Clinical Kidney Journal

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Leading European Nephrology

Clinical Kidney Journal, 2015, vol. 8, no. 6, 681–685

doi: 10.1093/ckj/sfv106
Advance Access Publication Date: 16 October 2015
CKJ Review

CKJ REVIEW

Dengue-associated acute kidney injury

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Abstract

Dengue is presently the most relevant viral infection transmitted by a mosquito bite that represents a major threat to public health worldwide. Acute kidney injury (AKI) is a serious and potentially lethal complication of this disease, and the actual incidence is unknown. In this review, we will assess the most relevant epidemiological and clinical data regarding dengue and the available evidence on the frequency, etiopathogenesis, outcomes and treatment of dengue-associated AKI.

Key words: acute kidney injury, dengue, rhabdomyolysis, acute glomerulonephritis, hemorrhagic fever

Introduction

Dengue disease has emerged globally as the most frequent and medically relevant viral infection transmitted by a mosquito bite. Acute kidney injury (AKI) is a serious complication of dengue. This review summarizes the most relevant information available on dengue-associated AKI.

In terms of its morbidity and mortality, dengue is considered the most important disease among the arthropod-borne viral diseases that affect humans. It is believed that >50 million people residing in tropical areas worldwide are infected with the dengue virus every year and that >2.5 billion people reside in areas in which dengue is endemic. The incidence of dengue has increased 30-fold in the past 50 years, extending into countries that were previously disease free [1].

Dengue is a systemic acute febrile disease transmitted by mosquitoes of the genus *Aedes* (*aegypti* and *albopictus*), with *Aedes aegypti* as the main vector. The vector mosquito first appeared in Africa, then disseminated together with the slave trade from the fifteenth to nineteenth centuries. In the eighteenth and nineteenth centuries, it spread across Asia through commercial exchanges and finally emerged globally in the past 50 years as a result of the expansion of travel and trade [2]. Global trade and tourism transported the dengue virus from endemic areas to other parts of the world, where dengue became a global pandemic affecting not only tropical countries but also some regions of Europe and North America [3–6]. Cases of dengue have been detected among travelers to endemic areas upon their return home to disease-free regions, often with a late diagnosis followed by severe systemic complications [7–9].

The dengue virus is an RNA arbovirus from the genus *Flavivirus* (family Flaviviridae), which also includes the etiologic agents of yellow fever, Nile fever and Saint Louis encephalitis. Antigenic characteristics allow the classification of four serotypes of dengue virus: DEN-1, DEN-2, DEN-3 and DEN-4. More recently, a new serotype, DEN-5, was identified in serum samples collected during an epidemic of dengue in Malaysia in 2007 [10]. Several lineages and genotypes have been identified in each serotype, which indicates the wide genetic variability of the dengue serotypes.

The disease is transmitted through mosquito bites from female *Ae.aegypti* infected with the virus, which require blood meals to obtain the protein needed for oviposition. This mosquito is a domestic vector with diurnal anthropophilic and zoophilic habits. The virus multiplies inside the mosquito's digestive system then spreads to different tissues. After an extrinsic incubation period of 7–11 days, on average, the virus reaches the mosquito's salivary glands; the period of virus transmission then begins and lasts throughout its lifetime [11]. Climatic conditions such as

Received: September 1, 2015. **Accepted:** September 25, 2015

elevated temperature, rainfall and air humidity, as well as urban structures without adequate sanitation, are factors that contribute to the active dispersion of the mosquito and the dissemination of the various virus serotypes [12].

Dengue exhibits various patterns of clinical presentation with unpredictable clinical progression and outcomes, ranging from clinically unapparent forms to severe bleeding and shock, eventually resulting in death [1]. Reinfection with a different serotype is associated with severe clinical manifestations, likely due to cross-reactive antibodies [13]. The first manifestation of classic dengue is sudden onset of fever, which is usually 39–40°C, accompanied by headache, prostration, myalgia, arthralgia, retro-orbital pain and itchy or non-maculopapular exanthema. In addition, anorexia, nausea, vomiting and diarrhea might be present. The initial symptoms of severe dengue are similar to those of the classic form, quickly followed by bleeding and/or cavity effusion, hemodynamic instability and/or shock. The hemorrhagic manifestations are associated with thrombocytopenia (<100 000 platelets/mm^3), hemoconcentration and one or more of the following clinical events indicative of plasma extravasation: pleural effusion, ascites and an increase in the hematocrit above 20% of the basal value. The selective loss of plasma into the serous cavities, such as the peritoneal and pleural cavities, might cause hypovolemic shock. The hemorrhagic manifestations begin 3–7 days after the onset of the disease, characterized by a positive tourniquet test, petechiae (limbs, face and axillae), ecchymosis, epistaxis, gingival bleeding, uterine bleeding and upper gastrointestinal bleeding. In severe dengue, an elevated fever might last 2–7 days, and then the patients might develop intense abdominal pain, pallor, clammy and cold skin, agitation, sleepiness, breathing difficulties, a fast and weak pulse, shock and death [1].

The main laboratory tests for the diagnosis of dengue are based on the detection of viral genetic material using serological or molecular methods. An enzyme-linked immunosorbent assay (IgM or IgG) is the most widely used serological method due to its high sensitivity and easy performance. This method detects anti-dengue antibodies, and samples might be collected starting 6 days after the onset of symptoms [1]. In cases of primary infection, IgM antibodies become detectable starting 4 days after the onset of symptoms, reach their peak level on Day 7 or 8, then decrease and become undetectable several months later. Regarding the IgG antibodies, low levels are detectable 4 days after the onset of symptoms, and the levels gradually increase, reaching high levels after ∼2 weeks. These antibodies remain detectable for several years [1]. The molecular test consists of the detection of the viral nonstructural protein 1 (NS1) antigen, which is a glycoprotein produced in large amounts by the virus during the earliest stage of infection. NS1 is located in the cell membrane of the infected cells and secreted into the extracellular space. The main advantage of this test is its precocity because NS1 is present at the time of symptom onset [14]. A recent meta-analysis demonstrated the usefulness of this test to confirm the diagnosis of dengue and distinguish between the different virus serotypes [15].

Laboratory abnormalities found in patients with dengue include leukopenia (usually below 4000 cells/mm^3), relative lymphocytosis (60–80%) and, in severe dengue, intense thrombocytopenia and increased hematocrit values. In addition, the patients might exhibit abnormal results on the coagulation tests, increased urea and creatinine levels, low complement component 3 (C3) levels and alterations in urinalysis results (proteinuria, hematuria and leukocyturia) [1, 11].

Patients with clinical manifestations and warning signs compatible with dengue should be admitted to the hospital for monitoring and treatment with eventual transfer to the intensive care unit. Adequate management of these patients essentially depends on early recognition of the warning signs of severe dengue, which is crucial to reducing the mortality of the disease, continuous clinical and laboratory monitoring and immediate implementation of measures to ensure hemodynamic and ventilation stability, in addition to support measures for eventual physiological impairments [1, 11]. Because no antiviral medication specific for dengue is available, support therapy and fluid replacement play a crucial role in the management of the disease. The main aspect of treatment at the beginning of the critical stage of the disease is the delivery of intensive care including continuous monitoring of the arterial pressure, hematocrit, platelet count, urine output, hemorrhagic manifestations and level of consciousness. The first priority is to re-establish the circulatory volume quickly through administration of crystalloid solutions [1, 11]. The therapeutic guidelines formulated by the World Health Organization emphasize fluid replacement as a priority in the treatment of patients with dengue and indicate oral rehydration therapy for outpatients and more intense intravenous regimens for patients with severe dengue presenting hemorrhagic manifestations and hemodynamic instability [1, 11].

The lethality rate of severe dengue is ∼1.4%, but this rate might increase to 10% or even 20% if the medical staff at the hospital has no experience in the treatment of the disease [16, 17].

Dengue and AKI

Several forms of renal involvement have been identified in patients with dengue, including elevation of the serum creatinine level, AKI, acute tubular necrosis, hemolytic uremic syndrome, proteinuria, glomerulopathy and nephrotic syndrome [18, 19].

AKI is a significant, albeit poorly studied, complication of dengue. The data available are heterogeneous and mostly originate from retrospective case series and case reports. The reported frequency of this association exhibits wide variation in accordance to the particular population being assessed, severity of dengue, criteria used for the diagnosis of AKI and time of evaluation. Laoprasopwattana *et al.* [20] reported an incidence of 0.9% among children in Thailand, and Lee *et al.* [21] reported an incidence of 3.3% among adults in Taiwan. In a Brazilian intensive care unit for infectious diseases, dengue was the cause of 4% of the cases of AKI diagnosed using the risk, injury, failure, loss of kidney function and end-stage acute kidney disease (RIFLE) criteria [22]. In a more recent study that employed the Acute Kidney Injury Network (AKIN) criteria for diagnosis, the incidence of AKI was 10.8% [23]. Using the AKIN criteria in a retrospective analysis, Khalil *et al.* [24] identified AKI in 13.3% of a series of patients with dengue confirmed by the presence of IgM antibodies, independent of the severity of disease; 64.8% of the patients were in Stage 1, 18.3% Stage 2 and 16.9% Stage 3 of the disease. In another study, the RIFLE classification was used to investigate the occurrence of AKI in patients with tropical acute febrile disease. The results showed that the incidence of AKI among patients with dengue upon admission to the hospital was 35.7% [25].

Retrospective studies of case series of dengue have shown that the development of AKI was associated with a longer hospital stay and higher mortality [24, 26, 27].

The limited data available on the kidney histology in dengue fever-induced AKI include tubular abnormalities such as acute tubular necrosis, thrombotic microangiopathy and acute glomerulopathy [26, 28–31].

Several mechanisms have been proposed to account for the etiopathogenesis of dengue fever-induced AKI, including direct

action by the virus, hemodynamic instability, rhabdomyolysis, hemolysis and acute glomerular injury [32]. While none of the available evidence patently favors any such mechanisms at the expense of the others, often two or more mechanisms coexist simultaneously in the same patient.

Virus action on the renal tissue

Viral infection-induced renal injury might be due to a direct cytopathic effect of the viral protein on the glomerular and tubular cells, an *in situ* immune-mediated mechanism triggered by viral antigens bound to glomerular structures, tissue injury caused by immune complexes composed of viral antigens and antiviral antibodies and damage caused by inflammatory mediators released in response to the glomerular or tubular cytopathic effects of the viral antigens [33].

Analyses of autopsies or biopsies of human cells infected with the dengue virus using immunohistochemical and *in situ* hybridization techniques have detected viral antigens in the tubular epithelial cells [34–36]. Jessie *et al.* [35] analyzed tissue samples of rats infected with DEN-1 and did not find viral RNA in the samples, which suggests that viral replication does not occur in the renal tissue.

Hemodynamic instability

Dengue causes an intense inflammatory process that involves the release of inflammatory cytokines, activation of the complement system and platelets, and endothelial injury, which results in increased vascular permeability with a consequent loss of intravascular fluid [37, 38]. This process might cause hemodynamic instability and even shock, resulting in AKI due to a reduction of renal perfusion and acute tubular injury.

In a retrospective study of 223 patients with dengue confirmed by serological testing, the occurrence of AKI was associated with a higher frequency of hypotension and sepsis and the need for inotropic drugs [23]. In ∼80% of the cases of dengue-induced AKI that have been described in the literature, shock or hypotension are mentioned [39–43]. However, the literature also includes reports of the occurrence of AKI in patients with dengue without hemodynamic instability [28–39].

Rhabdomyolysis

Although rhabdomyolysis is considered a rare complication of dengue, more recent data are conflicting. Histological abnormalities in kidney biopsy samples, muscle weakness, myalgia and elevated serum creatine kinase (CK) levels have been described with variable frequencies in different populations of dengue patients [44–49]. The pathogenesis of dengue-associated rhabdomyolysis has not been well elucidated. The muscle damage might be caused by direct viral invasion, as some *in vitro* studies have shown [50], or mediated by myotoxic cytokines, such as tumor necrosis factor [51]. Muscle biopsy samples of patients with dengue were found to exhibit a range of abnormalities from inflammatory infiltrates to areas of myonecrosis [45].

Rhabdomyolysis is a well-known cause of AKI; it causes renal damage by intrarenal vasoconstriction, direct tubular injury and/or tubular obstruction [52]. Six cases of dengue with AKI and rhabdomyolysis are reported in the literature [29, 44, 53–56]. All of the patients had elevated CK levels and four exhibited myoglobinuria. Regarding the clinical symptoms, five patients exhibited myalgia and oliguria; three survived and one died (the outcome in one case is unknown). A biopsy was performed in only one case, which showed histological findings characteristic of acute tubular necrosis, and myoglobin deposits were detected in the kidney tubules by immunohistochemical analysis [29]. However, the literature also includes reports of cases of dengue with rhabdomyolysis and a striking elevation of the CK levels, but without AKI [54, 57, 58]. Possibly, in addition to rhabdomyolysis, hemodynamic instability, acidosis and aciduria are also required for AKI to develop in dengue patients.

Glomerulonephritis

The glomeruli might also be affected by dengue. Self-limited proteinuria that disappears together with the resolution of disease occurs in up to 74% of cases [18]. Proteinuria seems to be associated with the severity of the disease and is elevated in cases of severe dengue, showing a positive correlation with the degree of thrombocytopenia [59, 60]. Analyses of renal biopsy samples from patients with severe dengue and kidney injury have shown IgG, IgM and C3 deposits in the glomeruli, basement membrane thickening and hypertrophy of the mesangial cells in the areas with immune complex deposits [34, 61].

One case of acute glomerulonephritis and dialysis-dependent AKI in a patient with dengue was recently described. The renal biopsy sample exhibited mesangial proliferation with mesangial IgA-dominant immune complex deposits and acute tubular necrosis. A repeated biopsy 6 weeks after the clinical recovery of the patient from both dengue and AKI showed reversal of the glomerular changes [31]. Two probable cases of acute glomerulonephritis were described in patients with dengue (an adult and a child). These patients developed AKI, which was accompanied by edema and hypertension, in the absence of hypotension, hemolysis, rhabdomyolysis or use of nephrotoxic drugs. The serum C3 levels were reduced, and the urinalysis results revealed proteinuria and hematuria. All of these changes disappeared following the resolution of dengue [39, 62]. Finally, one case of an antiglomerular basement membrane associated with perinuclear anti-neutrophil cytoplasmic antibodies and crescentic glomerulonephritis in the renal biopsy was diagnosed in a patient with dengue [63].

Hemolytic uremic syndrome

Dengue fever-induced hemolytic uremic syndrome, characterized by a triad consisting of hemolytic anemia, thrombocytopenia and AKI, has been described in three patients [30, 64, 65]. One of the cases was subjected to a renal biopsy, which showed thrombotic microangiopathy with arteriolar and glomerular microthrombi, and electronic microscopy revealed the presence of microtubuloreticular structures, suggesting a viral infection [30]. All three patients survived with recovery of renal function.

Management

Careful assessment of the warning signs of severe dengue and the patient's blood volume are crucial for the prevention of AKI. Fluid replacement should be performed carefully to avoid overload producing a consequent worsening of intravascular fluid extravasation, which might increase morbidity and mortality. Fluid replacement must be initially performed with crystalloid solutions, while use of colloids should be restricted to cases of unresponsive shock [66]. The amount of infused fluid should be the minimum needed to stably maintain the hemodynamic conditions until the increased vascular permeability is reversed.

The use of parenteral corticosteroids in cases of severe dengue is controversial, and there are no recommendations for their use in patients with AKI [67]. Serum CK levels should be monitored to allow for early diagnosis of rhabdomyolysis and the institution of adequate preventive measures [29]. Once a diagnosis of AKI is established, support treatment should be timely and adequately performed to prevent worsening of the condition [68].

Renal replacement therapy is currently indicated as conventionally used, because there are no specific recommendations for the proper time to begin treatment, dosing or modality in dengue patients.

Summary

AKI seems to be a frequent complication of severe dengue that increases the morbidity and mortality of the affected patients. Its etiopathogenesis is probably multifactorial, caused by intense systemic inflammation, hemodynamic instability, hemolysis, rhabdomyolysis and acute glomerulitis. Currently, there are no specific recommendations for either conservative treatment or dialysis of patients with dengue, and the effects of AKI on the quality of life, survival and kidney function of survivors are unknown. Prospective studies aimed at establishing the incidence of and risk factors for dengue-associated AKI, its etiopathogenesis, and the best therapeutic approach for patients with dengue and AKI are urgently needed.

Funding

E.A.B. receive research grants from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil) and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo, Brasil).

Conflicts of interest statement

The authors have no conflict of interest related to this article.

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