Dengue haemorrhagic fever-induced acute kidney injury without hypotension, haemolysis or rhabdomyolysis

Emerson Q. Lima1, Fernanda S. Gorayeb1, Jeferson R. Zanon1, Mauricio L. Nogueira2, Horácio J. Ramalho1 and Emmanuel A. Burdmann1

1Division of Nephrology, Hospital de Base and 2Laboratory of Virology, Division of Infectious Diseases, São José do Rio Preto Medical School, Brazil

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Introduction

Dengue fever (DF) is currently the most important human viral mosquito-borne infection of public health significance, with millions of infections each year. The main dengue vector is the female of the Aedes aegypti mosquito. There are four serotypes of the dengue virus (DEN-1–DEN-4), a RNA flavivirus. They are antigenically closely related, but whereas infection with one serotype produces lifelong immunity to that serotype, immunity to other serotypes lasts only a few months [1,2].

Approximately half the world’s population lives in areas potentially at risk for dengue and 50–100 million cases are estimated to occur annually [1,3]. Brazil is the leading American country in absolute number of cases and has the highest incidence rate of the disease in this geographic area [4]. The epidemiology of dengue in Brazil comprised two distinct periods. In the first (1986–1993), epidemic waves occurred in localized areas. In the second (1994–2002), there was a nationwide epidemic and endemic virus circulation. In this period, a total of 2 826 948 cases of dengue were reported, giving an incidence of 454/100 000 inhabitants. The number of infested municipalities increased from 44.5% in 1996 to 58.3% in 2002 [5].

Dengue virus infection may manifest clinically as undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) [3]. Renal injury comprising creatinine increase, proteinuria, glomerulonephritis, acute kidney injury (AKI) and haemolytic uraemic syndrome has been reported in dengue patients [6–22]. To date, all DHF-induced AKI described cases have occurred in association with shock, haemolysis or rhabdomyolysis [11,12,14,15]. We describe, to the best of our knowledge for the first time, a case of DHF-induced AKI, where the renal injury occurred without haemodynamic instability, haemolysis, rhabdomyolysis or use of nephrotoxic drugs.

Case report

A previously healthy 48-year-old female was transferred to our University Hospital with an 8-day history of fever, headache, retro-ocular pain, myalgia, gingival and vaginal bleeding, mental disorientation, vomiting, generalized oedema, exanthematic skin lesions in the arms and urinary volume reduction. Laboratory tests at a previous hospital disclosed creatinine 9 mg/dl, white blood cell (WBC) count 3100/mm3, platelets count 13 000/mm3, coagulation time of 25 min and activated partial thromboplastin time of 66 s. The patient had never had hypotension and was not taking any nephrotoxic drug. On admission at the University Hospital, she was confused (Glasgow Coma Scale 14), icteric, afebrile, blood pressure of 180/110 mmHg and with anasarca. Laboratory tests disclosed haemoglobin 14g/dl, haematocrit 43%, WBC count 11 400/mm3, platelets count 110 000/mm3, serum creatinine 9.9 mg/dl, BUN 107.5 mg/dl, serum potassium 6 mEq/l, arterial blood pH 7.32 and bicarbonate 12 mEq/l, serum lactate 1.4 mEq/l, aspartate aminotransferase 399 UI/l, alanine aminotransferase 2178 UI/l, total bilirubin 1.8 mg/dl, creatine phosphokinase 35 UI/l, lactic dehydrogenase 2551U/l, albumin 2.2 g/dl, C3 46.4 mg/dl (NR: 50–160), C4 6.50 mg/dl (NR: 10–40), negative antinuclear antibody. Urinalysis showed pH 6.5, densitometry 1012, WBCs 96 000/mm3, red blood cells >500 000/mm3 and proteins ++/3. An abdominal
The haemorrhagic fever differential diagnosis was performed using in-house procedures, with support from a national reference laboratory (Adolfo Lutz Institute, Sao Paulo, Brazil). Blood and urinary cultures were negative. Serology for HIV, hepatitis B and C was negative. Serology (IgM antibodies, ELISA, Adolfo Lutz Institute, Sao Paulo, Brazil) against leptospirosis, hantavirus (Andes virus recombinant antigen) and yellow fever was also negative. Dengue diagnosis was performed by Multiplex-Nested-PCR. RNA was extracted from serum (day 4 of disease) using QIAMP Viral RNA Mini Kit (Qiagen, Germany), cDNA was obtained using Superscript III (Invitrogen, Brazil) and flavivirus generic primer, followed by a multiplex PCR using primers designed for the most important flaviviruses in Brazil (DENV1, DENV2, DENV3, DENV4, yellow fever virus, Rocio virus, SLEV and Ilheus virus). The sample was positive for DENV3, which was confirmed by sequencing of the amplified product using BigDye v3.1 (ABI377 automated sequencer, ABI, Foster City, CA, USA).

The patient remained oliguric for 7 days, on haemodialysis (5 sessions total). Her clinical status improved gradually and she was discharged on day 17 of hospitalization, with serum creatinine of 3 mg/dl and diuresis of 2.81/day. Thirty-five days after the beginning of symptomatology she was asymptomatic, with normal physical exam and serum creatinine of 1.2 mg/dl. The patient denied a previous dengue episode, but informed us that her daughter had already been hospitalized due to dengue.

**Discussion**

DHF is a severe form of the disease characterized by fever, haemorrhagic phenomena, thrombocytopenia and evidence of plasma leakage (increased haematocrit, pleural effusion, ascites and hypoalbuminaemia). All of these features were present in the described patient. DHF usually occurs in secondary dengue infections, although it may follow primary infections, particularly in infants [3]. In Southeast Asia, DHF affects predominantly children, whereas in America, all age groups are involved [1,2,4]. In Brazil, DHF shows an unusual epidemiological pattern usually affecting adults [5]. Until 2000, there were relatively few cases of DHF reported in Brazil, in contrast to the thousands of cases of dengue fever [23]. This situation changed dramatically after the fourth epidemic of dengue, beginning in Rio de Janeiro in 2001. This epidemic was characterized by the introduction and predominance of serotype DEN-3 [5,23], which is the one isolated in the current patient. In contrast with the previous epidemics, DEN-3 serotype spreads rapidly, affecting previously dengue-free areas. Two and a half years after its first detection DEN-3 was present in 22 of 27 Brazil's states [23]. This epidemic was distinguished by a significant raise in DHF incidence [5,23]. In 2002, the absolute number of DHF-related deaths surpassed malaria-induced deaths for the first time in Brazil [5].

The differential diagnosis for DHF includes malaria, leptospirosis, hantavirus infection, typhoid fever, HIV, enteroviral infection, influenza and sepsis, as well as autoimmune disorders as polymyositis, dermatomyositis and vasculitis [2,3]. In particular, leptospirosis and hantavirus infection may mimic DHF in almost all aspects, including renal injury and renal histology [24,25]. However, ELISA serology for these diseases was negative and the patient had no suggestive epidemiological clues for them. RT-PCR confirmed DENV3 as the aetiological agent in the present case. As previously stated, serology for hepatitis B and C, HIV and other flaviviruses found in Brazil was negative, as were blood and urinary cultures. The clinical picture and laboratory tests excluded or made unlike other possible conditions.

AKI is a poorly studied complication of DHF. The available information comes from small series of patients or case reports. Futrakul et al. [6] reported ‘mild elevation in serum creatinine’ in 43% of 24 DHF cases in Thailand. Tanphaichitr et al. [11] found one case of ‘transient azotemia’ and one case of ‘acute renal shutdown’ among 17 patients with DHF and G-6-PD deficiency. Méndez and Gonzáles [13] found 1.6% of acute renal failure (ARF) among 617 children with DHF in Colombia. More recently, Lee et al. [16] reported 4.9% of ARF in 81 Chinese patients suffering from DHF/DSS and Abboud [17] reported 5% of ARF in DHF. Wiwanitky [18] revised the literature concerning fatal cases of DHF in Thailand, finding 51 fatalities in a total of 6154 DHF cases. Among these patients, 17 had AKI, yielding a percentage of 33.3% of AKI in the patients who died and a percentage of 0.3% of AKI for all DHF cases [18]. Besides these series of patients, there are eight cases of AKI reported in patients with DF [8–10,19,20] and 5 cases reported in DHF or DSS [12,14,15,21, 22]. The mortality rate was very high among these patients (five deaths in 13 cases, 38%). Details of these cases can be seen in Table 1.

In contrast with the previous reports of DHF-induced renal injury, the current patient developed AKI without hypotension, rhabdomyolysis, haemolysis or the use of nephrotoxic drugs. This case demonstrates, for the first time, the possibility of direct renal injury due to haemorrhagic dengue. The presence of proteinuria, haematuria, generalized oedema and hypertension associated with low C3 and C4 suggests an immune-mediated acute glomerular injury. In a consistent way, Futrakul [6] reported 71% of albuminuria, 12.5% of haematuria and 82% of low C3 in DHF patients. As already mentioned, 43% of them had increased creatinine. The same group performed renal biopsies in 20 children with DHF and proteinuria, haematuria or both (18 of the patients...
Table 1. Description of dengue-induced AKI cases reported in the literature

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>Country</th>
<th>Case numbers, gender; age</th>
<th>Type of dengue</th>
<th>Oliguria</th>
<th>Dialysis</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>George et al. [8]</td>
<td>1988</td>
<td>Malaysia</td>
<td>3 M, 1 F; 7 months, 6 years, 18 years</td>
<td>DF</td>
<td>NA</td>
<td>NA</td>
<td>3 recoveries</td>
<td>1 death; patient with shock; no CK dosage; no reference to haemolysis; all patients with increased SGOT.</td>
</tr>
<tr>
<td>Hommel et al. [9]</td>
<td>1999</td>
<td>French Guiana</td>
<td>1 M; 64 years</td>
<td>DF</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovery</td>
<td>No hypotension; no CK dosage; no reference to haemolysis.</td>
</tr>
<tr>
<td>Gunasekera et al. [10]</td>
<td>2000</td>
<td>Sri Lanka</td>
<td>1 F; 28 years</td>
<td>DF?</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovery</td>
<td>Hypotension; rhabdomyolysis (CK increase and myoglobinuria); no reference to haemolysis.</td>
</tr>
<tr>
<td>Radakovic-Fijan et al. [12]</td>
<td>2002</td>
<td>India</td>
<td>1 F; 44 years</td>
<td>DHF</td>
<td>NA</td>
<td>No</td>
<td>Recovery</td>
<td>Hypotension; normal CK; haemolysis (increased LDH, decreased haptoglobin and increased free Hb); increased liver enzymes.</td>
</tr>
<tr>
<td>Chacko et al. [14]</td>
<td>2004</td>
<td>India</td>
<td>1 F; 13 years</td>
<td>DHF/DSS</td>
<td>NA</td>
<td>No</td>
<td>Death</td>
<td>Shock; no CK dosage; haemolysis? (increased LDH); increased liver enzymes; renal transplant recipient.</td>
</tr>
<tr>
<td>Davis and Bourke [15]</td>
<td>2004</td>
<td>Australia</td>
<td>1 M; 33 years</td>
<td>DHF</td>
<td>NA</td>
<td>NA</td>
<td>Death</td>
<td>No reference to blood pressure; CK increase; no reference to haemolysis; developed multiple organ failure.</td>
</tr>
<tr>
<td>Nair et al. [19]</td>
<td>2005</td>
<td>India</td>
<td>1 M; 13 years</td>
<td>DF</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovery</td>
<td>No hypotension; normal CK; no reference to haemolysis; increased liver enzymes.</td>
</tr>
<tr>
<td>Wiersinga et al. [20]</td>
<td>2006</td>
<td>Suriname</td>
<td>1 M; 48 years</td>
<td>DF</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>No hypotension; no CK dosage; haemolysis (decreased haptoglobin); renal biopsy: thrombotic microangiopathy.</td>
</tr>
<tr>
<td>Garcia et al. [21]</td>
<td>2006</td>
<td>Brazil</td>
<td>1 M; 66 years</td>
<td>DSS</td>
<td>Yes</td>
<td>NA</td>
<td>Death</td>
<td>Shock; no CK dosage; no reference to haemolysis; increased liver enzymes; liver transplant recipient.</td>
</tr>
<tr>
<td>Karakus et al. [22]</td>
<td>2007</td>
<td>Suriname</td>
<td>1M; 66 years</td>
<td>DSS</td>
<td>Yes</td>
<td>NA</td>
<td>Death</td>
<td>Shock; rhabdomyolysis (CK increase); bleeding; no reference to haemolysis; developed multiple organ failure.</td>
</tr>
<tr>
<td>Lima et al.</td>
<td>2007</td>
<td>Brazil</td>
<td>1 F; 48 years</td>
<td>DHF</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovery</td>
<td>No hypotension; normal CK; no haemolysis; increased liver enzymes.</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td>14 cases (9 M, 5 F)</td>
<td>8 DF, 4 DHF, 2 DSS</td>
<td>6/6</td>
<td>5/7</td>
<td>8 recoveries, 5 deaths</td>
<td>3 patients without shock, rhabdomyolysis, haemolysis (2 DF and 1 DHF).</td>
</tr>
</tbody>
</table>

M, male; F, female; DF, dengue fever; NA, not available; CK, creatine phosphokinase; SGOT, serum glutamic oxalacetic transaminase; DHF, dengue haemorrhagic fever; LDH, lactic dehydrogenase; Hb, haemoglobin; DSS, dengue shock syndrome.
presented proteinuria ranging from traces to 3+). All biopsies showed glomerular changes characterized by hypertrophy and hyperplasia of mesangial and endothelial cells, presence of monocytoid-like cells in some of the glomerular capillary lumen and focal thickening of the glomerular basement membrane. Immunocomplexes (IgG, IgM or both, and C3) were found at glomeruli and arterioles wall in 10 cases biopsied 2 weeks after the onset of symptoms. Dense, spherical particles were found in the 12 cases where electronic microscopy was carried out. The authors hypothesized that these particles might be nucleocapsid cores of dengue virions [7]. In fact, Jessie et al. [26] demonstrated the presence of viral antigens in the renal tubular cell of DHF and DSS patients. Horvath et al. [27] also reported 74% of proteinuria during a dengue-3 epidemic in Australia, including a patient with nephrotic syndrome (proteinuria 10.8 g/24 h). More evidence that the dengue virus can induce glomerulopathy comes from two studies where dengue virus type 2 was inoculated in mice. In the first, diffuse proliferative glomerular injury was seen 14 days after the inoculation [28]. In the second, there was enlarged glomerular volume, increased endocapillary and mesangial cellularity and glomerular IgM deposition 48 h after virus inoculation [29]. Finally, the auto-immune-mediated mechanisms possibly involved in the pathogenesis of DHF might also be related to the renal injury observed [3,4,6,30].

In summary, we described a case of AKI related to DHF in the absence of shock, haemolysis, rhabdomyolysis or use of nephrotoxic drugs. This case suggests that the dengue virus may cause direct renal injury and that this lesion may occur in cases of DHF.

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Conflict of interest statement. None declared.

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