CASE REPORT

Acute necrotizing encephalopathy in a child secondary to dengue fever: A case report

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SUMMARY
Dengue fever (DF) is an important public health problem, and it is now endemic in more than 100 countries worldwide. Dengue associated neurological complication is estimated to be affecting 0.5 to 6.2% of patients. Even though this is rare, neurological manifestation of DF is an increasingly recognized entity in recent years due to significant mortality and morbidity reported/seen. Reported central nervous system manifestations due to dengue include encephalitis, encephalopathy, myelitis, myositis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, stroke and etc. We report here a case of acute necrotizing encephalopathy secondary to DF in a previously healthy 12-year-old girl.

INTRODUCTION
Dengue fever (DF) is an arthropod-borne disease caused by dengue virus. Dengue virus is a single-stranded RNA virus belonging to the family of Flaviviridae, transmitted by Aedes mosquitoes. Worldwide, the incidence of DF has increased dramatically in recent decades. World Health Organisation estimates around 390 million dengue infections per year, of which around 96 million manifest clinically with any disease severity.1 Thus far reported neurological manifestations of dengue include encephalitis, encephalopathy, myelitis, myositis, acute disseminated encephalomyelitis. We report here a case of acute necrotizing encephalopathy in a child secondary to DF.

CASE REPORT
A previously healthy 12-year-old girl presented to Hospital Lahad Datu, Sabah, Malaysia with fever for 4 days with vomiting and epigastric pain. There was no headache or altered sensorium. On arrival at the hospital, she was restless. Her Glasgow Coma Scale (GCS) was E4V4M 6. Her peripheries were cold with capillary refilling time of 3 seconds and reduced pulse volume. Her blood pressure was 85/37mmHg, pulse rate was 173 beats per minute and temperature was 40C. Her dengue NS-1 antigen was positive, dengue IgM and IgG were negative. She was treated as severe dengue in depsectated shock.

Her initial full blood count showed hemoglobin of 12.5g/dl, TWBC of 2.4x10^9/L, platelet of 97x10^9/L and hematocrit of 38%. Her renal function and liver function tests were normal. Her lactate dehydrogenase (LDH) was 1031U/ml. She was treated with fluid resuscitation with close monitoring in intensive care unit (ICU). Upon ICU admission, she became encephalopathic and not obeying command. Five hours later, she developed three episodes of generalized tonic-clonic seizures, each lasted 1-2 minutes. Her GCS deteriorated to E4V1M 5. Neurological examinations showed brisk reflexes with normal plantar responses. She also has bulbar weakness which she required a nasogastric tube. A loading dose of intravenous phenytoin was administered for seizure control. An urgent computed tomography (CT) scan of the brain (day 5 of illness) showed bithalamic hypodensities extending to the posterior limbs of internal capsule (Figure 1). Lumbar puncture was not done due to severe thrombocytopenia.

Subsequently, her neurological deficits did not improve despite in recovery phase where she still has persistent bulbar weakness. A magnetic resonance imaging (MRI) of her brain (day 19 of illness) was performed, which revealed corresponding bithalamic high signal on T2 weighted images with no evidence of restricted diffusion. Post contrasted images showed enhancing lesions with an incomplete ring configuration at the right high frontal lobe (Figure 1). Overall, MRI brain features were highly suggestive of Acute Necrotizing Encephalopathy of Childhood (ANEC). The patient was then treated with intravenous methylprednisolone 750mg daily for 5days, followed by intravenous immunoglobulin for 5 days. She did not have any recurrence of seizure after that and did not require additional anti-epileptics. Her serum dengue polymerase chain reaction was positive for DEN3. She had excellent neurological recovery with resolution of the brain lesions on follow up MRI brain done 3 months later (Figure 2). Her neurological deficits completely resolved on clinic follow up.

DISCUSSION
The exact neuropathogenesis of neurological manifestations of dengue is still poorly understood. Host and virus factors play essential roles. Isolation of dengue virus and specific
antibodies in cerebrospinal fluid have shown that the virus is capable of invasion of the CNS. In general, neurological manifestation of dengue can be classified as (1) direct neurotropic effect of virus (2) systemic or metabolic complication of dengue and (3) post-infection complications. All in all, we believe that neurological complications are likely to occur as a result of complex interactions of the above mechanisms. Associated systemic metabolic abnormalities, abnormalities of vascular permeability, cytokine storms can all contribute to the neurological complications of dengue.

In our patient, the clinical suspicion of dengue encephalitis was raised when she became encephalopathic and developed seizures. CT brain of our patient showed ill-defined hypodensities at bilateral thalami suggesting a fulminant inflammatory process involving the deep grey matter. The bilateral thalamic high signal on MRI, was suggestive of ongoing necrosis. The lack of restricted diffusion ruled out intra-axial abscess formation and the attenuated, hypodense signal on plain CT ruled out bithalamic haemorrhages. Critically, the presence of the enhancing incomplete ring lesions at the high frontal lobe demonstrated that underlying process was demyelination. Correlating with clinical history, these findings are consistent with Acute Necrotizing Encephalopathy of Childhood (ANEC).

ANEC, is a very specific subtype of encephalopathy which has a distinct clinical, radiological and pathological feature. It was first reported by Mizuguchi et al., where it usually affects the young and previously healthy children. The exact etiology of ANEC remains unclear. Infection by influenza virus, herpes simplex virus, mycoplasma, swine flu, respiratory syncytial virus have all been associated. It is believed that the virus can trigger the formation of cytokines, hypercytokinemia and subsequently cytokine storm, which eventually lead to the clinical syndrome of ANEC and multi-organ failure. Clinically, ANEC is characterized by rapid neurological decline, encephalopathy, seizure, coma and neurological deficits.

In general, the optimal treatment for ANEC is unknown. Management of ANEC is mainly supportive with ventilation and antiepileptics. Treatment with antiviral, methylprednisolone, intravenous immunoglobulin (IVIG), plasmapheresis, antithrombin III and therapeutic hypothermia have been reported. Additionally, immunotherapy with methylprednisolone and IVIG have all been tried with variable degree of success. Our patient was treated with methylprednisolone and IVIG. She showed good clinical improvement with brain lesions resolving observed on follow-up imaging study.
CONCLUSION
In conclusion, neurological manifestation of dengue, though rare, are diverse in presentation. ANEC is a rare neurological complication of DF. High clinical suspicion is needed for early diagnosis as ANEC progresses rapidly and any delay in management will potentially lead to profound neurologic morbidity. Methylprednisolone and IVIG are helpful drugs that can be used to treat this condition.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

INFORMED CONSENT
Written informed consent was obtained from the patient’s mother for publication of this manuscript.

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