

Case Report

Spontaneous haemorrhagic stroke associated with expanded dengue syndrome: a case report

Claraiva Mayung*, Fira Thiodorus, Desie Yuliani, I. Ketut Sumada, Kurnia Dwi Jayanti

Department of Neurology, Wangaya General Hospital, Denpasar, Bali, Indonesia

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*Correspondence:

Dr. Claraiva Mayung,

E-mail: claraclaraiva@gmail.com

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ABSTRACT

The term "expanded dengue syndrome" was introduced to describe the severe clinical manifestations that result from dengue fever (DF), namely severe multi-organ involvement including disorders of the nervous system. Neurological complications occur in 1-5% of dengue patients, including haemorrhagic stroke. A 68-year-old man presented with complaints of full-body convulsions for 1 minute. Four days earlier the patient complained of headache, fever, and nausea. Non-contrast CT scan of the head showed abnormal hyperdense lesions with focal intraparenchymal oedema in the frontoparietooccipital region, cortical sulci and gyri appeared dilated, ventricular system and sistrum were dilated. Anti-dengue IgG and IgM were positive. Neuropathogenesis that may play an important role in dengue-related neurological syndromes include direct CNS invasion by the virus, autoimmune reactions, and metabolic changes. The diagnosis of neurological complications related to dengue haemorrhagic fever (DHF) requires special attention, especially for areas where DF is still endemic.

Keywords: Haemorrhagic stroke, Expanded dengue syndrome, DHF, Intracerebral haemorrhage, Subarachnoid haemorrhage

INTRODUCTION

Dengue virus infection is a global health threat that infects at least 3.6 billion people living in more than 125 countries throughout the tropics and subtropics. Its incidence has increased drastically over the past three decades. The world health organization (WHO) estimates that 390 million dengue infections occur annually with 96 million cases manifesting clinically.^{1,2} There are four serotypes of dengue virus: DENV1, DENV2, DEN 3, DENV4. Transmitted by mosquitoes of the genus *Aedes*, with clinical manifestations ranging from asymptomatic to severe dengue.³

To better understand the disease, WHO has proposed a new classification scheme. The term "expanded dengue syndrome" was introduced to describe the severe clinical manifestations that result from DF, namely severe multi-organ involvement including the occurrence of

neurological complications. Neurological complications occur in 1-5% of dengue patients. Neurological involvement including encephalopathy, stroke either intracranial haemorrhage or infarction are rare but fatal complications.^{4,5} DHF has various bleeding manifestations. Intracranial haemorrhage in DHF can present as subdural haematoma, extradural haematoma, haemorrhagic stroke namely intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH).¹ The incidence of multiple intracerebral haemorrhage alone only occurs in 2% of haemorrhagic cases.⁶ Unfortunately, haemorrhagic fever associated with haemorrhagic stroke has high morbidity and mortality, but little is known about it.⁵

We report a case of spontaneous intracerebral haemorrhagic stroke and subarachnoid haemorrhage related to DHF in an elderly man with cerebral atrophy.

CASE REPORT

A 68-year-old man was brought by his family to the emergency room of Wangaya hospital in Denpasar with complaints of seizures 1 hour before admission. The seizure occurred with full body twitching, eyes darting upwards, occurred once for approximately 1 minute, after the seizure the patient fell asleep and then woke up and was confused. Before the seizure, the patient seemed to be sleepy. The patient also complained of headache, nausea and fever that had been felt since 4 days ago. History of head trauma and previous seizure was denied. History of hypertension since the age of 50 years controlled with amlodipine and candesartan. History of other diseases was denied. Family history of similar complaints, seizures, hypertension, diabetes is denied, cancer is denied. It was known 1 week before the incident that the patient's housemate had DHF. The family said the patient had been diagnosed with DF approximately 5 years ago.

At the initial examination in the emergency room, the patient's admission Glasgow coma scale (GCS) was found to be E3V4M6, vital signs blood pressure 122/62 mmHg, pulse 83x/min, respiration 20x/min, temperature 37.8 degrees celsius, oxygen saturation 99% with nasal cannula 3 litres per minute. General physical examination was within normal limits. No cranial nerve paresis and motor weakness were found. Physiological reflexes were good. Pathological reflexes were not found. Sensory examination showed sensibility within normal limits.

In the supporting examination, the following laboratory results were obtained: Hemoglobin 11.4 g/dL, hematocrit 32.5%, leukocytes 4600/uL, platelets 77,000/uL, electrolytes sodium 137 mmol/L, potassium 4.2 mmol/L, chloride 95 mmol/L, renal function, liver, and blood sugar levels within normal limits. The COVID-19 rapid test was non-reactive. Electrocardiogram showed sinus rhythm results. PA thorax X-ray showed cor and pulmo within normal limits. Non-contrast CT scan of the head showed abnormal hyperdense lesions with focal edema in the intraparenchyma in the frontoparietooccipital region, cortical sulci and gyri appeared dilated, ventricular system and sistrum were dilated, no midline shifting structure was seen. Initial therapy given was ringer lactate infusion 16 tpm, citicoline 2x500 mg intravenously, nimodipine 6x60 mg orally, phenytoin 2x100 mg intravenously, paracetamol 3x1 gr intravenously. The patient was then referred to an internal medicine specialist for fever and thrombocytopenia.

On the second day of treatment, the patient still complained of headache. Contact was adequate and cooperative. There was no fever, seizures, or other complaints. Additional supporting examination found CRP 31 mg/L, IgG anti dengue +, IgM anti dengue +, coagulation factor PT, APTT, INR within normal limits. Routine DL examination per 24 hours was performed to monitor the patient's condition. Whole abdominal ultrasound examination was performed to look for other

sources of bleeding and the results were within normal limits. The patient had an up and down fever on the third to fifth day of hospitalization with a fever range of 37.6-38.0 degrees Celsius. The headache was no longer felt by the patient on day six. Routine DL examination on day three till day nine showed platelets of 57,000/uL, 40,000/uL, 54,000/uL, 91,000/uL, 108,000/uL, 126,000/uL, and 226,000/uL. After normal platelet levels, serial DL examinations were no longer performed but were still observed for signs of bleeding. The patient's condition was stable until the seventeenth day of treatment with GCS E3V4M6, there were no seizures, fever or weakness with normal vital signs. Routine DL had no abnormalities. The patient was discharged home and has been given education for post-stroke home care.

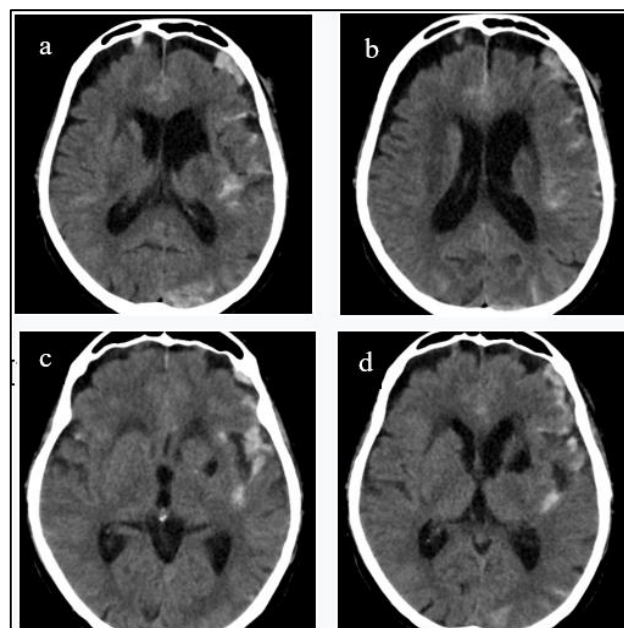


Figure 1 (A-D): Non-contrast computer tomography (CT) brain showing abnormal hyperdense lesions with focal intraparenchymal oedema in the frontal, parietal, occipital regions. The cortical sulci and gyri appear dilated. The ventricular system and cisterns appear dilated with hydrocephalus and cerebral atrophy.

DISCUSSION

Dengue virus infection is an arboviral disease transmitted by the *Aedes* mosquito vector and can present with a spectrum of clinical manifestations varying from asymptomatic to symptomatic. The infection may be asymptomatic or may lead to a febrile illness that is difficult to differentiate (viral syndrome), DF without or with bleeding to involvement of other organs i.e., Expanded dengue syndrome (EDS).⁵ In recent years with the geographical spread of dengue virus and more adults being diagnosed, there has been an increase in reports of dengue virus infection with EDS. These findings include major organ involvement, such as the liver, kidneys, heart, lungs and nervous system. EDS is closely associated with

the patient's previous comorbid factors, dengue shock, or other co-infections. EDS can also occur without evidence of plasma leakage.⁷

The initial suspicion of DF refers to the findings of leucopenia and thrombocytopenia from a complete blood examination. The most common tests used are anti dengue IgM, anti dengue IgG, and NS-1 antigen. Each of these tests has disadvantages and cannot be used in every case. In primary infection, IgM antibodies are detected in 50% of patients on days 3-5, increasing to 80% on day 5, 99% on day 10, and peak around 2 weeks of illness before decreasing to undetectable levels over the following 2-3 months. IgG antibodies are generally detected at low titres at the end of the first week of illness and increase slowly thereafter.⁵ In secondary infections, IgG is the predominant antibody and is detected at very high levels even in the acute phase. In the early recovery phase, IgM levels are significantly lower in secondary infection than primary infection and may even be undetectable. In secondary dengue infection, only IgM is detected in 78% of patients after day 7. If anti-dengue IgM antibody is the only test performed, it is reported that 28% of secondary dengue infections will be missed. This is a drawback limiting the usefulness of IgM detection to diagnose dengue infection in the acute phase of the disease when most patients present with complications such as intracranial haemorrhage. In this case, the patient had a previous history of DHF, and the IgG and IgM anti-dengue tests were positive, confirming that there was a secondary DHF infection in this patient.

In addition, NS1 antigen detection screening was significantly better in the acute phase of the disease. Unfortunately, the antigen is best examined on days 1-3 of the disease to make an accurate diagnosis and its usefulness decreases on days 4-5. However, there are other studies that suggest that NS1 antigen may still be detectable until day 14.^{5,8}

Intracranial haemorrhage due to DHF is rarely reported. Intracerebral haemorrhage, subarachnoid haemorrhage and subdural haemorrhage have been reported. In a case series report, of nine patients with intracranial haemorrhage, fever, vomiting and altered level of consciousness were common presenting complaints. The prognosis for some of them was poor; five patients died, three were discharged, one remained with GCS 3. Intracranial haemorrhage is associated with thrombocytopenia $>20,000/\text{mm}^3$, so brain imaging should still be considered in DHF patients with decreased consciousness even without severe thrombocytopenia.⁹ Thrombocytopenia is thought to be the result of bone marrow suppression caused by direct infection of progenitor cells or by macrophages that will activate T-cells and release pro-inflammatory cytokines that suppress the haematopoiesis system. In addition, the destruction of platelets mediated by the immune system through dengue virus binding to platelets in the presence of NS1 antibodies causes the platelet half-life to decrease in DHF patients.¹⁰

The neuropathogenesis of EDS due to the involvement of viral and host factors may play an important role in dengue-related neurological syndromes. Three mechanisms are involved: direct CNS invasion by the virus, autoimmune reactions, and metabolic changes.³

In this case, the patient was diagnosed with haemorrhagic stroke, namely intracerebral haemorrhage and subarachnoid haemorrhage. Haemorrhagic stroke associated with dengue infection can be in the form of basal ganglia haemorrhage, lobar haemorrhage (either single or multiple), cerebellar haemorrhage (may occur bilaterally), pons haemorrhage, acute subdural haematoma (unilateral or bilateral), pituitary apoplexy, and subarachnoid haemorrhage (generally non-aneurysmal associated with transient thrombocytopenia).³ The pathogenesis of haemorrhagic stroke in both intracerebral haemorrhage and subarachnoid haemorrhage in dengue is multifactorial. The pathogenesis involves complex interactions between coagulopathy, thrombocytopenia, plasma leakage, vasculopathy and platelet dysfunction. In addition, host factors, dengue virus and cytokines are also thought to play a role. Dengue virus involvement in the brain along with the presence of pro-inflammatory cytokines such as TNF-alpha enhances the immunopathological mechanism of plasma leakage and bleeding in DHF. In addition, NS-1 antigen released from dengue virus-infected cells can have immunomodulatory effects on the complement system. Activation of the complement system can increase the production of other pro-inflammatory cytokines that ultimately lead to bleeding and shock.¹¹

To date, there are no studies that show a definite correlation between platelet count and the incidence of haemorrhagic stroke. There are studies that suggest that platelet counts below 50,000/ul and haematocrit greater than 50% are associated with bleeding manifestations. The opposite study showed that there was no correlation between platelet count and bleeding manifestations.⁵ Jayasinghe et al reported a case of intracerebral haemorrhage where the platelet count was not too low. Haemorrhage with a normal clotting profile may occur due to defects in platelet function that are known to occur in dengue infection.^{8,12} Factors such as old age, high haematocrit, low platelet count, prolonged APTT, female gender, high absolute lymphocyte count, and elevated aspartate aminotransferase/SGOT are associated with severe bleeding in dengue patients.¹¹ In this case, an 86-year-old patient with a decrease in platelet levels to $<50,000$ is a high risk factor for bleeding due to thrombocytopenia in DF.

C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to infection or inflammation. High levels of CRP are found to be associated with bacterial and viral infections and are mainly used as a biomarker for bacterial infections. CRP concentrations typically increase from 10 to 40 mg/L in viral infections with levels around 30 mg/L being

associated as the highest risk of dengue virus infection and more than 40 mg/L in acute bacterial infections. In this case, the CRP value was 31 mg/L, indicating the presence of acute phase dengue virus infection in the patient.^{13,14} Coagulopathy is also found in most cases of DHF. activated partial thromboplastin time (APTT) is more often abnormal than prothrombin time (PT). However, in the study conducted by Bashir et al it was proven that PT values were abnormal in only a few cases (30/334) while prolongation of APTT values occurred in only 42/334 cases. Lin et al and Chuang et al. said the opposite, prolongation of PT and APTT indicates impaired coagulation in patients with DHF. Mairuhu et al and Orsi et al concluded that the relationship between DF and activation of the coagulation pathway is still controversial.¹⁵ In this case, there was no prolongation of PT or APTT values.

Spontaneous atraumatic multiple intracerebral haemorrhage is an extremely rare case. The pathological mechanism and predisposing factors are still unknown. Hypertension, cerebral amyloid angiopathy and vasculitis may be responsible for the haemorrhage. High blood pressure has been reported as a major risk factor for multifocal haemorrhage in several studies. Chronic hypertension may lead to structural and functional haemodynamic changes in the cerebral arteries and the occurrence of vascular degeneration responsible for the formation of microaneurysms, which may lead to the occurrence of multiple simultaneous haemorrhages. Cerebral amyloid angiopathy in elderly patients accounts for 5%-20% of multifocal intracerebral haemorrhages. It is a risk factor for focal spontaneous intracerebral haemorrhage associated with lobar haematoma. Another risk factor contributing to the occurrence of multiple intracerebral haemorrhage is vasculitis of the central nervous system.¹⁶ In this case, spontaneous multiple haemorrhage can occur due to several etiologies, namely chronic hypertension suffered by the patient for 30 years, the onset of coagulopathy, vasculitis in the CNS due to dengue virus infection.

The clinical manifestations of multiple intracerebral haemorrhages generally depend on the side and location of the haemorrhage. Patients may present with various symptoms, such as confusion syndrome, motor deficits, neuropsychological deficits, language impairment, and seizures. Cerebrovascular disease is the most common cause of seizures in old age, which is also the case here. Seizures in PIS may arise due to the mechanical effects of widespread haemorrhage and/or irritation of the cortex due to blood metabolic products acutely and from haemosiderin deposition and gliotic scarring chronically. In SAH, similar to ICH, the mechanical effects of expanded haemorrhage volume and irritation from blood products result in a decreased seizure threshold.¹⁷

Acute hydrocephalus is common in SAH patients, with 20% occurring in the first 24 hours. It is caused by obstruction of cerebrospinal fluid flow from the

ventricular system. Clinical manifestations vary from gradual loss of consciousness to sudden coma with symptoms of brain herniation. Headache is caused by rupture of blood vessels leading to extravasation of blood into the subarachnoid space with high pressure resulting in increased intracranial pressure, direct damage to local tissues and the toxic effects of oxy-hemoglobin can cause meningeal irritation, vasospasm, and changes in consciousness. PSA outcomes can be improved with early aggressive, appropriate and professional management.¹⁸ Good consciousness in intracranial haemorrhage is influenced by several factors such as old age and brain atrophy. There was a higher GCS improvement in the atrophy group compared to the group without brain atrophy ($p < 0.001$). The proportion of patients with GCS > 13 was more in the group with brain atrophy.¹⁹ This patient was found to have a stable consciousness where the initial GCS until the patient was discharged was E3V5M6.

Management of intracranial haemorrhage in dengue is often difficult. The choice of surgical intervention must be carefully considered especially in patients with thrombocytopenia, platelet dysfunction and plasma leakage which can lead to uncontrolled bleeding and potentially harm the patient. It remains unclear whether conservative management or surgical management is optimal. There is also no evidence that prophylactic platelet transfusion improves patient outcomes.¹

CONCLUSION

Expanded dengue syndrome is a multi-organ complication caused by DHF, where neurological manifestations such as haemorrhagic stroke can occur and are potentially fatal. The doctor's accuracy in detecting and diagnosing neurological complications due to DHF is needed to achieve therapeutic success and good functional outcomes, especially in areas that are still endemic to DHF, including Indonesia.

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