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MINIREVIEWS

Clinical features of acute kidney injury in patients with Kawasaki disease

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Abstract

Although acute kidney injury (AKI) is a common complication in hospitalized children, AKI has rarely been reported in patients with Kawasaki disease (KD). Herein, we review the clinical trajectories of AKI in patients with KD. A total of 39 patients with KD who developed AKI have been reported in 28 publications as case reports. The causes of AKI include prerenal AKI associated with acute heart failure (AHF), intrinsic AKI caused by tubulointerstitial nephritis (TIN), acute nephritic syndrome (ANS), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, rhabdomyolysis, and KD shock syndrome (KDSS). Six of the 39 patients (15.4%) underwent renal replacement therapy. While AHF and multiple organ dysfunction syndrome developed in 41% and 68% of KD patients with AKI, respectively, all patients recovered without any renal sequelae. Although the precise pathogenic mechanism underlying the development of AKI in patients with KD is unknown, several possible mechanisms have been proposed, including T-cell-mediated immunologic abnormalities for TIN, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune complex-mediated nephropathy and ASN, and capillary leak and an increased release of cytokines with myocardial dysfunction for KDSS.

Key words: Kawasaki disease; Acute kidney injury; Kidney involvement; Multiple organ dysfunction syndrome

Core tip: Acute kidney injury (AKI) has rarely been reported in patients with Kawasaki disease (KD). We review the clinical characteristics of AKI in patients with KD and show that AKI is caused by a number of pathologic changes induced by KD. Patients with KD and AKI had good outcomes, despite the developed of multiple organ dysfunction syndrome. The possible mechanisms underlying the development of AKI in KD include T-cell-mediated immunologic abnormalities, renal and glomerular endothelial injury resulted from vasculitis, immune complex-mediated kidney injury, and capillary leak and the increased release of cytokines with myocardial dysfunction.

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INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis that occurs mainly in infants and children[1]. Although clinical and epidemiologic studies suggest an infectious etiology, the causative agent has yet to be determined[2]. Recent studies have suggested that an immunologic reaction is induced in genetically-susceptible hosts upon exposure to the KD trigger[2]. Because KD is a systemic vasculitis, KD can involve multiple organs and tissues, including the kidneys[3].

Kidney complications in KD include pyuria, trace proteinuria, prerenal acute kidney injury (AKI), intrinsic AKI resulted from tubulointerstitial nephritis (TIN), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, intrinsic AKI associated with KD shock syndrome (KDSS), acute nephritic syndrome (ANS), nephrotic syndrome (NS), and renal tubular abnormalities[4]. Although patients with KD often present with sterile pyuria and trace proteinuria, other kidney complications in KD are uncommon[4]; however, several laboratory and imaging studies have shown that a number of patients with KD develop subclinical kidney injury[5,6].

AKI is a common complication in hospitalized children[7]. Recent studies have shown that AKI developed in 26.9% of children and young adults admitted to the intensive care unit (ICU)[8], and in at least 5% of non-critically ill hospitalized children and young adults[9]. Because AKI is associated with poor outcomes, including a high mortality rate and long-term morbidity[7,10], it is important to establish the causes and clinical features of hospitalized children with AKI, as well as patients with KD. The clinical trajectories of AKI in patients with KD are the subject of this mini-review.

We conducted a computerized search of the English, French, and Spanish literature using the PubMed database with a search engine and the Japanese literature using the Japan Medical Abstract Society database with a search engine from January 1967 through April 2018. The search used a combination of the following terms: "Kawasaki disease" with "acute kidney injury" or with "acute renal failure". Also, a direct search of cited references was conducted. The clinical criteria in the 2004 American Heart Association/American Academy of Pediatrics guidelines were used to diagnose KD[11]. AKI is usually defined as serum creatinine level elevation ⩾ 1.5 times the baseline level, according to Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury[12]. Because the baseline level of serum creatinine was not documented in most of the patients searched in this study, AKI was defined as a serum creatinine level ⩾ 1.5 times the upper limit of the normal age-specific serum creatinine reference level[13,14]. Studies which had insufficient clinical information for each patient were excluded from detailed analysis of the clinical manifestations of KD patients with AKI.

PREVALENCE OF AKI IN PATIENTS WITH KD

Chuang *et al*[13] studied the clinical characteristics and laboratory data of 336 Taiwanese patients with KD, including serum creatinine levels, and reported that 28% of the patients with KD developed AKI. Moreover, young age and elevated alanine transaminase level were reported to be the main factors associated with AKI. Based on our review of the clinical and laboratory data of 249 Japanese children with KD, however, no patients developed AKI[15]. Although it is not clear why the two reports yielded a different prevalence for AKI in patients with KD, it is possible that differences in disease severity influenced the results[15].

EPIDEMIOLOGY

Thirty-nine patients with KD who developed AKI have been reported in 28 publications as case reports[16-43]. The median age was 4.8 years (range, 3 mo-to-45 years). Twenty-seven patients were male (male-to-female ratio, 2.07:1). Thirty-two patients developed complete KD, while 7 patients had incomplete KD.

CAUSES OF AKI

The causes of AKI are usually divided into the following three pathophysiologic categories: prerenal AKI, which is characterized by effective hypoperfusion of the kidneys and a lack of parenchymal damage to the kidney; intrinsic AKI, which involves renal parenchymal damage; and postrenal AKI, which is associated with acute obstruction of the urinary tract[44]. In patients with KD, prerenal AKI associated with acute heart failure (AHF)[16,17] and intrinsic AKI have been reported. The causes of intrinsic AKI in KD include TIN[18-21], ANS[22-24], HUS[25-27], immune complex-mediated nephropathy[28], rhabdomyolysis[29], and KDSS[30-34] (Table 1); however, because only 8 of the reported KD patients with AKI underwent renal biopsies, the etiology of AKI was unknown in 25% of the patients[35-43].

CLINICAL MANIFESTATIONS

Oliguria, edema, hypotension, and hypertension occurred in 62% (18/29), 31% (2/29), 41% (16/39) and 15.4% (6/39) of the KD patients, respectively, and AHF developed in 41% (16/39) of the KD patients. Based on the Goldstein diagnostic criteria, 68.4% of patients had multiple organ dysfunction syndrome (MODS)[45], and the median number of affected organs was 2 (range, 1-5).

Table 1 Causes of acute kidney injury in patients with Kawasaki disease

Cause	*N*
1 Prerenal AKI associated with acute heart failure	2
2 Intrinsic AKI	
Tubulointerstitial nephritis	4
Acute nephritic syndrome	3
Hemolytic uremic syndrome	3
Immune complex-mediated nephritis	1
Rhabdomyolysis	1
Kawasaki disease shock syndrome	14
Undetermined etiology	11

AKI: Acute kidney injury.

The dysfunctional systems included the cardiovascular system in 41% (16/39) of the patients, the respiratory system in 10.2% (4/39), the nervous system in 25.6% (10/39), the hematologic system in 5.1% (2/39), and the hepatobiliary system in 33.3% (13/39).

The median blood urea nitrogen level was 58 mg/dL (range, 8-194 mg/dL), and the median serum creatinine level was 2.2 mg/dL (range, 0.5-7.43 mg/dL). Sixteen of 20 patients (80%) had hyponatremia (serum sodium < 135 mEq/L), 82.1% had proteinuria, 46.4% (13/28) had hematuria, and 73.9% (17/23) had pyuria. Three patients with KDSS developed NS, and 3 patients with ANS had macroscopic hematuria.

Only 8 patients underwent renal biopsies, which revealed TIN in 4 patients, ATN in 2, immune complex-mediated nephropathy in 1, and minor abnormalities in 1. Thirty of the 39 patients (76.9%) underwent intravenous immunoglobulin (IVIG) therapy. IVIG therapy was effective in 73.3% (22/30) of the patients, while 26.7% (8/30) were IVIG-resistant. Six of the 39 patients (15.4%) had renal replacement therapy, which included hemodialysis in 4 patients, continuous hemodialysis in 1, and peritoneal dialysis in 1.

All patients recovered from AKI without any renal sequelae. Although transient coronary artery dilatation occurred in 28.2% (11/39) of the patients, coronary artery aneurysms (CAAs) developed in 5.1% (2/39).

Prerenal AKI

Two patients with KD who developed prerenal AKI have been reported. Senzaki *et al*[16] reported an 8-year-old boy with KD who developed AHF and AKI. The results of the fractional excretion of sodium (0.04%), the renal failure index (0.02), the urine-to-plasma creatinine ratio (54), and the urine-to-plasma osmolality ratio (1.7) were consistent with prerenal AKI. Adachi described a 2-year-old girl with KD who developed prerenal AKI caused by hypovolemia due to gastrointestinal losses and AHF[17]. An intravenous fluid infusion and IVIG therapy resolved AKI following improvement of AHF in both patients, probably due to correction of hypovolemia and myocardial dysfunction, respectively.

AHF causes renal hypoperfusion due to decreased cardiac output[44]. In addition, KD is associated with hypovolemia due to decreased oral intake, gastrointestinal losses, or third spacing resulting from increased vascular permeability[16]. Therefore, both hypovolemia and AHF may have central roles in the development of prerenal AKI in patients with KD.

Intrinsic AKI

TIN: AKI due to TIN has been reported in 5 patients with KD. None of the patients had a *Yersinia pseudotuberculosis* infection[46]. Veiga *et al*[18] reported a 2-year-old boy with KD who developed AKI based on a renal biopsy, which showed diffuse interstitial infiltration of mononuclear and polymorphonuclear leukocytes. The patient was treated with IVIG, oral aspirin, fluid restriction, and furosemide, and recovered without any untoward sequelae. Kawamura[19] reported a 9-year-old girl with KD who developed AKI based on a renal biopsy, which showed mild interstitial mononuclear cell infiltration. The patient underwent hemodialysis and recovered without any renal sequelae. Ashida *et al*[20] reported a 5-year-old boy with KD who developed AKI based on a renal biopsy, which revealed interstitial infiltration of mononuclear cells. After fluid restriction and IVIG therapy, the boy recovered without sequelae. Bonany *et al*[21] reported an 8-year-old boy with KD who developed AKI and NS based on a renal biopsy, which showed TIN and acute tubular necrosis; the patient recovered with supportive care alone.

TIN is an immune-mediated cause of AKI that is characterized by the presence of an inflammatory cell infiltrate in the interstitium of the kidney[47]. Although acute TIN is largely due to medications, autoimmune diseases are associated with acute TIN, including anti-tubular basement membrane disease, TIN with uveitis, and KD[48]. Although the pathogenesis underlying TIN has not been completely described, T cell activation and the resultant cytokine and protease activity may play central roles in TIN. Because T cell activation and extensive cytokine release also occur in KD[1,2], these immunologic abnormalities may cause acute TIN in some patients with KD.

ANS: AKI due to ANS has been reported in 3 patients with KD. Suzue *et al*[22] reported a 5-mo-old boy with KD who developed AKI due to ANS 2 wk after IVIG therapy with a transient decrease in serum C3 and C4 levels. The patient recovered with supportive care alone. Yoshida *et al*[23] reported a 3-mo-old girl with KD who developed AHF and AKI due to ANS 6 d after IVIG therapy with a transient decrease in serum C3 and C4 levels. While the pathogenesis underlying the development of ANS in these patients with KD was not established, an immune complex-mediated mechanism was suspected because both patients had transient hypocomplementemia following IVIG therapy.

In contrast, Motoyama *et al*[24] reported a 6-year-old boy with ANS and AKI who subsequently developed KD. The patient was administered intravenous corti-

costeroids and oral aspirin and recovered without any sequelae.

HUS: AKI due to HUS has been reported in 3 patients with KD. Ferriero and Wolfsdorf[25] reported a 2-year-old girl with KD who developed AKI and metabolic encephalopathy due to HUS. She recovered with supportive care alone[25]. Heldrich *et al*[26] reported a 3-year-old girl with KD who developed AKI due to HUS and Henoch-Schönlein purpura, which required adjustment to therapy. Saviour *et al*[27] reported a 2-year-old boy with KD who developed AKI due to HUS. The patient underwent IVIG therapy and supportive management of fluids and electrolytes. She recovered without any sequelae.

Without renal biopsy findings, the pathogenesis of HUS in patients with KD cannot to be ascertained; however, it is possible that vasculitis-associated KD may involve the kidney causing injury to the renal and glomerular endothelium, thus leading to HUS[25].

Immune complex-mediated nephropathy: Nagamatsu *et al*[28] reported a 3-year-old boy with KD who developed AKI. The patient was treated with IVIG, dopamine, and furosemide. Electron microscopy of a renal biopsy specimen showed electron-dense deposits in the subepithelial spaces and podocytes, which suggested the possibility of glomerular derangement by immune complexes.

Rhabdomyolysis: Sevin *et al*[29] reported a 10-year-old girl with KD who developed AKI due to rhabdomyolysis that was possibly caused by hyperthermia. A renal biopsy showed renal tubular necrosis without glomerular or vascular changes[29]. The patient recovered from AKI with IVIG and supportive care alone.

KDSS: KDSS is a condition characterized by systolic hypotension or clinical signs of poor perfusion in patients with KD[49,50]. Although the pathogenesis underlying KDSS is unknown, intensive vasculitis with capillary leak and hypercytokinemia with myocardial dysfunction may cause KDSS[49-51].

Mac Ardle *et al*[30] reported a 2-year-old boy with KDSS who developed encephalopathy, respiratory failure and AKI. A renal biopsy showed normal glomeruli and a patchy immune-type infiltrate consisting of plasma cells and eosinophils, with evidence of recovering acute tubular necrosis. The patient received an intravenous fluid infusion, underwent peritoneal dialysis, and was mechanically ventilated. The boy recovered with mild neurologic sequelae. Nakanishi *et al*[31] reported a 12-year-old boy with KDSS who developed AHF, a coagulopathy, and AKI. A renal biopsy showed no glomerular or tubular abnormalities. The patient recovered with IVIG, hemodialysis, and the intravenous administration of catecholamines. An 11-year-old girl with KDSS who developed AKI and AHF due to myocarditis was reported[32]. The patient was mechanically ventilated, and received a diuretic intravenously, and IVIG therapy. She recovered but had CAAs. Umei *et al*[33] reported a 12-year-old boy with KDSS who developed AHF, hepatic dysfunction, a coagulopathy, and AKI. The patient was treated with IVIG, plasma exchange, continuous hemodialysis, and the intravenous administration of catecholamines. He recovered without any sequelae. Gatterre *et al*[34] studied 11 patients with KDSS and reported that 10 developed AKI. Nine of the patients had proteinuria, 3 of whom exhibited NS. All of the patients underwent IVIG therapy and recovered without sequelae.

Undetermined etiologies: Eleven patients with AKI of unknown etiologies have been reported. Yamawaki *et al*[35] reported a 5-year-old boy with KD who developed oliguric AKI. The patient underwent hemodialysis and recovered without any sequelae. Nardi *et al*[36] reported a 6-year-old girl with KD who developed oliguric AKI and hepatic dysfunction. The patient recovered with supportive care alone. Lande *et al*[37] reported a 3-year-old girl with KD who developed oliguric AKI. The patient received IVIG and underwent hemodialysis. She recovered without any sequelae. Ashida *et al*[20] reported a 3-year-old boy with KD who developed AKI. He was treated with IVIG and recovered without any sequelae. El Karoui *et al*[38] reported a 45-year-old man with adult-onset KD who developed AKI. He was treated with IVIG, which resulted in rapid improvement and recovery of normal renal function. Nandi and Mondal[39] reported a 4-year-old boy with KD who developed oliguric AKI. The patient recovered with supportive care alone. Keeswijk and Walle[40,41] reported a 2-year-old boy with KD who developed oliguric AKI. The patient recovered completely with IVIG therapy, fluid restriction, and a diuretic. Tiewsoh *et al*[42] reported 3 boys with incomplete KD who developed AKI. All of the patients were treated with IVIG and recovered without any sequelae. Martínez Vázquez *et al*[43] reported a 9-year-old girl with KD who developed oliguric AKI and cholestasis. The patient was treated with IVIG and intravenous pulses of methylprednisolone, which led to an improvement in the AKI and clinical features of KD, but she had CAAs.

THERAPEUTIC STRATEGIES TO KD PATIENTS WITH AKI

Treatment of KD patients with prerenal AKI and AHF consists of appropriate restoration of the normal circulating blood volume, heart function support[44], and specific therapy for KD[44]. Among KD patients with intrinsic AKI, renal damage results from vasculitis of the renal arteries, or T cell- or B cell-mediated immunoregulatory abnormalities caused by KD. Therefore, treatments adapted to the severity of KD can improve AKI in addition to supportive therapies to ameliorate derangements of fluid and electrolyte homeostasis, which include fluid restriction, diuretic usage and renal replacement therapy[10,44].

CONCLUSION

AKI in patients with KD is uncommon and includes the following conditions: prerenal AKI; intrinsic AKI caused by TIN; ANS; HUS; immune complex-mediated nephropathy; rhabdomyolysis; KDSS; and undetermined etiologies.

Although the pathogenic mechanism underlying renal involvement in patients with KD who develop AKI is unknown, several possible mechanisms have been proposed, which include T-cell-mediated immunologic abnormalities for TIN, muscle injury caused by hyperthermia for rhabdomyolysis, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune-complex mediated nephropathy and ANS, and capillary leak and hypercytokinemia with myocardial dysfunction induced by intensive vasculitis for KDSS.

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