

Hippocampal involvement in dengue fever

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ABSTRACT

Flaviviruses are among the most important emerging viruses known to man. Dengue is the most common flavivirus infection in Singapore, and is transmitted between humans by the *Aedes* mosquito. We report a 25-year-old man with dengue fever complicated by selective hippocampal involvement manifesting as amnesia. This has not been described in the literature previously. Dengue polymerase chain reaction and serology were positive. Magnetic resonance imaging of the brain showed bilateral hippocampal involvement.

Keywords: amnesia, dengue fever, encephalitis, hippocampus, neurological manifestation

Singapore Med J 2005; 46(11):647-650

INTRODUCTION

The dengue virus is an arbovirus of the family *Flaviviridae*. There are four serotypes and transmission to humans is via inoculation from a mosquito bite – usually *Aedes aegypti*, and occasionally, *Aedes albopictus*⁽¹⁾. After an incubation period of seven to 14 days, this virus causes a febrile illness of several days duration characterised by delayed thrombocytopaenia occurring together with the eventual resolution of the fever⁽²⁾. With the advent of the global village and convenient cross-continent mobility of its human reservoirs, dengue fever has spread beyond the tropics to temperate regions such as Germany⁽³⁾. Every year, an estimated 100 million people are infected⁽⁴⁾.

In Singapore, it is of prime public health importance, with the incidence increasing from 9.3 per 100,000 in 1988 to 138.6 per 100,000 in 1997⁽⁵⁾. More recently, there were a reported 3,945 cases in 2002, up from 2,372 in 2001. This gives a raw incidence of about 95 cases per 100,000 population. There were four deaths, yielding a case fatality rate of about one in 1,000^(6,7). In 2003, the number of reported cases increased to 4,788, raising the incidence to 114 per 100,000⁽²⁾. Neurological manifestations of dengue infection

are rare and have only recently begun to be recognised^(5,8-11). We report a case of selective bilateral hippocampal encephalitis in a patient with dengue fever. This has not been previously reported in the literature.

CASE REPORT

A 25-year-old man was admitted in July 2004 after a syncopal episode resulting in a fall and a small haematoma over the occiput. He was found by a relative who did not report any movement to suggest a seizure. There was no past history of seizures. He recovered consciousness after five minutes. At the time of presentation, he also had three days of fever, rhinitis, and a dry cough. 14 days prior to the onset of symptoms, he had returned to Singapore from an 11-day back-packing trip to Vietnam – specifically Hanoi, Sapa and Northern Vietnam. He did not undergo any pre-travel vaccination or take malaria prophylaxis. He travelled alone and stayed in inexpensive hotels. He hiked in the countryside with hill tribal people and their livestock, wading through some rivers and waterfalls in the process. He was bitten by mosquitoes, and denied any specific contact with rodents. His only past medical history was of recurrent mouth ulcers for many years. There was no past history of genital ulcers, sexual intercourse, intravenous drug use, or smoking. He consumed at most two units of alcohol a week. He had recently completed a post-graduate degree.

Physical examination revealed a fever of 38.8°C with mild terminal neck stiffness. He was disoriented to date and time and had retrograde amnesia with impaired immediate and delayed recall. There were no other neurological deficits. There was no petechial or other rash. Examination of the other systems was normal. The chest radiograph was normal. The full blood count showed normal haemoglobin level of 15.4g/dL, haematocrit of 45.5%, mild thrombocytopaenia of $155 \times 10^9/L$ (normal $160-390 \times 10^9/L$), and normal total white blood cell count of $6.3 \times 10^9/L$, with a predominance of polymorphonuclear leucocytes (86.1%), and a

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differential count of 3.8% lymphocytes, 10.1% monocytes, 0% eosinophils and 0% basophils. The erythrocyte sedimentation rate (two mm/hr) and coagulation parameters were normal. Three samples of blood film for malaria parasites were negative on admission, two days, and seven days later. Electrolytes, renal and liver function tests were normal.

Computed tomography (CT) of the brain on the day of admission was normal. Magnetic resonance (MR) imaging of the brain performed the next day (Fig. 1) showed T2 prolongation with hyperintense signal on the fluid attenuated inversion recovery (FLAIR) sequence at the hippocampi bilaterally, with suggestion of minimally increased leptomeningeal enhancement. There was no enhancement of the hippocampi after administration of intravenous contrast, indicating that the blood-brain barrier was still intact. The rest of the brain parenchyma was normal.

Cerebrospinal fluid (CSF) examination was clouded by a traumatic lumbar puncture, precluding accurate measurement of CSF white cell count. However, most of the white cells were lymphocytes. Total CSF protein was slightly raised at 47 mg/dL (normal 10 - 40 mg/dL). CSF glucose was 2.7mmol/L, low compared with a simultaneous capillary blood glucose of 5.6mmol/L. Microscopy for cryptococcus (India Ink) and culture for fungus of the CSF were both negative. Due to an administrative error, a sample of CSF sent for herpes simplex virus (HSV) polymerase chain reaction (PCR) was not received by the laboratory.

In view of the clinical and imaging pictures of viral encephalitis (commonly due to either HSV or Japanese B encephalitis [JE]), he was treated with empirical intravenous acyclovir for ten days followed by four days of oral acyclovir to target HSV. There is no specific anti-viral treatment for JE. In addition, he was also given intravenous ceftriaxone and oral doxycycline. Blood for JE virus complement fixation antibody (CF Ab) was negative on both day 11 and day 35 of the illness. A HSV enzyme immuno-assay (EIA) was negative on day 35 of the illness. Rickettsial serology on day four was negative. Dengue virus PCR was positive on day four of illness. On the same day, dengue rapid screen was negative for both IgM and IgG. Dengue IgM became positive on day eight of illness.

His fever broke on day five of his illness, on the third day of antibiotics. The platelets dropped to their nadir of $102 \times 10^9/L$ on day seven, and recovered by day 13 to a normal $249 \times 10^9/L$. His memory slowly improved, with immediate recall recovering first. Long-term memory was largely intact, but delayed

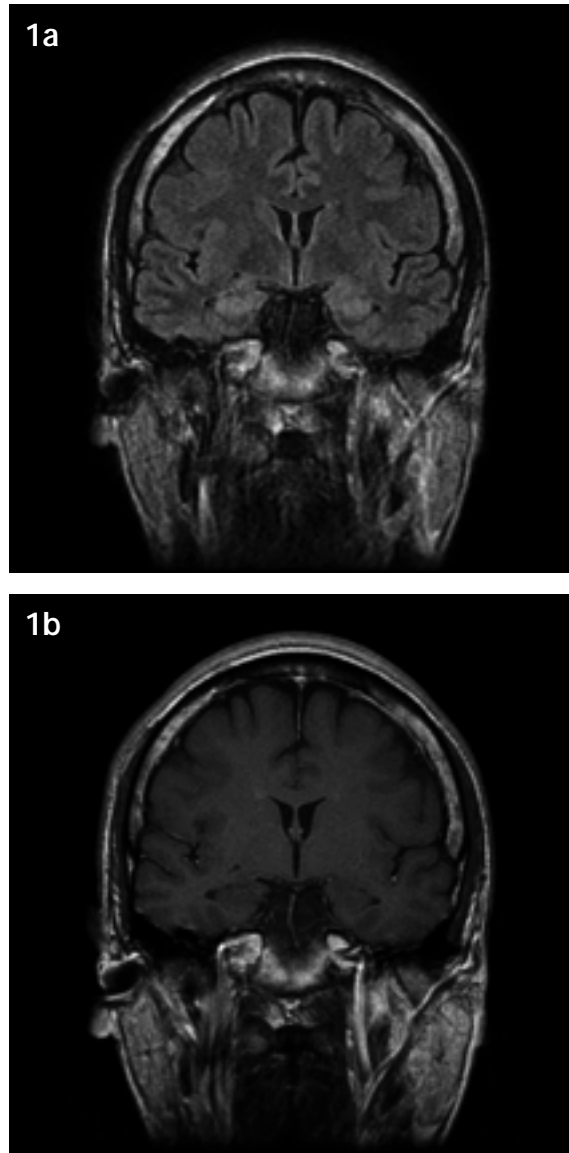


Fig. 1 (a) Coronal FLAIR MR image of the brain shows T2 prolongation at bilateral hippocampi. (b) Enhanced coronal T1-W MR image shows no significant hippocampal enhancement.

recall was poor. On day 13 of illness, he was assessed by a clinical psychologist using the Weschler Adult Intelligence Scale (Revised) (WAIS-R). He was noted to be cooperative and motivated to complete the assessment. He was eloquent and forthcoming, with intact comprehension and good attention throughout. He had very superior verbal IQ (VIQ) of 140. However, his performance IQ (PIQ) was only 98 (average). The full-scale IQ (FS IQ) was 125 (superior). There were no significant strengths or weaknesses in the verbal and performance domain. His freedom from distractibility was "very superior". He was discharged 16 days after admission, clinically well apart from the said residual cognitive shortcomings.

70 days after the first assessment, he was re-assessed by the same psychologist using the Weschler

Memory Scale (Revised) (WMR-R). His verbal memory was average (97), visual memory was very superior (138), general memory was high average (113), attention and concentration was very superior (136), and delayed recall was average (103). He has since commenced employment in his chosen career.

DISCUSSION

Dengue is now endemic in Vietnam, with epidemics during the rainy season from June to November⁽¹³⁾. The incubation period of dengue fever is four to seven days (range of three to 14 days). Therefore, his infection, if attributable to dengue virus, could have been acquired either in Vietnam, or more probably, in Singapore. Dengue encephalitis is rare and until recently, has previously only been described in case reports^(5,8-11,14). Other than encephalitis, other neurological manifestations that have been described include acute disseminated encephalomyelitis⁽¹⁵⁾, post-infectious disseminated acute encephalitis⁽¹⁶⁾, acute polyradiculoneuritis (Guillain Barré Syndrome)⁽¹⁶⁾, mononeuropathies⁽¹⁷⁾, and even encephalopathy without encephalitis⁽¹⁸⁾.

A prospective study of patients with suspected central nervous system infections admitted in 1995 to an infectious diseases referral hospital in Vietnam reported that 4.2% (16 patients out of 378) had acute dengue infection. Nine had encephalitis, five had hepatic encephalopathy, four had encephalopathy, two had transverse myelitis, and one had meningism. Non-specific signs such as headache, reduced consciousness and convulsions were common. All were discharged alive, but six had residual neurological deficits⁽¹⁹⁾.

In our patient, MR imaging of the brain showed isolated bilateral hippocampal involvement. This imaging abnormality correlated with the clinical picture of memory deficits. Although not formally documented prior to presentation, his pre-morbid intelligence was likely to be above average as he had completed a post-graduate degree. The discrepancy of 42 points between VIQ and PIQ is significant. Gross disparity between a higher VIQ and a lower PIQ (≥ 20 points) suggests organic deterioration as verbal function tends to be preserved longer than non-verbal function⁽¹²⁾. Hippocampal involvement has not previously been reported and provides further evidence for the neurotropical ability of the dengue virus.

CSF examination was negative for bacteria, acid-fast bacilli, or fungi. We considered the two most likely differentials of JE and HSV. JE, another flavivirus, may cross-react with serological tests for dengue⁽⁴⁾. It is endemic to Vietnam and has an incubation

period of six to 16 days, corresponding with the time-frame of the patient's presentation⁽²⁾. However, blood serology for JE by complement fixation was negative. In addition, dengue PCR, which does not suffer from cross-reactivity with JE, was positive. *Herpes simplex*, which is well-known to cause encephalitis⁽²⁰⁾, was excluded as HSV EIA was negative.

Most of the viral encephalitides resemble each other on imaging, with diffuse parenchymal involvement showing oedema, mass effect, hyperintensity on T2-weighted images, and even petechial haemorrhages. The changes of herpes simplex encephalitis are characteristic – MR imaging shows mild hypointensity on T1-weighted and marked hyperintensity on T2-weighted images at the hippocampi, insular strips, cingulate and rectus gyri. Subarachnoid enhancement suggestive of meningeal involvement is unusual. Late follow-up MR imaging in HSV encephalitis may show widespread encephalomalacia of the temporal and frontal lobes, with corresponding residual neurological deficits^(21,22).

Although neuroimaging was not incompatible with HSV encephalitis, only the hippocampi were involved. The MR imaging of the brain did not reveal any other area of abnormality – specifically, no abnormalities were seen at the insular strips, cingulate or rectus gyri. As clinical recovery was swift, lumbar puncture was not repeated. Dengue PCR was positive on day four, and there was documented seroconversion on day eight, thus confirming acute dengue infection. We therefore conclude that this patient had encephalitis due to the dengue virus. The selective hippocampal involvement is unusual, and is correlated clinically. A repeat sample of the CSF for JE and HSV serology would have been of academic interest, but was not performed as it was not clinically warranted.

Involvement of the central nervous system in dengue fever and dengue haemorrhagic fever has previously been thought to be secondary to vasculitis – which causes the blood-brain barrier to be breached. The cognitive deficits have therefore previously been classified as encephalopathy rather than encephalitis. However, contrast-enhanced MR imaging shows that the blood-brain barrier was intact in this patient. In the past, encephalitis – i.e. direct involvement of the brain by the virus – was thought to be unlikely. However, some authors have postulated that encephalitis can occur by direct invasion of the brain by the virus crossing the blood-brain barrier^(23,24). Others have postulated that encephalitis occurs via an immunopathological

process^(16,17). This is certainly an important direction for further study on the pathogenesis of dengue encephalitis.

In conclusion, we present a case in which there were typical features of dengue fever, with laboratory confirmation by PCR and paired serology, presenting with bilateral hippocampal involvement. In this instance, the patient achieved excellent neurological recovery. Such hippocampal involvement has not been previously reported in the literature, and represents a rare complication of dengue fever.

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