013. Medical records were reviewed to confirm the diagnosis of AKI and ALI and to quantify NSAID administration.

RESULTS: Seven of 59 patients (11.8%) were identified with acute hepato-nephrotoxicity induced by NSAIDs. Five patients (71.4%) received over the recommended NSAIDs dose. Compared with NSAIDs-associated mere AKI, the risk factors of NSAIDs-induced acute hepato-nephrotoxicity are age older than 60 years (57.1%), a high prevalence of alcohol use (71.4%) and positive hepatitis B virus (HBV) markers (85.7%). Compared with NSAIDs-associated mere ALI, the risk factors of NSAIDs-induced acute hepato-nephrotoxicity are age older than 60 years (57.1%), increased extracellular volume depletion (71.4%), and renin-angiotensin-aldosterone system (RAAS) inhibitor combined use (57.1%). Acute interstitial nephritis and acute tubulointerstitial disease were apparent in three out of six (42.9%) kidney biopsy patients, respectively. Acute hepatitis was found in four out of six (66.7%) liver biopsy patients. Overall complete recovery occurred in four patients within a mean of 118.25 ± 55.42 d.

CONCLUSION: The injury typically occurred after an overdose of NSAIDs. The risk factors include age older than 60 years, alcohol use, positive HBV markers, extracellular volume depletion and RAAS inhibitor combined use.

Key words: Nonsteroidal anti-inflammatory drug; Hepato-nephrotoxicity; Acute interstitial nephritis; Acute hepatitis; Cholestasis

Core tip: This is the largest series to date demonstrating that nonsteroidal anti-inflammatory drugs are a common cause of acute combined hepato-nephrotox-

icity in the Chinese population. The risk factors include age older than 60 years, alcohol use, positive hepatitis B virus markers, extracellular volume depletion and renin-angiotensin-aldosterone system inhibitor combined use. Acute tubulointerstitial disease and acute hepatitis were the major histological findings. Treatment for the patients comprised discontinuation of the implicated drugs and pulse methylprednisolone followed by oral steroids in some patients. Cyclophosphamide was added according to the histology. The prognosis was good with prompt diagnosis and treatment.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs, both as prescription and over-the counter drugs. Six percent of the adult populations in the United States report the use of at least one prescription of NSAID per month[1] and over 30 million people receive NSAIDs daily[2]. Although NSAIDs are effective and generally well tolerated, their use is associated with a broad spectrum of adverse reactions[3]. Renal dysfunction and liver function abnormalities are relatively common, and are often symptomatic only after serious toxic reactions have occurred[4,5]. NSAIDs account for 7% of reported cases of acute kidney injury (AKI) and 35% of drug-induced AKI in the general populations[6]. NSAIDs are responsible for roughly 10% of the total of cases of drug-induced hepatotoxicity[7-9] and the incidence of NSAID-related acute liver injury (ALI) resulting in hospitalization ranged from 3.1 to 23.4/100000 patient-year[10]. However, the characteristics of patients with NSAIDs-induced acute combined hepato-nephrotoxicity are poorly understood and have been limited to case reports and a few case series[11-15] (Table 1), because of the rarity of the condition. Thus, we initiated the present study with the aim of estimating the clinical and pathological features of patients with NSAIDs-induced combined hepato-nephrotoxicity.

MATERIALS AND METHODS

Patient selection

We screened all patients hospitalized at China-Japan Friendship Hospital, China from January 2004 to December 2013, identifying those who had a recorded International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) codes for AKI (584.5 or 584.9) and ALI (570.0 or 573.3). Medical records were reviewed to confirm the diagnosis of AKI and ALI and to quantify NSAIDs administered before diagnosis. The Human Ethics Review Committee of the China-Japan Friendship Hospital approved the study protocol. Our hospital is affiliated with China's Ministry of Health and is a teaching hospital of Peking University and Beijing University of Chinese Medicine. We designed a consent form that stated that the files of hospitalized patients would be used for teaching medical students and as the material for some retrospective researches.

Patients were not classified as having NSAID-associated AKI and ALI if they received other known drugs (*e.g.*, herbal remedies, antibiotics, mushroom intake, dietary supplements and other drugs) or if they had comorbid clinical conditions or diseases, such as complex congenital heart disease and malignancy. Patients were also excluded if they had a clear alternative diagnosis explaining their AKI (*e.g.*, hemolytic uremic syndrome, transplant rejection, or acute glomerulonephritis) and ALI (*e.g.*, acute viral hepatitis: hepatitis A, B, C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus and other forms of liver disease including autoimmune, metabolic liver disease such as hemochromatosis, Wilson disease, a-1 antitrypsin deficiency, and biliary obstruction). Although volume depletion is an independent risk factor for AKI, patients with a history of volume depletion in the absence of sepsis or multiorgan failure were not excluded because it is likely that volume depletion increases the risk of NSAID use leading to AKI. Estimates of volume depletion were obtained from the medical records as reported by the patients. Patients with convincing evidence of absent or minimal alcohol consumption (< 15 g alcohol/d for women and < 20 g alcohol/d for men) were also not excluded. For comparison, hospitalized patients with NSAID-associated mere AKI or ALI were also identified at the same periods. Criteria for inclusion were the same as the above.

Methods

The clinical and demographic parameters were recorded for each patient at the time of hospitalization. These included NSAID administration dose, duration of use, history of patients, Serological markers for viral infections [anti-hepatitis A virus (HAV) IgM, IgG, hepatitis B surface antigen (HbsAg), anti-HBs, hepatitis B e antigen (HbeAg), anti-HBe, anti-HBc IgM, IgG, anti-hepatitis C virus (HCV), anti-cytomegalovirus, anti-herpes simplex virus, and anti-Epstein-Barr virus], other drug concurrently used, clinical and laboratory markers consistent with AKI and ALI, and treatment data were collected and reviewed. Abdominal sonography and nuclear magnetic resonance imaging were performed when a cholestatic pattern injury was present.

The diagnosis of NSAIDs induced liver injury was based on the patients' history, clinical and biochemical characteristics, exclusion of other forms of liver disease, consideration of the relationships between NSAIDs drug intake and onset of liver test abnormalities and

Table 1 Clinical manifestations of non-steroidal anti-inflammatory drug-induced kidney and liver injury: Literature summary

No.	Age/Sex	NSAID: Dose and duration of use	Other drugs used concurrently	Peak creatinine	Peak ALT	Peak ALP	Peak bilirubin	Histology	Outcome	Ref.
1	5/F	Acetaminophen: 11 mg/kg per dose, two total doses over 5 h Ibuprofen: 5 mg/kg per dose every 8 h, three total dose	None	6.34 mg/dL	1229 U/L	NK	NK	ND	Recovery	Zaffanello *et al*[11]
2	25/F	Nimesulide 100 mg b.i.d. for 4 d	Slimming drug containing anthraquinones and ampicillin	431 μmol/L	72 U/L	206 U/L	16 μmol/L	Acute tubular necrosis	Recovery	Li *et al*[12]
3	70/F	Nimesulide 100 mg b.i.d. for 5 d	None	5.6 mg/dL	1240 U/L	285 U/L	33 mg/dL	Massive necrosis of hepatocytes with more cholestasis	Deceased	Schattner *et al*[13]
4	56/M	Celecoxib 200 mg one to two tablets per day for 10 mo	Ramipril 10 mg/d	5.2 mg/dL	3 U/L	77 U/L	32.4 mg/dL	Acute interstitial (tubulo)nephritis, acute cholestatic hepatitis	Recovery	Tabibian *et al*[14]
5	56/M	Diclofenac 100 mg total	Hepatoprotective agents, calcium carbonate, and diuretics	485.3 μmol/L	NK	NK	NK	ND	Recovery	Tomaszewski *et al*[15]

F: Female; M: Male; ALT: Alanine aminotransferase; ALP: Alanine aminotransferase; NK: Not-known; ND: Not-done; NSAID: Nonsteroidal anti-inflammatory drug.

histological criteria, when available[16]. An illness duration of < 26 wk was used to differentiate acute from chronic liver injury[17]. Patients with underlying liver disease, such as inactive hepatitis B virus (HBV) carrier or NAFLD having normal liver tests were included into the study if they developed superimposed ALI. HBV DNA levels in inactive HBV carriers with elevated liver enzymes were also checked using polymerase chain reaction to rule out HBV reactivation. The definition and pattern of ALI (hepatocellular, cholestatic, or mixed) were characterized based on the International Consensus Meeting criteria for liver injury. Hepatocellular pattern of ALI was defined as the ratio (R) of serum alanine aminotransferase (as a multiple of its upper limit of normal) to serum alkaline phosphatase (as a multiple of its upper limit of normal) greater than 5, cholestatic as R less than 2, and mixed as R greater than 2 to less than 5[18,19]. AKI was defined as increasing in serum creatinine of 0.3 mg/dL developing over 48 h or > 50% developing over 7 d or urine output of < 0.5 mL/kg per hour for > 6 h[20]. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to stage the level of AKI[20].

Percutaneous renal biopsy and liver needle biopsy were performed. Renal paraffin sections were stained for light microscopy with hematoxylin and eosin, periodic acid-Schiff (PAS), Masson trichrome and periodic acid-silver methenamine. IgG, IgA, IgM, C3 and C1q (DAKO A/S, Glostrup, Denmark) were detected with direct immunofluorescence on frozen tissue. The fluorescence intensity was determined using a semiquantitative scale of 0-4+. Renal ultrastructure was examined using a JEM-1230 transmission electron microscope (JEOL, Tokyo, Japan). Two pathologists reviewed each kidney biopsy. Hepatic tissue samples were subjected to histological examination. Formalin- or paraformaldehyde-fixed specimens were embedded in paraffin. Five-micrometer-thick sections were cut and stained with hematoxylin and eosin, Masson trichrome, reticulin and PAS. The samples were also subjected to immunohistochemical examination for CD38, CK19, CK7, hepatitis B core antigen (HBcAg), HBsAg, HCV, Pre-S1 and Ubiquitin. Two pathologists carefully assessed all hepatic histological findings.

Statistical analysis

Comparisons for categorical measures were performed using χ^2 tests or Fisher exact tests for small sample sizes. A P value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS statistical software package (version 11.0, Chicago, IL, United States).

RESULTS

Fifty-nine patients were identified through initial International Classification of Diseases, Ninth Revision screening. Nineteen patients had comorbid conditions and multifactorial liver and kidney injury. Twenty patients had an alternate cause of hepato-nephrotoxicity (*e.g.*, acute viral hepatitis, biliary obstruction, hemolytic-uremic syndrome, glomerulonephritis). Thirteen patients had acute hepato-nephrotoxicity caused by non-NSAID insult (*e.g.*, herbal remedies, mushroom intake, and dietary supplements). Seven (male/female: 3/4; mean age: 54.14 ± 20.28 years; range: 17-71 years) (11.8%) of the cohort were identified

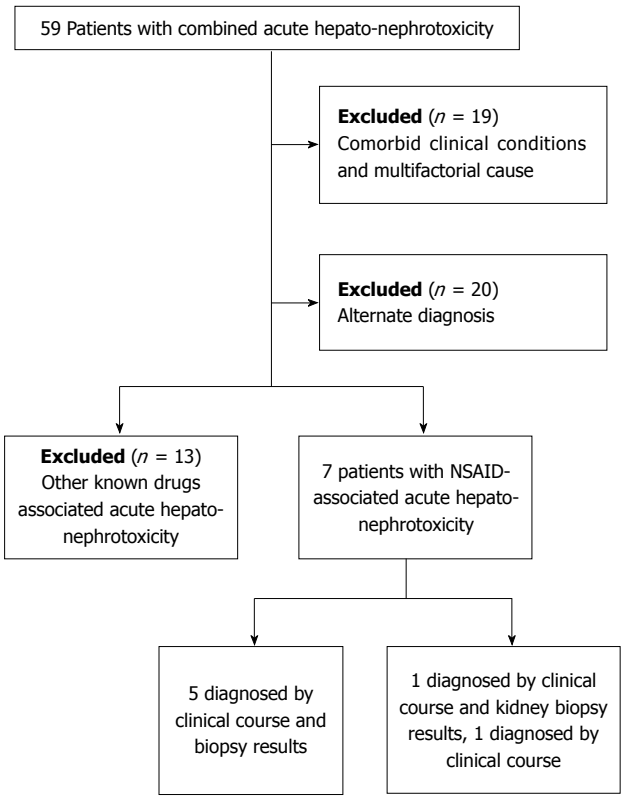

Figure 1 Classification of patients with combined acute hepato-nephrotoxicity. NSAID: Nonsteroidal anti-inflammatory drug.

to have NSAID-associated acute hepato-nephrotoxicity (Figure 1). Female sex was slightly predominant (57.1%); One patient (14.3%) had a known underlying kidney disease and six patients (85.7%) with inactive HBV carrier status. The median follow-up period was 320 d (range: 108-1080 d).

Demographic and clinical characteristics of the population are presented in Table 2. Two (28.6%) of the patients received NSAIDs in accordance with recommended dosing. Four patients (57.1%) received over twice the recommended single dose, and 1 patient (14.3%) received a dose that was < 25% above the recommended upper limit. With respect to concurrently used drugs, four patients (57.1%) received renin-angiotensin-aldosterone system (RAAS) inhibitor, four patients (57.1%) received antibiotics and two patients (28.6%) received herbs. Five patients (71.4%) had a history of volume depletion. By KDIGO criteria at the time of peak creatinine, two patients (28.6%) were classified as having Stage 2 AKI (serum creatinine 2.0 to 2.9 times baseline), and the remaining five patients (71.4%) were classified as having Stage 3 by KDIGO criteria (3.0 times baseline or increase in serum creatinine to ⩾ 4.0 mg/dL) and received renal replacement therapy. A hepatocellular pattern of liver injury was more commonly observed (four of seven, 57.1%) followed by a cholestatic pattern (two of seven, 28.6%). The frequent complaints were vomiting (six patients, 86%), fatigue (four patients, 57%), abdominal pain (four patients, 57%), and decreased urine output (four patients, 57%); pruritus (three patients, 43%), and jaundice (two patients, 29%).

To identify the risk factors of NSAIDs-induced acute combined hepato-nephrotoxicity, we performed the comparison between the patients with NSAIDs-induced combined hepato-nephrotoxicity and patients with NSAIDs associated mere AKI (n = 124) and ALI (n = 96), respectively. As shown in Table 3, in the combined hepato-nephrotoxicity group, there were more patients older than 60 than among mere AKI patients (P = 0.03). There were more patients with alcohol use (P = 0.006) and positive hepatitis virus markers (P = 0.001) in this cohort. Similarly, compared with mere ALI patients, there were more patients older than 60 in the combined hepato-nephrotoxicity cohort (P = 0.03). There were more patients with extracellular volume depletion (P = 0.002) and RAAS inhibitor combined use (P = 0.006) in the combined hepato-nephrotoxicity cohort than among the mere ALI patients (Table 4).

The renal and liver histological findings are summarized in Table 5. Five of the seven patients had both renal and liver biopsy. One patient had only a renal biopsy and another had a liver biopsy. Findings consisted of acute tubulointerstitial disease, one predominantly consisting of tubular necrosis (Figure 2A) and another with a pattern of proximal tubular injury more consistent with toxic than with ischemic injury. Two patients had acute interstitial nephritis (AIN), with eosinophils consistent with acute drug reaction in three patients (Figure 2B). One patient had focal proliferative IgA nephropathy accompanied with acute tubulointerstitial disease (Figure 2C and D). There were five patients manifested as acute hepatitis ranging from mild hepatitis with spotty cell death to submassive, bridging necrosis (Figure 3A-D). One patient with acute cholestasis recognized by cholestasis in the form of visible bile accumulation in hepatocytes and bile canaliculi (Figure 3E and F). Another patient had liver transplantation and the histology before transplantation presented as chronic cholestatic hepatitis with significant bile duct loss and the presence of cholate stasis.

As shown in Table 5, treatment for all the patients was discontinuation of the implicated drugs and pulse methylprednisolone, followed by oral steroids in three of seven patients. In two patients, cyclophosphamide was added with the above therapy. In the remaining two patients, no steroids and immunosuppressive therapy were given. Recovery occurred in 6 patients within a mean of 66.67 ± 42.57 d (median: 48 d, range: 33-145 d) for ALI, in five patients with a mean of 98.8 ± 88.5 d (median: 60 d, range: 12-205 d) for AKI and overall complete recovery occurred in four patients within a mean of 118.25 ± 55.42 d (median: 116 d, range: 60-182 d).

DISCUSSION

NSAIDs are frequently useful for pain relief and taken with food to reduce gut complaints, but patients are generally less aware of the potential nephrotoxicity.

Table 2 Clinical characteristics of non-steroidal anti-inflammatory drug-induced acute hepato-nephrotoxicity

No.	Sex/Age	Serology of infections	History	NSAID: Dose and duration of use	Other drug concurrent used	Extracellular volume depletion	Peak creatinine	Peak ALT	Peak ALP	Peak bilirubin
1	M/64	HBcAb(+)	Diabetes's mellitus, alcohol use	Tylenol 0.5 g × 5 pills, Ibuprofen 0.3 g for 2 d	Erythromycin, Telmisartan	Fever (40 ℃) watery diarrhea for 2 d	6.7 mg/dL	2565 U/L	141 U/L	131.3 μmol/L
2	M/71	HBsAg(+)	Hypertension, alcohol use	Lysine acetylsalicylate 1.5 g × 2 pills, Nimesulide 0.1 g × 2 pills for 3 d	Cefoxitin, Fosinopril	Fever (39 ℃-40 ℃) for 3 d	5.3 mg/dL	8960 U/L	598 U/L	265.6 μmol/L
3	M/69	HBcAb(+)	Spondylolisthesis lumbar backaches, alcohol use	Celecoxib 25 mg/d, for 1 yr, Diclofenac Sodium 1/d, for 1 mo	Rhizoma Cibotii, Herba Epimedii, Rhizoma Drynariae, Radix Aucklandiae, Caulis Spatholobui, Radix Dipsaci	No evidence	2.2 mg/dL	619 U/L	224 U/L	21.6 μmol/L
4	F/53	HBcAb(+) HBeAb(+)	IgA nephropathy, Alcohol use for 20 yr	Indomethacin 75 mg × 2 pills for 2 d	Lotensin, Cefaclor	Fever (39 ℃) for 2 d	7.6 mg/dL	1336 U/L	74 U/L	39.1 μmol/L
5	F/68	HBeAb(+)	Arthritis, hypertension, alcohol use	Rofecoxib 25 mg/d, for 1 mo	Irbesartan, Nifedipine, Herb including cinnabar and flower of silktree albizzia	Diarrhea for 3 d	3.9 mg/dL	1186 U/L	209 U/L	336.4 μmol/L
6	F/37	(-)	Polycystic ovary syndrome, dysmenorrhea	Piroxicam 40 mg/d for 10 d, Paracetamol, 0.1 × 35 pills intermittent for 3 mo	Herb for regulating the menstrual cycle, slimming herb	No evidence	2.1 mg/dL	105 U/L	488 U/L	214 μmol/L
7	F/17	HBsAb(+)	Chronic diarrhea for 1 yr, acute pancreatitis for 1 mo	Ibuprofen 0.3 g × 5 pills, Indomethacin 75 mg × 10 pills intermittent for 1 mo	Norfloxacin Bactericidal, Rifampicin, Cefoperazone, Meropenem, Hepatoprotective herbs, Diflucan	Diarrhea, intermittent fever for 1 mo	5.6 mg/dL	1548 U/L	600 U/L	350 μmol/L

F: Female; M: Male; NSAID: Nonsteroidal anti-inflammatory drug; ALT: Alanine aminotransferase; ALP: Alanine aminotransferase; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HBeAb: Hepatitis B e antibody; HBsAb: Hepatitis B surface antibody.

Table 3 Comparison between patients with combined acute hepato-nephrotoxicity and patients with mere acute kidney injury

	Combined acute hepato-nephrotoxicity (n = 7)	AKI (n = 124)	P value
Age (≥ 60 yr)	4	23	0.030
Hypertension	3	56	0.910
Diabetes mellitus	1	19	0.940
Alcohol use	5	24	0.006
Positive hepatitis B virus markers	6	29	0.001
Extracellular volume depletion	5	85	0.870
RAAS inhibitor combined used	4	68	0.910

AKI: Acute kidney injury; RAAS: Renin-angiotensin-aldosterone system.

Table 4 Comparison between patients with combined acute hepato-nephrotoxicity and patients with mere acute liver injury

	Combined acute hepato-nephrotoxicity (n = 7)	ALI (n = 96)	P value
Age (≥ 60 yr)	4	17	0.030
Hypertension	3	21	0.350
Diabetes mellitus	1	10	0.560
Alcohol use	5	69	0.910
Positive hepatitis B virus markers	6	75	0.640
Extracellular volume depletion	5	14	0.002
RAAS inhibitor combined used	4	11	0.008

ALI: Acute liver injury; RAAS: Renin-angiotensin-aldosterone system.

Our study is the largest series to date that demonstrates that NSAIDs are a common cause of acute combined hepato-nephrotoxicity in the Chinese population. During a 10-year period, NSAID use accounted for 11.8% of episodes of acute combined hepato-nephrotoxicity at our institution. It should be stated that the frequency of

Table 5 Histology and outcome of non-steroidal anti-inflammatory drug-induced acute hepato-nephrotoxicity

No.	Sex/Age	Immunofluorescent staining	Renal lesion	Liver lesion	Treatment and outcome
1	M/64	IgM++, IgA±, C3±	Acute tubulointerstitial disease	Acute hepatitis	Steroid 0.5 mg/kg, tappered to zero in 3 mo, ALT normalized in day 33, Scr normalized in day 182
2	M/71	Negative	Acute interstitial nephritis	Acute hepatitis	Anti-hepatitis B virus, steroid 0.5 mg/kg, tappered to zero in 3 mo, ALT normalized in day 50, Scr normalized in day 60
3	M/69	IgM±, IgA±, C3±	Acute tubulointerstitial disease	Acute hepatitis	Steroid 1 mg/kg, tappered to zero in 6 mo, cyclophosphamide accumulated to 6 g, potassium supplement, correction of acidosis, ALT normalized in day 40, Renal tubular acidosis normalized in day 15, Scr 140 μmol/L (10/8/2013)
4	F/53	IgA2+, C3+	Focal proliferative IgA nephropathy associated with acute tubulointerstitial nephropathy	Acute hepatitis	Steroid 1 mg/kg, tappered to 10 mg/d in 1 yr, cyclophosphamide accumulated to 6 g, ALT normalized in day 46, Scr 154 μmol/L (11/16/2013)
5	F/68	IgM+, C3±	Acute interstitial nephritis	ND	Steroid 0.5 mg/kg, tappered to zero in 3 mo, ALT normalized in day 145, Scr normalized in day 12.
6	F/37	Negative	Acute interstitial nephritis	Acute cholestasis	symptomatic treatment, Scr normalized in day 35, ALT normalized in day 86
7	F/17	ND	ND	Chronic cholestatic hepatitis (during transplantation)	Symptomatic treatment, Scr normalized in day 205, liver transplantation

F: Female; M: Male; ND: Not-done; ALI: Acute liver injury.

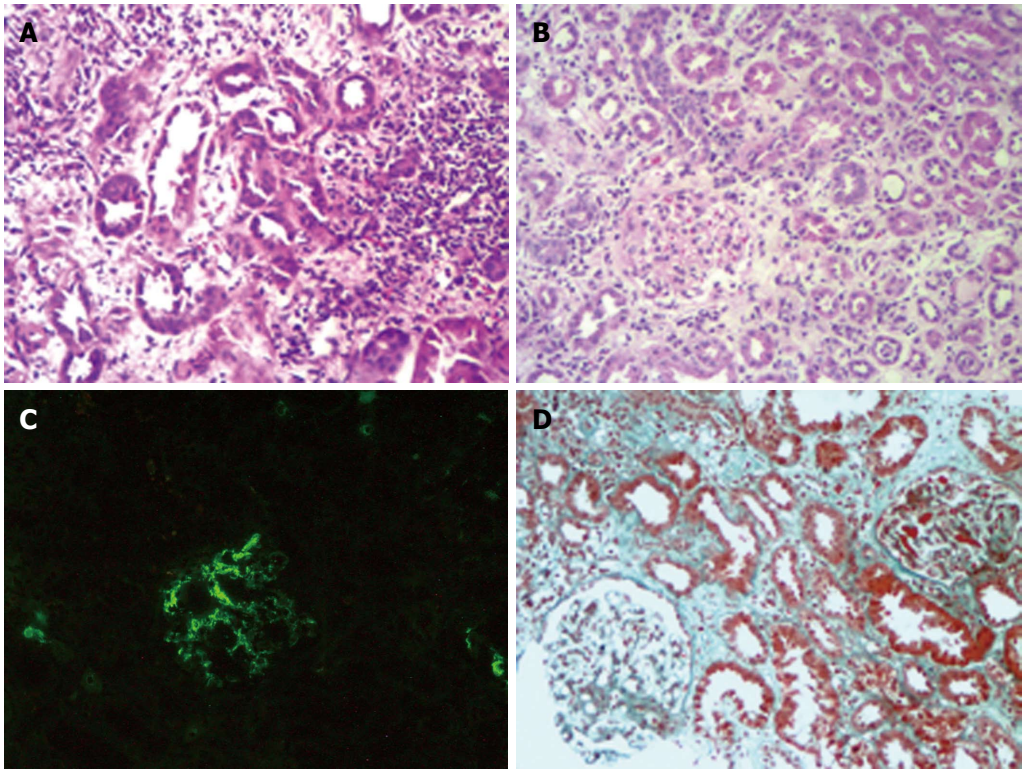

Figure 2 Nonsteroidal anti-inflammatory drugs-induced acute interstitial nephritis and acute tubulointerstitial disease. A: Substantial inflammatory cells, including lymphocytes and eosinophils infiltrate, can be seen in the renal interstitium. The tubular epithelium undergoes necrosis, which can be seen by denudation of tubular epithelial cells with the rupturing of the tubular basement membrane (HE, × 200); B: Edema and inflammatory infiltrate in the interstitium cause the renal tubules to be abnormally widely spaced with no changes to the glomerulus. The infiltrate includes inflammatory cells (eosinophils and lymphocytes), and there is obvious disorder of the renal tubular epithelium with significant edema (HE, × 200); C: Presence of IgA is seen throughout the mesangium by immunofluorescence (Fluorescein isothiocyanate anti-IgA, × 200); D: Proliferation of mesangial cells is seen along with focal inflammation of glomeruli. The denudation of the tubular epithelial cells, the edema and inflammatory infiltration in the interstitum are indicted (Masson staining, × 200). HE: Hematoxylin and eosin staining.

NSAID-related hepato-nephrotoxicity is too low to assess accurately in clinical trials[21]. Spontaneous reports do not allow the determination of incidence or relative risk, and available databases are scarce and based on hetero-

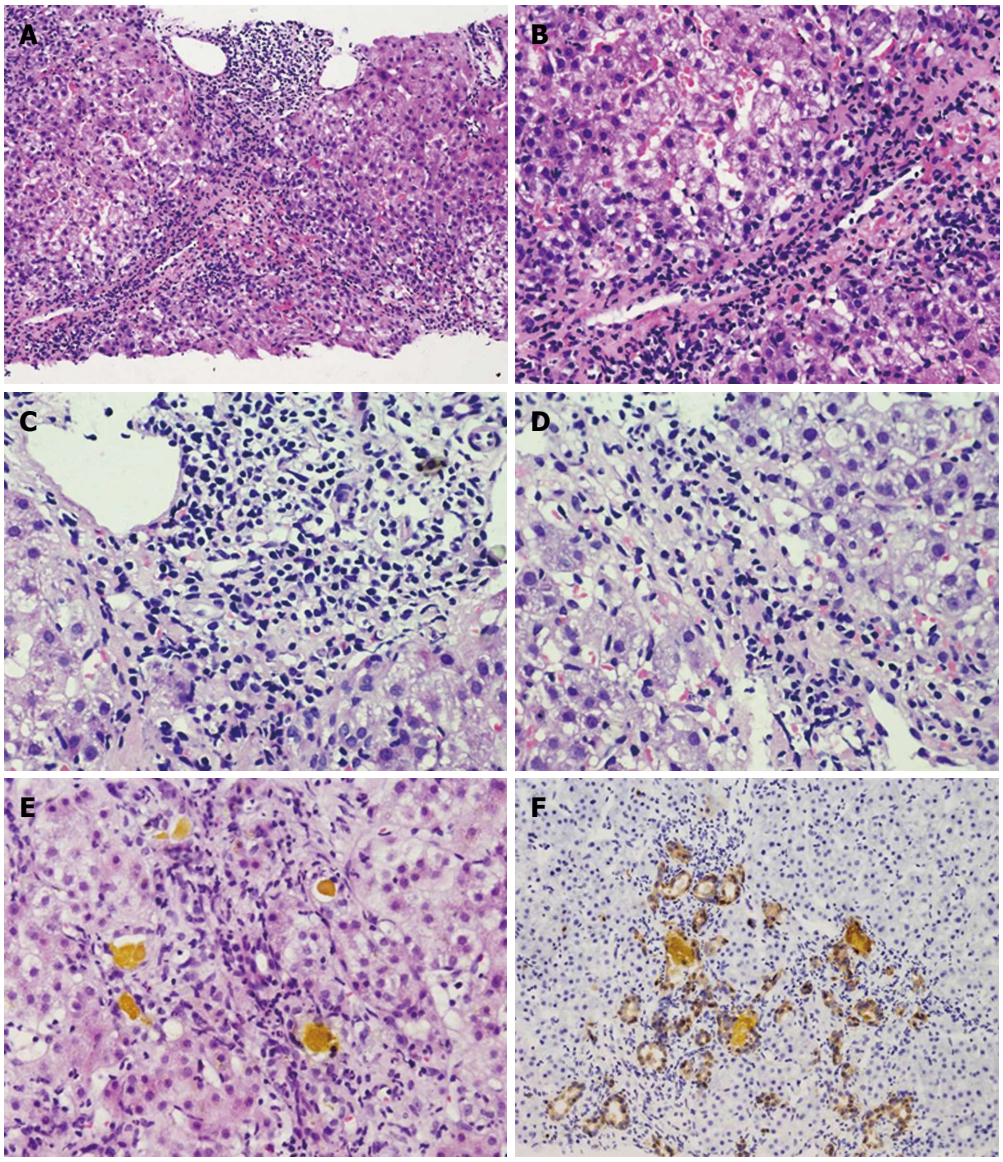

Figure 3 Nonsteroidal anti-inflammatory drugs-induced acute hepatitis. A: There is a bridging necrosis zone around the central vein (HE, × 100); B: Vacuole and necrosis are found in hepatic cells around the necrosis zone (HE, × 400); C: A substantial inflammatory cells including lymphocytes, plasma cells, and eosinophils infiltrate can be seen in the portal tract (HE, × 400); D: Hepatic necrosis and lymphocytic infiltration, including some eosinophils (arrow), in the collapsed parenchyma can be observed (HE, × 400); E: NSAID-induced acute cholestasis; E: Small bile duct dilation and cholestasis can be seen in the portal area (HE, × 400); F: The cholestasis accompanying hepatocellular vacuolation is presented (HE, × 100). HE: Hematoxylin and eosin staining; NSAID: Nonsteroidal anti-inflammatory drug.

geneous criteria. In this study, the diagnosis in each case was made on the basis of clinical assessment, biochemical parameters, and histological evaluation when available, and we also ruled out other causes of acute hepato-nephrotoxicity. Thus, this analysis more clearly characterized the diagnosis of NSAIDs-induced acute hepato-nephrotoxicity and its clinical outcome in the long-term follow-up. In this study, NSAIDs-associated acute hepato-nephrotoxicity typically occurred in older patients who had ingested NSAIDs at over the recommended dose. However, in the literature cases, there was only 1 patient older than 60 years and the patients ingested NSAIDs at the recommended dose[11-15].

In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function (< 1%)[22]. However, in situations in which renal perfusion may be diminished, including what we have demonstrated in this study by the comparison between NSAIDs induced combined ALI-AKI and mere ALI, elderly age, decreased effective circulating volume, RAAS inhibitor combined use, the inhibition of prostaglandin-induced vasodilation with the use of NSAIDs may further compromise renal blood flow and exacerbate ischemic injury. Furthermore, evidence shows that some NSAIDs induce significant decreases in the glomerular filtration rate (GFR), urine flow, excretion rates of sodium and potassium, osmolality clearance and free water clearance in chronic heart failure (CHF) patients treated with angiotensin-converting enzyme (ACE)-inhibitors[23]. The presence of renal disease might represent a contraindication for NSAIDs use. Whelton *et al*[24] reported how almost 30% of patients with renal disease have a relevant risk of worsening renal

function when exposed to non-selective NSAIDs. In our study, there was one patient with IgA nephropathy (normal kidney function) who developed chronic renal failure after exposure to the NSAIDs. In a report of 100 patients with chronic kidney disease and worsening AKI while receiving angiotensin inhibiting agents, there was a clear association with the concurrent use of NSAIDs in 10 patients[25]. An Australian report described the potential nephrotoxic harm from combining diuretics, angiotensin converting enzyme inhibitors, and NSAIDs - the "triple whammy"[26].

Although drugs causing acute hepatocellular injury tend to do so in younger patients, agents leading to cholestatic injury tend to occur in older individuals, which suggests that age may play a role in this type of injury pattern[27]. However, in our study, four of six cases (66.7%) were reported to have hepatocellular injury. In western countries, NSAIDs are widely consumed and, in addition to antimicrobial agents, are the most frequent causes of drug induced liver injury (DILI)[9,28,29]. In contrast, NSAIDs are not one of the top three causes of DILI in China. In a systematic analysis, NSAIDs were the fourth cause and only accounted for 7.6% of the 24112 Chinese DILI patients[30]. However, in our acute combined hepato-nephrotoxicity, NSAIDs are a very common causes (11.7%). Although differences in the association of NSAIDs across databases are observed[7], factors have been proposed to influence the risk of developing drug-induced liver injury, including age, gender, chronic alcohol consumption, concomitant drugs, underlying disease states, obesity, diabetes mellitus type 2 and insulin resistance[31]. To differentiate alcoholic liver disease and drug induced ALI, we only included patients with minimal alcohol consumption (< 15 g alcohol/d for women and < 20 g alcohol/d for men) and demonstrated that chronic alcohol consumption was a risk factor for NSAIDs associated acute hepato-nephrotoxicity. Positive hepatitis markers were another risk factor and this has not been demonstrated by the previous study. Chronic infection with HBV affects over 400 million individuals[32] and there is a very high endemic state for HBV infection in China. Although the patients in our cohort were in the inactive (carrier) phase, which is characterized by the positive HBV marker, persistently normal ALT levels and low or undetectable levels of serum HBV DNA, they were more likely to develop NSAIDs-associated hepato-nephrotoxicity than non-HBV carriers.

Acute hepatitis accounts for approximately 70% of NSAIDs-induced acute hepato-nephrotoxicity. This liver injury pattern resembles acute viral hepatitis, ranging from mild hepatitis with spotty cell death to submassive or massive necrosis. There was one patient diagnosed as acute cholestasis induced by Piroxicam, which can produce both hepatocellular and cholestatic pattern in the literature. Another patient did not have a liver biopsy at the onset of acute hepato-nephrotoxicity. Her biopsy was taken during the transplantation and showed chronic cholestatic hepatitis. On the basis of several clinical and immunohistological findings, mechanisms involved in NSAIDs-induced interstitial nephritis are considered cell mediated. The interstitial infiltrate is distinguishable from the pathological patterns seen in other causes[33,34], including edematous interstitium containing eosinophils, mononuclear cells, and plasma cells and the tubulitis, characterized by lymphocytes invading the tubules with variable ranges of tubular epithelial cell damage. Pathological diagnosis of NSAIDs-induced acute hepato-nephrotoxicity, however, remains challenging and should always be included in the differential diagnosis, especially when, after excluding other possible causes, the origin of the liver injury remains unclear. The diagnosis usually rests on a careful medical history, which includes prescribed and over the-counter medications, the latent period between drug and/or toxin exposure to clinical symptoms or abnormal liver tests, and biopsy results. Overall, complete recovery after the withdrawal of the drug occurred in the majority of patients with NSAIDs-associated acute hepato-nephrotoxicity.

In conclusion, NSAIDs are a common cause of acute combined hepato-nephrotoxicity in the Chinese population. The injury typically occurred after the over-administration of NSAIDs. The treatment for the patients was discontinuation of the implicated drugs and steroids in some patients. Cyclophosphamide was added according to the histology. The prognosis was good with prompt diagnosis and treatment.

COMMENTS

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs, both as prescription and over-the counter drugs. Although NSAIDs are effective and generally well tolerated, their use is associated with a broad spectrum of adverse reactions. However, the clinical and pathological characteristics of NSAIDs-induced acute hepato-nephrotoxicity among Chinese patients are poorly understood and have been limited to case reports and a few case series, because of the rarity of the condition.

Research frontiers

In this study, the authors demonstrate that the prevalence of NSAIDs-induced acute hepato-nephrotoxicity was 11.8%. Most of the patients received over the recommended NSAIDs dose. The risk factors of NSAIDs-induced acute hepato-nephrotoxicity include age older than 60 years, a high prevalence of alcohol use and positive hepatitis B virus markers, increased extracellular volume depletion and renin-angiotensin-aldosterone system inhibitor combined use. Acute interstitial nephritis and acute hepatitis were common histological findings.

Innovations and breakthroughs

Recent reports have highlighted that NSAIDs induced mere acute kidney injury and mere acute liver injury. This is the first study to report the clinical and pathological characteristics of NSAIDs-induced acute hepato-nephrotoxicity among Chinese patients.

Applications

By understanding the clinical and pathological characteristics of NSAIDs-induced acute hepato-nephrotoxicity, this study indicates the prevalence of this disease among Chinese patients. The characteristics of the patients in this study and their treatment may help physicians to make a diagnosis and choose the correct therapy for this disease.

Peer review

The authors examined the clinical and pathological characteristics of NSAIDs-induced acute hepato-nephrotoxicity among Chinese patients. The treatment for such patients was discontinuation of the implicated drugs and pulse methylprednisolone followed by oral steroids in some patients. cyclophosphamide

was added according to the histology. The prognosis was good with prompt diagnosis and treatment. The results are interesting and may help physicians to make a diagnosis and choose the correct therapy for this disease.

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