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Dengue-associated kidney disease

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ABSTRACT

Context: A mosquito-borne viral illness highly prevalent in the tropics and subtropics, dengue is considered a major global health threat by the World Health Organization.
Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), LISTA (EBSCO) and Web of Science have been searched.
Results: An RNA virus from the genus Flavivirus, dengue virus is transmitted by Aedes aegypti, the yellow fever mosquito. Dengue is asymptomatic in as many as one half of infected individuals. Dengue fever is an acute febrile illness accompanied by constitutional symptoms. Dengue hemorrhagic fever and dengue shock syndrome are the severe forms of dengue infection. Dengue infection has been associated with a variety of renal disorders. Acute renal failure is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis. Acute renal failure complicates severe dengue infection in 2-5% of the cases and carries a high mortality rate. Proteinuria has been detected in as high as 74% of patients with severe dengue infection. Hematuria has been reported in up to 12.5% of patients. Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection. Mesangial proliferation and immune complex deposition are the dominant histologic features of dengue-associated glomerulonephritis. On a rare occasion, dengue infection is associated with systemic autoimmune disorders involving the kidneys.
Conclusions: In the vast majority of cases, dengue infection and associated renal disorders are self-limited.

Short-Review

Implication for health policy/practice/research/medical education:
Dengue infection has been associated with a variety of renal disorders. Acute renal failure is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis. Acute renal failure occasionally complicates severe dengue infection and carries a high mortality rate. Transient proteinuria has been detected in most patients with severe dengue infection. Hematuria has been reported in a significant subset of patients with severe dengue infection. Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection. Mesangial proliferation and immune complex deposition are the dominant histologic features. On a rare occasion, dengue infection is associated with systemic autoimmune disorders involving the kidneys. In the vast majority of cases, dengue infection and associated renal disorders are self-limited.

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1. Context

Dengue infection has been associated with a variety of renal disorders. Acute renal failure is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis.

2. Evidence Acquisition

Directory of Open Access Journals (DOAJ), Google Scholar, PubMed, and Web of Science were searched with key words relevant to Dengue infection, acute renal failure, proteinuria, hematuria, glomerulonephritis.

3. Results

Twenty research and review articles relevant to this topic directly or indirectly have been found. From the information given in these papers, the following aspects were drawn out.

3.1. Dengue infection

A mosquito-borne viral illness highly prevalent in the tropics and subtropics, dengue is considered a major global health threat by the World Health Organization (1,2). Approximately one third of the world population is at risk for dengue infection (HealthMap, Figure 1). The worldwide infection rate approaches 50-100 millions each year. Travelers to endemic areas are also at risk for dengue infection.

An RNA virus from the genus Flavivirus, dengue virus is transmitted by Aedes aegypti, the yellow fever mosquito (1,2). There are four similar serotypes of dengue virus. While the Infection with one serotype produces lifelong immunity to that serotype, the immunity lasts only a few months for other serotypes. Dengue has an incubation period of 3–14 days, during which viral replication takes place in the reticuloendothelial system, particularly in the dendritic and endothelial cells. This is followed by viremia and the production of immune mediators. Dengue is asymptomatic in as many as one half of infected individuals. Dengue fever is an acute febrile illness accompanied by retro-orbital, headache, rash, myalgia, leukopenia, or hemorrhagic manifestations (Table 1). Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are the severe forms of dengue infection (Table 1).

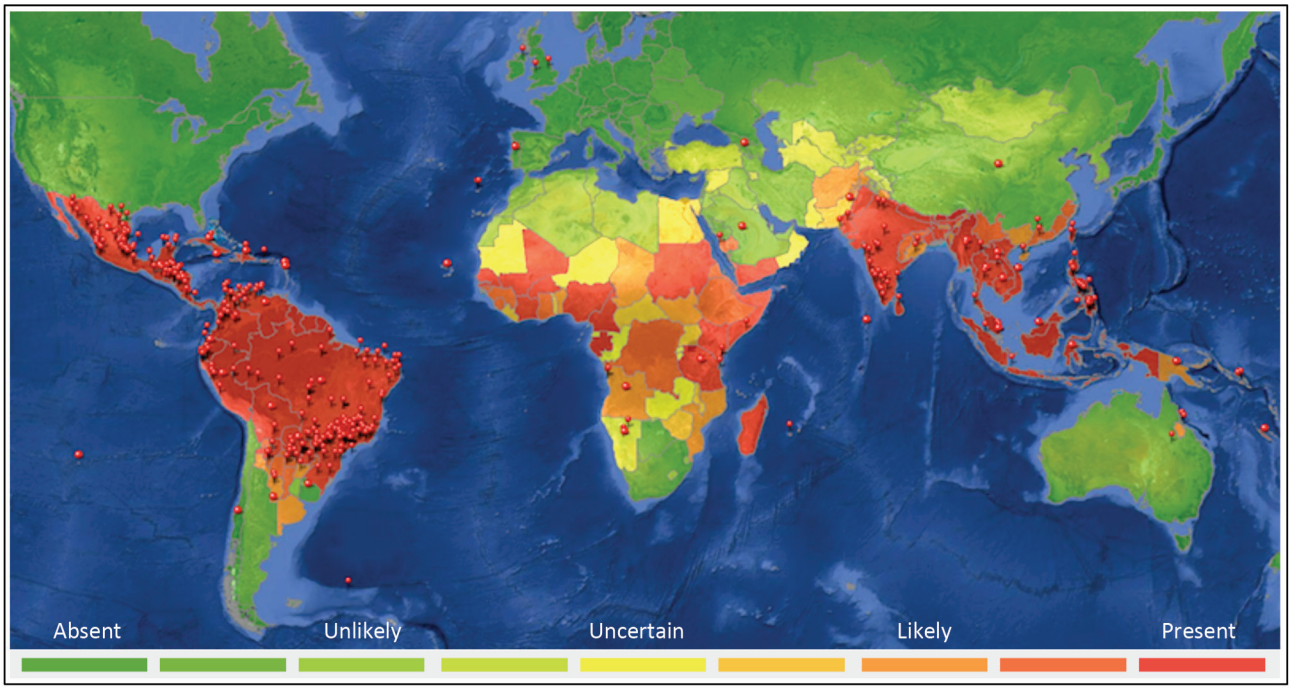

Figure 1. Global dengue activity. Courtesy of HealthMap at www.healthmap.org.

Table 1. Clinical manifestations and laboratory confirmation of dengue Infection (2)

Dengue Fever (DF)
Acute febrile illness with ≥ 2 of the following: • Headache • Retro-orbital pain • Myalgia • Rash • Hemorrhagic manifestations • Leukopenia
Dengue Hemorrhagic Fever (DHF)
All of the following must be present: 1. Fever, lasting 2 to 7 days, occasionally biphasic 2. Hemorrhagic manifestations with at least one of the following: • Positive tourniquet test • Petechiae, ecchymoses, or purpura • Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations • Hematemesis or melena 3. Thrombocytopenia (≤100,000/mm^3) 4. Evidence of plasma leakage manifested by at least one of the following: • Increase in the hematocrit level 20% for age, sex, and population • Decrease in the hematocrit after volume replacement ≥20% of baseline • Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia
Dengue Shock Syndrome (DSS)
Criteria for DHF associated with: • Tachycardia • Pulse pressure <20 mm Hg • Hypotension for age • Cold skin • Restlessness
Laboratory criteria confirmation
At least one of the following: • Isolation of dengue virus from serum or autopsy samples • ≥4-fold change in IgG or IgM antibody specific to dengue virus • Detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or enzyme-linked immunosorbent assay

3.2. Dengue and Kidney disease

Dengue infection has been associated with a variety of renal disorders. Acute renal failure, proteinuria, hematuria, and glomerulonephritis have been reported during or shortly after acute dengue infection.

3.3. Acute renal failure

Severe dengue infection, particularly DHF and DSS, may give rise to multi-organ dysfunction. Acute renal failure (ARF) is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis (3). The prevalence of ARF was 1.6% among 617 children with DHF in Colombia, 3.3% in hospitalized adults with DHF, 4.9% in 81 Chinese patients with DHF/DSS, and 5% in DHF patients in Qatar (4-7).

The development of ARF in patients with dengue infection is associated with increased mortality. In Thailand, the prevalence of ARF in fatal DHF was 33.3%, compared with 0.3% in all DHF cases (8). In a retrospective series, 60% of hospitalized DHF patients with ARF died. DHF patients with ARF were predominantly older men and had other comorbidities. Multivariate analysis showed that DSS was an independent risk factor for the development of ARF in patients with DHF.

3.4. Proteinuria

Proteinuria has been detected in as high as 74% of patients with DHF (3,9). During a dengue-3 epidemic in Queensland, Australia, Horvath et al. recorded proteinuria in 74% of patient in whom urinalysis was performed (9). In this cohort, one patient had 10.8 g/day proteinuria and was diagnosed with the nephrotic syndrome. Vasanwala and colleagues reported two DHF patients with nephrotic-range proteinuria (10). Daily protein excretion was 8.1 g/day and 9.0 g/day based on a random urine protein to creatinine ratio. These patients did not have hematuria or elevated serum creatinine concentrations. Garcia et al. retrospectively studied 74 patients with dengue fever or DHF who had a platelet count of less than 125,000/mm^3 (11). The prevalence of proteinuria in this cohort was 30%.

Hutspardol and coworkers reported a 9-year-old boy with no significant medical history who presented with a 4-day history of high-grade fever, headache, diarrhea, hepatomegaly, and azotemia (12). A diagnosis of dengue infection was sug-

gested by a positive tourniquet test and confirmed when dengue IgM antibodies were detected. Daily urinary protein excretion was 3.4 g/day based on a random urine protein to creatinine ratio. Renal biopsy was not performed. Supportive care was provided and the patient's condition improved. One month following discharge from the hospital, urinary protein excretion was normal.

3.5. Glomerulonephritis

Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection.

Barreto et al, infected mice with dengue virus type 2 (13). Forty-eight hours later, glomerular enlargement, increased endocapillary and mesangial cellularity as well as glomerular IgM deposition were noted. Similarly, Boonpucknavig and colleagues examined mice with dengue virus type 2 infection (14). By the third week of infection, immune-complex deposition and proliferative lesions were evident in the glomeruli.

Hematuria has been reported in up to 12.5% of patients with DHF by Futrakul et al. (15). Boonpucknavig and colleagues observed glomerular IgG, IgM, and C3 deposition in 10 of 20 patients (50%) with DHF and renal disease (16). Ultrastructural examination demonstrated glomerular immune complex type deposits associated with mesangial cell hypertrophy. In addition, dense spherical particles 40-50 nm in diameter was found in 12 cases (60%). In the patients with renal disease and glomerular immunoreactants, renal biopsy was performed during the second week following the onset of fever. To localize viral antigen, Jessie et al. examined tissues obtained from patients whose dengue infection was confirmed serologically or virologically (17). Dengue antigen was detected in the renal tubular epithelial cells in 3 of 8 cases (37.5%).

A recent case report describes deranged renal function and hematuria in a 3-year-old boy with DHF (18). The patient also had fever, vomiting, hypertension, and oliguria. However, he did not have shock, sepsis, hemolysis, or rhabdomyolysis. Urinalysis demonstrated red blood cells and granular casts. Complement C3 level was reduced. The authors argued that the patient had glomerulonephritis. However, renal biopsy was not available. The patient recovered with supportive care.

We recently encountered a 66-year-old woman from Honduras who was diagnosed with acute dengue infection and rapidly progressive glomerulonephritis. A diagnosis of dengue infection was based on the clinical ground and an elevated dengue IgM titer. Renal biopsy revealed severe crescentic glomerulonephritis. Immunofluorescence examination demonstrated strong linear IgG deposition along glomerular capillary walls. Serologic tests demonstrated antibodies against GBM, MPO, and platelet glycoproteins. The patient was diagnosed with anti-GBM disease associated with ANCA with MPO specificity. Despite heavy immunosuppression and plasmapheresis, IgG titers against dengue virus continued to rise confirming the diagnosis of acute dengue infection.

3.6. IgA Nephropathy

Upadhaya and colleagues reported a 15-year-old boy who was diagnosed with dengue infection and ARF necessitating renal replacement therapy (19). Urinalysis showed hematuria and proteinuria. Renal biopsy demonstrated mesangial proliferation and IgA deposition consistent with IgA nephropathy as well as acute tubular necrosis. Resolution of mesangial proliferation and IgA deposition was documented on renal biopsy six weeks later.

3.7. Lupus Nephritis

A case of dengue infection evolving into systemic lupus erythematosus and lupus nephritis has been reported. Rajadhyaksha et al. reported a 22-year-old woman who presented with high-grade fever, skin rash, shortness of breath, retro-orbital pain, abdominal pain, arthralgia, and myalgia (20). She was diagnosed with dengue infection on the clinical ground and elevated dengue IgM titers. At

the time, serum creatinine concentration was 1.0 mg/dL. Supportive care was provided and the patient was discharged home. Four weeks later, she developed fever, arthralgia, rash, and anasarca. Serum creatinine concentration was 5.0 mg/dL. Urinalysis revealed proteinuria and hematuria. Daily urinary protein excretion was 6.3 g/day based on a 24-hour urine collection. Antibodies directed against nuclear antigens including ANA and double-stranded DNA were detected. Complements C3 and C4 were reduced. Renal biopsy showed diffuse proliferative glomerulonephritis consistent with lupus nephritis.

4. Conclusions

Dengue infection has been associated with a variety of renal disorders. Acute renal failure is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis. Acute renal failure occasionally complicates severe dengue infection and carries a high mortality rate. Transient proteinuria has been detected in most patients with severe dengue infection. Hematuria has been reported in a significant subset of patients with severe dengue infection. Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection. Mesangial proliferation and immune complex deposition are the dominant histologic features. On a rare occasion, dengue infection is associated with systemic autoimmune disorders involving the kidneys. In the vast majority of cases, dengue infection and associated renal disorders are self-limited.

Authors' contributions

KJL and AN conducted literature search and wrote the manuscript.

Conflict of interests

The author declared no competing interests.

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