Netherlands
The Journal of Medicine

CASE REPORT

Dengue shock syndrome and rhabdomyolysis

A. Karakus, N. Banga, G.P. Voorn, A.J. Meinders*

St. Antonius Hospital, Department of Internal Medicine/Medical Microbiology, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands, tel.: +31 (0)30-609 91 11, *corresponding author, e-mail: a.meinders@antonius.net.

INTRODUCTION

Dengue shock syndrome (DSS) is a life-threatening manifestation of one of the most common arboviral infections in humans. With the increased air travel to dengue endemic areas, healthcare providers in non-endemic countries are now frequently confronted with the initial symptoms of dengue in short-term travellers.[1] Although the course of dengue among this group of travellers is mostly subclinical, severe manifestations are also increasingly being reported.[2] This is the first case report concerning a short-term traveller describing the unusual presentation of dengue shock syndrome and serious rhabdomyolysis.

CASE HISTORY

A 66-year-old male with a history of hypertension and non-insulin-dependant diabetes mellitus (NIDDM) was admitted with complaints of fatigue, shivering, muscle, bone and joint pain, nausea, abdominal pain, diarrhoea, and tea-coloured urine. Five days before admission he returned from a two-week visit to Suriname, which he visited several times a year. He stayed in Paramaribo as well as in rural areas before the recent flooding. The abdominal symptoms started in Suriname two days before his return. The other symptoms presented on the day of his arrival. At that time he had not developed fever. He had not used any malaria prophylaxis, was not vaccinated against yellow fever and had not been bitten by a snake. One of his co-travellers developed abdominal symptoms that resolved spontaneously.

On admission the patient was moderately ill with a blood pressure of 119/87 mmHg, pulse 96 beats/min, breathing frequency of 14/min, oxygen saturation of 97% and a temperature of 37.2 °C. Physical examination was normal except for enlarged palpable submandibular lymph nodes.

Initial laboratory results (*table 1*) showed a thrombocytopenia and high levels of creatinine kinase, and elevated asparate aminotransferase and lactate hydrogenase. Also acute renal failure, mild hyponatriaemia, hypokaliaemia and hyperglycaemia were noted. Urine showed proteinuria and myoglobinuria. The ECG was normal. No fragmentocytes were seen in a blood smear.

Differential diagnosis included dengue, malaria, typhoid fever, leptospirosis, HIV, enteroviral infection and influenza. Also autoimmune disorders as polymyositis, dermatomyositis and vasculitis were considered.

Malaria was excluded by repeated negative blood smears. Serological tests for leptospirosis, HIV, hepatitis B and C virus, influenza A and B virus, para-influenza virus, RS virus, adenovirus, *Chlamydia psittaci*, *Chlamydia pneumoniae* and *Coxiella burnetii* were all negative. There was no serological evidence of active hepatitis A, Epstein Barr virus, or cytomegalovirus infection. Cell cultures were negative for respiratory viruses. Stool examination revealed no pathogens. Bone marrow aspiration showed no evidence of tuberculosis or leishmaniasis. Finally serological tests for autoimmune diseases were also negative (*table 1*).

During the first day of admission, the patient developed high fever up to 39.3 °C with an increasing CK level up to a maximum of 156,900 U/l on day 2. On day 3, the patient complained of severe abdominal pain accompanied by dyspnoea and tachycardia. Inflammatory response parameters were now substantially elevated. Additional computed tomography imaging showed no pathology except for inhomogenic consolidation of the lower lung lobes. Despite empiric treatment with broad-spectrum antibiotics for a suspected pneumonia, the patient deteriorated and was transferred to the intensive care unit the following day and intubated because of respiratory failure. The condition of the patient further deteriorated. A septic shock developed, complicated by multiple organ failure. Anuric renal failure and progressive generalised oedema developed accompanied by oropharyngeal and nasal bleeding. Fever persisted from day one to three and day five to seven. Nine

Table 1. *Laboratory values*

	Day 1	Day 2	Day 4	Day 5	Reference values
CRP (mg/l)	12	33	492	510	<5
ESR (mm/h)	23	31			<7
Hemoglobin (mmol/l)	10.3		8.0	5.8	8.6-10.7
Hematocrit (l/l)	0.47	0.41	0.38	0.27	0.39-0.49
Platelets (G/l)	18	26	147	93	150-300
Leukocytes (G/l)	6.8	6.7	6.3	11.8	3-10
Sodium (mmol/l)	127	128	134	139	137-143
Potassium (mmol/l)	3.0	3.9	3.1	3.4	3.5-5.0
Creatinine (µmol/l)	138	138	160	315	50-120
Urea nitrogen (mmol/l)	12.2	10.1	10.5	19.8	3.0-8.3
CK (U/l)	141,010	156,900	61,700	18,413	<175
ASAT (U/l)	1520	1583	1337	1494	<30
ALAT (U/l)	202	201	250	421	<40
LDH (U/l)	12,496	11,703	7299	5431	225-450
Bilirubin (µmol/l)	24	24	46	44	<17
APTT (sec)			60		31-39
PTT (sec)			19		11.7-15.7
Fibrinogen (g/l)			7.8		1.7-3.3
D-dimer (µg/l)			1719		<500

Autoimmune serology negative (ANA, ANCA, anti-dsDNA, ENA RNP, SS-A/SS-B antibodies, Sm/Jo-1 antibodies, ACLA). CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; CK= creatine phosphokinase; ASAT = aspartate aminotransferase activity; ALAT = alanine aminotransferase activity; LDH = lactic dehydrogenase activity; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; anti-dsDNA = anti-double-stranded DNA antibodies; ENA RNP = extractable nuclear antigen ribonucleoprotein ACLA = anticardiolipin antibodies.

days after admission dengue virus infection was diagnosed by high levels of IgM and IgG antibodies against dengue virus antigen.

Despite aggressive shock treatment and adequate treatment of secondary infections (pneumonia, central catheter infections, oral candidiasis), bleeding complications and renal failure, the patient developed a progressive respiratory failure due to fibroproliferative ARDS with hypercapnia and low compliance resulting in death on day 47.

DISCUSSION

Dengue virus is an arbovirus and a member of the *Flaviviridiae* family. The virus is transmitted from humans to humans by the bite of infective female *Aedes aegyptii* mosquitoes during daytime in endemic (sub)tropical regions. To a lesser degree *Aedes albopictus* and *Aedes polynesienses* are involved in the transmission of this virus. So far four distinct serotypes of dengue viruses have been reported (DENV-1, DENV-2, DENV-3 and DENV-4). As a result of uncontrolled urbanisation in tropical countries and increased global air travel, dengue has now become the most important arthropod-borne viral disease in humans.[3] Today approximately 50 to 100 million cases of dengue fever (DF) and 500,000 cases of dengue haemorrhagic fever (DHF) occur annually, resulting in about 24,000 deaths worldwide (average mortality rate of 5%).

So far a fatal course of dengue has primarily been reported from tropical regions. DHF and dengue shock syndrome (DSS) are the leading causes of morbidity and mortality among children in South East Asia.[4] DSS is reported to be the third leading cause of ARDS in paediatric intensive care in Dengue endemic areas after sepsis and pneumonia.[5,6]

The incidence of dengue infection in short-term travellers returning from dengue endemic areas is underestimated due to its subclinical course. In a prospective study among 447 Dutch short-term travellers to Asia an incidence of 2.9% was found.[1] Since repeated infection with another serotype has been associated with increased risk of severe manifestation, the number of short-term travellers developing a potentially life-threatening DHF/DSS is expected to increase.

The clinical spectrum of dengue ranges from an asymptomatic course to serious manifestations of a potentially fatal dengue shock syndrome (*table 2*). Prognosis is usually good and the disease is self-limiting in most cases. But the fatality rate once shock has set in may be as high as 44%.[7,8]

No specific treatment of dengue exists.[8] High-dose methylprednisolone failed to reduce mortality in severe DSS; however prolonged thrombocytopenia in DHF has responded well to corticosteroids.[4] So far effective drugs that block the increased vascular permeability are not available.[9] Positive results from high-dose immunoglobulin and activated factor VII on haemostasis have been reported.[10-12]

Table 2. *Clinical spectrum of dengue ranges from an asymptomatic course to a potentially fatal dengue shock syndrome*

Dengue fever (DF)
- Fever lasting 5-7 days, sometimes biphasic or 'saddle-back' fever curve
- Symptoms of frontal headache, retro-ocular pain, myalgia, arthralgia, nausea, vomiting, diarrhoea and maculopapular or diffusely erythematous rash
- Leucopenia and mild thrombocytopenia are frequent findings
- Minor haemorrhagic manifestations such as petechiae, epistaxis and gingival bleeding usually 3-4 days after onset of fever
- Prognosis favourable and recovery usually after 7-10 days

Dengue haemorrhagic fever (DHF)
- Acute febrile illness similar to DF with haemorrhagic manifestation
- Thrombocytopenia <100 x 10 x 6/l
- Evidence of plasma leakage caused by increased vascular permeability leading to oedema, serous effusion, haemoconcentration, hypoalbuminaemia

Dengue shock syndrome (DSS)
- DHF with circulatory failure characterised by a rapid, weak pulse with narrowing of the pulse pressure (<20 mmHg, regardless of blood pressure levels), or hypotension with cold clammy skin and restlessness

The extent of thrombocytopenia does not predict clinically significant bleeding so platelets should not be administered just upon platelet count. In contrast, prolonged duration of shock and haematocrit within the normal low range at the time of shock have been associated with increased risk of severe haemorrhage.[13]

Patients with secondary infections with dengue virus are at more risk of developing DHF/DSS. The already existing non-neutralising cross-reactive antibodies seem to enhance virus uptake and replication in mononuclear cells leading to high viral load with subsequent enhanced release of cytokines, which may explain the increased risk of developing DHF/DSS. Other risk factors include infection with a more virulent genotype, young age, Caucasian race and a history of asthma, diabetes and sickle cell anaemia.[4] Lower incidence in blacks suggests genetic susceptibility. Surprisingly malnourished patients are relatively protected probably due to suppressed immune response.[12-14]

Although we could not distinguish by antibody response between a primary or secondary infection in our patient, a secondary infection seems more likely. The patient travelled frequently to endemic areas and furthermore IgG antibodies against other arboviruses with the same vector (Yellow Fever and Japanese encephalitis) were present.

Several unusual manifestations of dengue virus infections have been reported, such as hepatic failure, cardiomyopathy, encephalopathy and encephalitis. However, severe rhabdomyolysis and its complications are not mentioned as a potential manifestation of dengue in review articles and textbooks. It is believed to be an underrecognised and underreported entity which has been reported in only five patients.[15,16] Our patient presented with severe rhabdomyolysis with a peak CK level of 156,900 U/l complicated by renal failure. It should be emphasised that the risk of renal failure could be decreased by early detection of rhabdomyolysis by routine measurement of CK level in patients with suspected dengue infection and subsequent adequate treatment.

Although in our patient dengue was included in the differential diagnosis at first presentation, alarming signs of impending shock were not recognised. The severe abdominal pain was explained as a symptom of developing pneumonia, which was noted in lower lobes on CT-abdomen. Established shock and elevated CK level subsequently resulted in a cascade of renal failure, haemostatic derangement with bleeding complications, secondary infections, and respiratory failure due to progressive ARDS with eventually a fatal course. Perhaps the clinical outcome would have been different if alarming signs had been recognised on time and shock could have been prevented.

CONCLUSION

The number of short-term travellers presenting with primary and secondary dengue infections after returning from dengue endemic regions is expected to increase. So far no specific treatment or effective vaccine is available, and vector eradication programmes have not been successful. In addition, the extent of this disease could even increase by potential extension of the habitat of dengue transmitting vectors due to climate change. Therefore healthcare providers in non-endemic regions should be aware of the alarming symptoms of severe dengue infections since early recognition and prevention of shock by fluid resuscitation is the only effective treatment in patients with DSS. Finally, CK levels should be routinely measured in patients with suspected dengue in order to prevent acute myoglobinuric renal failure due to severe rhabdomyolysis.

REFERENCES

1. Cobelens FGJ, Groen J, Osterhaus ADME, et al. Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. Trop Med Int Health 2002;7:331-8.
2. Bakker RC, Veenstra J, Dingemans-Dumas AM, Wetsteyn JCFM, Kager PA. Imported Dengue in the Netherlands. J Travel Med 1996;23:204-8.
3. World Health Organization. Dengue. Available at http://www.who.int/tdr/dw/dengue2004.htm; Internet accessed July 15, 2005
4. Jose GRP, et al. Dengue and dengue haemorrhagic fever. Lancet 1998;352:971-7.

5. Thong MK. Dengue shock syndrome and acute respiratory distress syndrome. Lancet 1998;352:1712.

6. Goh AYT, Chan PWK, Lum LCS, Roziah M. Incidence of acute respiratory distress syndrome: a comparison of two definitions. Arch Dis Child 1998;79:256-9.

7. Lei HY, Yeh TM, Liu HS, Lin YS, Chen SH, Liu CC. Immunopathogenesis of Dengue Virus Infection. J Biomed Sci 2001;8:377-88.

8. Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis 2001;32:204-13.

9. Delia BB, et al. Noninvasive Measurement of Microvascular Leakage in Patients with Dengue Hemorrhagic Fever. Clin Infect Dis 2001;32:243-53.

10. Pea L, Roda L, Moll F. Desmopressin treatment for a case of dengue hemorrhagic fever/dengue shock syndrome. Clin Infect Dis 2001;33:1611-2.

11. Chuansumrit A, Wangruansatid S, Lektrakul Y, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. Blood Coagul Fibrinolysis 2005;16:549-55.

12. Ostronoff M, Ostronoff F Florencio R, et al. Serious thrombocytopenia due to dengue hemorrhagic fever treated with high dosages of immunoglobin. Clin infect Dis 2003; 36:1623-4.

13. Lum LC, Goh AY, Chan PW, El-Amin AL, Lam SK. Risk factors for hemorrhage in severe dengue infections. J Pediatr 2002;140:629-31.

14. Thisyakorn U, Nimmannitya S. Nutritional status of children with dengue hemorrhagic fever. Clin Infect Dis 1993;16:295.

15. Davis JS, Bourke P. Rhabdomyolysis associated with dengue virus infection. Clin Infect Dis 2004;38:e109-11.

16. Lim M, Goh HK. Rhabdomyolysis following dengue virus infection. Singapore Med J 2005;46:645-6.