

Rhabdomyolysis following dengue virus infection

M Lim, H K Goh

ABSTRACT

We describe a 27-year-old man who developed prolonged myalgia and dark red-coloured urine following dengue virus infection. The patient was found to have raised serum creatine kinase levels, consistent with rhabdomyolysis. He was treated with intravenous hydration and recovered uneventfully. Despite dengue fever being endemic in Singapore and South-east Asia, this is the first case report of such complication in this region.

Keywords: Creatine kinase, dengue fever, myalgia, myositis, rhabdomyolysis

Singapore Med J 2005; 46(11):645-646

INTRODUCTION

Dengue is an acute mosquito-borne infection with dengue viruses from the genus flavivirus. It is endemic in South-east Asia, including Singapore⁽¹⁾. Uncommon complications include mononeuropathies, polyneuropathies, encephalitis, Guillain-Barre syndrome, cardiomyopathy^(2,3) and rhabdomyolysis⁽⁴⁻⁶⁾. Rhabdomyolysis as a sequelae of dengue fever is not well described. We present a patient who developed rhabdomyolysis following dengue virus infection. Despite the illness being endemic in Singapore and South-east Asia, this is the first case report of such complication in this region.

CASE REPORT

A 27-year-old man with no significant medical history was referred to our hospital by his primary healthcare physician with the problem of four-day history of fever, nausea and myalgia. His primary healthcare physician had done a full blood count and he had been found to be thrombocytopenic with a platelet count of $88 \times 10^3/\text{UL}$. He was noted to have a temperature of 38.1 degrees Celsius. While he was warded, his platelet count was monitored and investigations were done. As his platelet count normalised and his fever subsided, he was discharged on day six of his hospitalisation. Dengue virus immunoglobulin (Ig) M and IgG titres were negative on

day one of hospitalisation but IgM became positive on day five suggesting a recent dengue virus infection. Dengue IgG titres were repeated on day five and were found to be negative. Results of blood cultures and urine culture for bacteria infection as part of the initial septic work-up were negative. Chest radiograph was also normal.

The patient was subsequently readmitted 18 days after his discharge. His primary healthcare physician had, following a review, referred him back to the hospital. He had been experiencing myalgia since his discharge. These aches had worsened after exercise and sport. He did not have any history of trauma. He had noted his urine to be dark red in colour for the preceding five days. The patient did not have any other symptoms. On admission, physical examination revealed no abnormality. The patient had normal vital signs. Urine sample was noted to be dark red and dipstick analysis was strongly positive for blood with only 5 red blood cells per high-power field on urine microscopy.

During this second admission, the patient's creatine kinase (CK) and creatinine were monitored daily. His creatinine remained in the normal range while the CK gradually decreased from 58,961 U/L (range 40-210 U/L) on day one to 12,754 U/L on day seven. Serological tests for hepatitis viruses A, B and C and for leptospira performed were negative. Urine culture was negative and a repeat chest radiograph during the second admission was normal too. He was treated with intravenous hydration with three litres of normal saline per day. His stay in the hospital was uneventful and he was discharged on day seven. The patient remained well on follow-up in the outpatient clinic, with CK levels gradually normalising.

DISCUSSION

Unusual complications of dengue infection include neurological presentations such as mononeuropathies, polyneuropathies, encephalitis, and Guillain-Barre syndrome⁽²⁾. Muscular complications including cardiomyopathy⁽³⁾ and myositis are other atypical presentations. This present report is not the first to record an association between dengue and rhabdomyolysis. To

Department of
Emergency
Medicine
Tan Tock Seng
Hospital
11 Jalan Tan
Tock Seng
Singapore 308433

M Lim, MBBS
Medical Officer

H K Goh, MBBS,
MRCP, MRCSE
Registrar

Correspondence to:
Dr Hsin Kai Goh
Tel: (65) 6357 8777
Fax: (65) 6254 3772
Email: hsin_kai_goh@
tsh.com.sg

our knowledge, it has been reported three times previously^(4,6). Myositis and rhabdomyolysis associated with a viral infection is a well-described entity^(7,8), but not with dengue virus infection⁽⁴⁾.

Two possible mechanisms have been postulated: direct viral invasion of the muscle fibres and toxin generation⁽⁷⁾. Virus-like particles had been found in muscle specimen of a patient with myositis secondary to an influenza infection on electron microscopy⁽⁸⁾. This supported the possibility of direct viral invasion and damage to the infected muscles. However, viral particles within the muscles have not been consistently demonstrated⁽⁹⁾. In his case report⁽⁴⁾, Davis et al noted that the more likely cause of myositis and rhabdomyolysis by dengue virus is myotoxic cytokines, particularly tumour necrosis factor (TNF) released in response to viral infection. Dengue virus infection had been shown to increase production of TNF in humans⁽¹²⁾. Studies of muscle biopsies in patients with dengue reported varied findings from inflammatory infiltrate to foci of myonecrosis⁽¹³⁾.

It is of interest to note that our patient was involved in sports shortly after recovery from his dengue virus infection. However, he was experiencing myalgia even before he started any exercise regime. Our patient did not have any history of trauma. Strenuous muscular exertion is a known cause of rhabdomyolysis. Although there was a likelihood that our patient's exercise regime contributed to the process of rhabdomyolysis, the persistence of myalgia following his first discharge which occurred prior to his sporting activity would suggest that the precipitating cause is that of his recent dengue virus infection.

There is currently a resurgence of dengue fever in the world⁽¹¹⁾. The reasons for this resurgence are complex, but one of the main factors is uncontrolled urbanisation resulting in substandard water, sewer and waste management systems⁽¹¹⁾. Locally, we are also seeing a resurgence of dengue cases since 1986. Decreased herd immunity to dengue viruses as a cause to this local resurgence has been proposed⁽¹⁾. The adaptation of the *Aedes* mosquito to the vector control programme so that they now breed and feed in places other than residences⁽¹⁴⁾ may be another reason.

The scarcity in the medical literature regarding this complication as an association with dengue illness may be due to under-reporting and under-recognition of such a complication by physicians⁽⁴⁾. Another reason could be its rare occurrence. However, with the increase in dengue fever in the community, it is important to be vigilant about this problem. Unfortunately, we are currently unable to predict who is likely to suffer this complication. More studies into the pathogenesis of dengue fever will likely shed

light in this area. Whether early strenuous exercise following a dengue infection would make a patient more likely to suffer this complication is also unknown.

The clinical presentation of rhabdomyolysis includes symptoms of myalgia, weakness and dark urine. Predisposing conditions that may lead to rhabdomyolysis include a history of seizures, unconsciousness, strenuous exertion frequently associated with altered mental status. Swollen, tender muscles or skin changes consistent with pressure injury may be found on clinical examination. Elevated CK levels remain the most sensitive indicator of rhabdomyolysis⁽¹⁵⁾. Meanwhile, it has been suggested⁽⁴⁾ that all patients with dengue fever should have a dipstick urinalysis to screen for this complication and if positive, to proceed with a serum CK level. It is also important to remember that the benzidine urinary dipstick does not differentiate between myoglobin, haemoglobin and red blood cells and a CK should be performed if rhabdomyolysis is suspected. This is reasonable as the test is easily available and early diagnosis of rhabdomyolysis can prevent its complications⁽¹⁰⁾. Rhabdomyolysis, though a rare complication of dengue, should be kept in mind by healthcare workers as the incidence of dengue infection increases.

REFERENCES

- Goh KT. Dengue – a re-emerging infectious disease in Singapore. *Ann Acad Med Singapore* 1997; 26:664-70.
- Solomon T, Dung NM, Vaughn DW, et al. Neurological manifestations of dengue infection. *Lancet* 2000; 355:1053-9.
- Gibbons RV, Vaughn DW. Dengue: an escalating problem. *BMJ* 2002; 324:1563-6.
- Davis JS, Bourke P. Rhabdomyolysis associated with dengue virus infection. *Clin Infect Dis*. 2004; 38:e109-11. Available at: www.journals.uchicago.edu/CID/journal/issues/v38n10/33040/33040.html Accessed October 10, 2004.
- Gunasekara HH, Adikaram AV, Herath CA, et al. Myoglobinuric acute renal failure following dengue viral infection. *Ceylon Med J* 2000; 45:181.
- Beauvais P, Quinet B, Richardet JM. [Dengue. Apropos of 2 cases.] *Arch Fr Paediatr* 1993; 50:905-7. French.
- Seibold S, Merkel F, Weber M, et al. Rhabdomyolysis and acute renal failure in an adult with measles virus infection. *Nephrol Dial Transplant* 1998; 13: 1829-31.
- Greco TP, Askenase PW, Kashgarian M. Postviral myositis: myxovirus-like structures in affected muscle. *Ann Intern Med* 1977; 86:193-4.
- Pratt RD, Bradley JS, Loubert E, et al. Rhabdomyolysis associated with acute varicella infection. *Clin Infect Dis* 1995; 20:450-3.
- Vanholder R, Sever MS, Ereik E, et al. Rhabdomyolysis. *J Am Soc Nephrol* 2000; 11:1553-61.
- Gubler OJ, Clark GG. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. *Emerg Infect Dis* 1995; 1:55-7.
- Gagnon SJ, Mori M, Kurane I, et al. Cytokine gene expression and protein production in peripheral blood mononuclear cells of children with acute dengue virus infections. *J Med Virol* 2002; 67:41-6.
- Malheiros SM, Oliveira AS, Schmidt B, et al. Dengue. Muscle biopsy findings in 15 patients. *Arq Neuropsiquiatr* 1993; 51:159-64.
- Ooi EE. Changing pattern of dengue transmission in Singapore. *Dengue Bulletin* 2001; 25:40-4.
- Will MJ, Hecker RB, Wathen PI. Primary varicella-zoster-induced rhabdomyolysis. *South Med J* 1996; 89:915-20.