

A fatal case of cerebral oedema and myocarditis associated with secondary dengue infection

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Abstract

Background: Secondary dengue infection (SDI), in the form of two sequential infections by different serotypes, will lead to severe dengue. Concomitant organ failure in particular cardiovascular (CVS) and central nervous system (CNS) carries further rise in the mortality rate.

Case report: We report a confirmed SDI in a 27-year-old man who presented with hypovolemic shock due to persistent vomiting and diarrhoea. He was stabilized after fluid resuscitation. However, he developed sudden onset of seizure and myocarditis with unstable haemodynamic thereafter. After stabilization, his gag and cough reflexes were absent with dilated pupils. Imaging of the brain showed extensive cerebral oedema with poor flow beyond the internal carotid arteries and its branches above circle of Willis. He remained comatose with subsequent complications of diabetes insipidus, secondary

bacterial infection, and acute kidney injury. He passed away after 19 days of admission.

Discussion: There is a higher risk of severe dengue with SDI as it is associated with antibody-dependent enhancement (ADE) mechanism. The pre-existing dengue antibodies enhance virus replication by activating memory T-cells causing surges in inflammatory cytokines. The increased capillary permeability with massive vascular leak most likely led to the extensive cerebral oedema in this patient. The concomitant cardiovascular failure also led to his irreversible outcome.

Conclusion: Severe cardiovascular and neurological manifestations can occur in SDI with resultant in the fatality. Therefore, early recognition of risk factors in the early phase of severe dengue is important to prevent the irreversible outcome.

Key words: Secondary dengue infection, severe dengue, antibody-dependent enhancement, myocarditis, dengue encephalopathy.

Introduction

Dengue infection was first recognized in Philippines and Thailand during dengue epidemics in the 1950s. Since then, the incidence has dramatically increased and became endemic in over 100 countries in World Health Organization (WHO) regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. (1)

The clinical presentations of dengue infection vary, ranging from self-limiting febrile illness to life-

threatening dengue shock syndrome. In 2009, WHO reclassified dengue infection into the levels of severity - dengue fever with or without warning signs to severe dengue. The warning signs included abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement and laboratory changes of haemoconcentration and thrombocytopenia. (2) For severe dengue, the patients would be characterized by severe plasma leakage leading to shock, fluid accumulation leading to respiratory distress, severe bleeding and severe organ impairment. (2)

Secondary dengue infection (SDI) in a form of two sequential infections by different serotypes has been identified as one of the important epidemiological risk factors for severe dengue. (3,4) Antibody-dependent enhancement (ADE) mechanism has been proposed as an immune-mediated mechanism that responsible for higher blood and/or tissue viral load in SDI, which causing severe dengue. (3,5,6)

In this case, the patient was confirmed with SDI and developed severe dengue with myocarditis and

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rapidly progressed cerebral oedema, which causing irreversible brain damage.

Case report

A 27-year-old male, who has no past medical illness, sought treatment at the emergency department following 4 days history of fever with chills and rigors. He also had headache, vomiting, and loose stools with a brief period of syncope attack. Upon admission, he was febrile with a temperature of 38.9 °C, tachycardic and postural hypotension. He was lethargic, dehydrated with cold peripheries. There was mild epigastric tenderness but hepatomegaly was not detected. Otherwise, neck stiffness and photophobia were not present and there were no abnormalities on systemic review.

Initial blood investigations revealed an elevated haematocrit level of 55% and low white blood cell count of $3.1 \times 10^9/L$. There was no initial thrombocytopenia. His liver function, coagulation profile, and electrolytes were within normal ranges. Venous blood gas showed lactic acidosis and it was likely due to dehydration. After fluid resuscitation, peripheral perfusion improved. However, he remained febrile and was admitted to the ward for further observation. In the ward, he developed sudden onset of generalised seizure which coincided with the fifth day of illness. His non-structural protein 1 (NS1) dengue antigen, immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies for dengue infections were positive which confirmed the diagnosis of SDI. He was intubated and a computerized tomography (CT) scan of the brain was performed. There was no cerebral oedema, meningeal enhancement or bleeding in the immediate CT scan of the brain (**Figure 1**). Cerebrospinal fluid (CSF) analysis was not performed as thrombocytopenia was present. He was appropriately transferred to the general intensive care unit (GICU). His Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were 3 and 6, respectively, on admission.

On initial GICU admission, his haemodynamic was unstable. He was diagnosed with dengue myocarditis as developed Mobitz type I second degree atrio-ventricular (AV) block and transthoracic echocardiogram showed all heart chambers were dilated with poor left ventricular ejection fraction. However, there were no signs of pulmonary oedema clinically and radiologically. The haemodynamic instability was transient and was stabilized with inotropic support.

On the 9th day of the illness, his pupils were non-reactive, the gag and cough reflexes were absent.

There was extensive cerebral oedema on the repeated CT scan of the brain (**Figure 2**). Magnetic resonance imaging (MRI) and angiography (MRA) of the brain (**Figure 3** and **4**, respectively) showed poor signal flow within the intracranial internal carotid arteries and at the level of circle of Willis and its branches secondary to extensive cerebral oedema.

He was then developed central diabetes insipidus with severe hyponatremia, which persisted despite fluid replacements with desmopressin therapy. His neurological recovery remained poor. There was generalized reduced amplitude on the electroencephalogram of the brain which was consistent with severe generalized cerebral disturbances. He was then complicated with secondary bacterial infection and acute kidney injury, which required renal replacement therapy. He was then expired on the 19th day following GICU admission.

Discussion

Dengue is an arboviral infection, which caused by one of the four single-stranded, ribonucleic acid (RNA) viruses which originated from the Flaviviridae family. (2) There are distinct, but closely related serotypes dengue viruses (DENV-1, DENV-2, DENV-3, and DENV-4). Lifelong immunity is provided by recovery from a specific serotype, (2) while SDI by heterogeneous stereotypes will lead to severe dengue. (3,4) Other epidemiological risk factors associated with severe dengue included young age, female sex, high body-mass index, genetic predisposition and comorbidities. (3,4,6) Therefore, the interactions between viral and host factors were accountable for the disease severity.

Cardiovascular complications are not uncommon in dengue patients. Lee et al. (2010) reviewed 339 dengue-affected patients with cardiac complications, found that the manifestations varied from self-limiting tachy-brady arrhythmias to severe myocardial damage leading to significant hypotension and pulmonary oedema. Most patients were supported symptomatically, but yet fatal outcome was reported in some patients. (7) As in our case, the patient developed Mobitz type I second-degree AV block with impaired left ventricular function transiently and was stabilized in the early critical phase. However, he developed an extensive cerebral oedema leading to severe brain damage consequently.

Numerous neurological complications have been reported in severe dengue. These included dengue encephalitis, Guillain-Barre syndrome, transverse myelitis, acute disseminated encephalomyelitis and

myositis. (8) Several pathogenic mechanisms were proposed included direct neuronal infiltration, post-infectious immune-mediated complications, and encephalopathy secondary to liver failure, cerebral hypoperfusion, deranged electrolytes and intracranial haemorrhage from severe thrombocytopenia or coagulopathy. (9) We were unable to exclude the possibility of direct neuronal injury by dengue viruses in this patient as no cerebrospinal fluid analysis was performed due to thrombocytopenia. But yet, a massive vascular leak, which associated with ADE activation leading to extensive cerebral oedema was plausible.

During ADE activation, it was believed that the sub-neutralizing or non-neutralizing level of dengue virus-reactive antibodies from the primary infection (IgG) will enhance the dengue viruses' replication in the Fc-receptor bearing cells (Fragment, crystallisable) such as monocytes and macrophages. The large infected cell mass will then activate the memory T-cells causing massive inflammatory cytokines released, vascular permeability increased and eventually severe plasma leakage. (3,5,6) This coincides with the neurological manifestations of this patient.

In addition, a multicentre, retrospective observa-

tional study by Schmitz et al. in 2011 found that most severe dengue patients with 3 or more organ failures that admitted to ICU were shown to be higher mortality rate. Furthermore, the presence of concurrent CVS and CNS failure had 4-fold increased the risk of death compared to non-organ failure patients. (10) Likewise, our patient developed concurrent myocarditis and extensive cerebral oedema leading to his fatal outcome.

Conclusion

Although most dengue patients recovered from a self-limiting course, but yet unpredictable outcome would happen in high-risk patients. Therefore, further studies are required to identify more relevant predictors and biomarkers in the early phase of the illness in order to provide early intervention with good supportive care for the better patient outcome.

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Figure 1. Computered tomography (CT) scan of the brain immediately post seizure showed no significant abnormality



Figure 2. Repeated CT scan of the brain showed generalised cerebral oedema

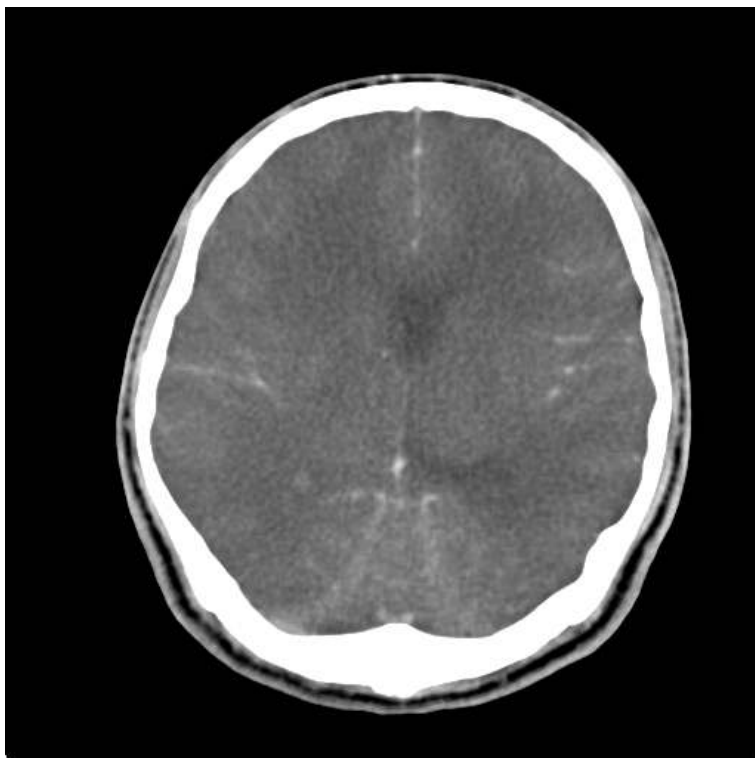


Figure 3. T2 axial of the magnetic resonance imaging (MRI) brain showing extensive white matter oedema

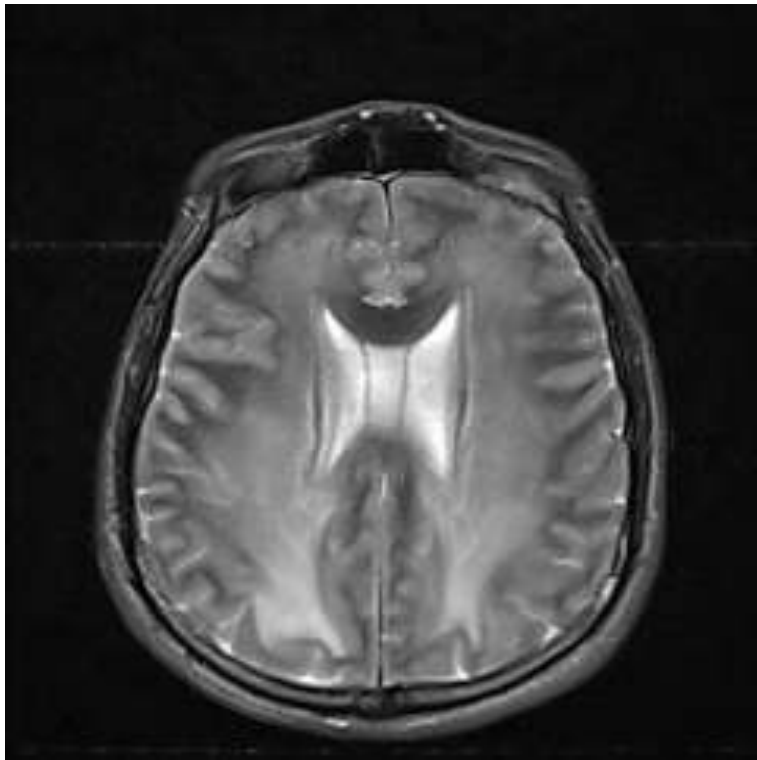


Figure 4. Magnetic resonance angiography (MRA) brain showing poor flow signal of the intracranial vessels



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