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 manifests clinically with any disease severity.[1] Thus far reported neurological manifestations of dengue include encephalitis, encephalopathy, Guillain-Barre Syndrome and 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 E4V4M6. 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 decompensated 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 E4V1M5. 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

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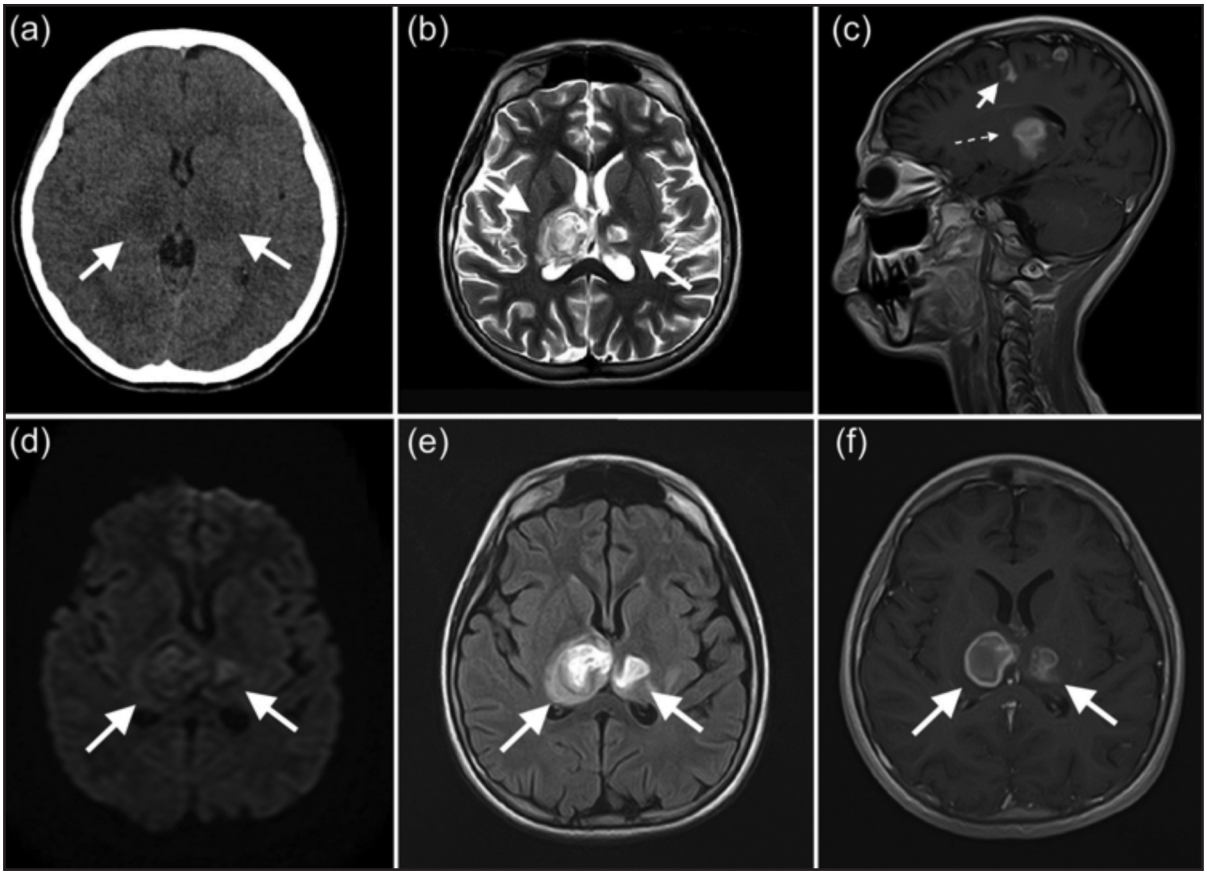

Fig. 1: Selected MR and CT images acquired prior to treatment. (a) Axial unenhanced CT brain shows ill-defined bithalamic hypodensities extending to the posterior limbs of internal capsule. (b) Axial T2 weighted MR brain images shows bithalamic high signal. (c) Post-gadolinium T1 weighted MR images demonstate rim-enhancing lesions at the grey-white matter junction of the right frontal lobe. One of the lesions demonstrates an incomplete ring configuration (white arrow). (d) Diffusion weighted MR image shows absence of restricted diffusion. (e)FLAIR MR brain images shows bithalamic high signal.(f) Post-gadolinium T1 weighted MR images demonstate rim-enhancing lesions at thalamus.

antibodies in cerebrospinal fluid have shown that the virus is capable of invasion of the CNS.[2] 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.[3]

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.[4] The exact etiology of ANEC remains unclear. Infection by influenza virus, herpes simplex virus, mycoplasma, swine flu, respiratory syncytial virus have all been associated.[5,6] 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.[6] 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.[7] Treatment with antiviral, methylprednisolone, intravenous immunoglobin (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.

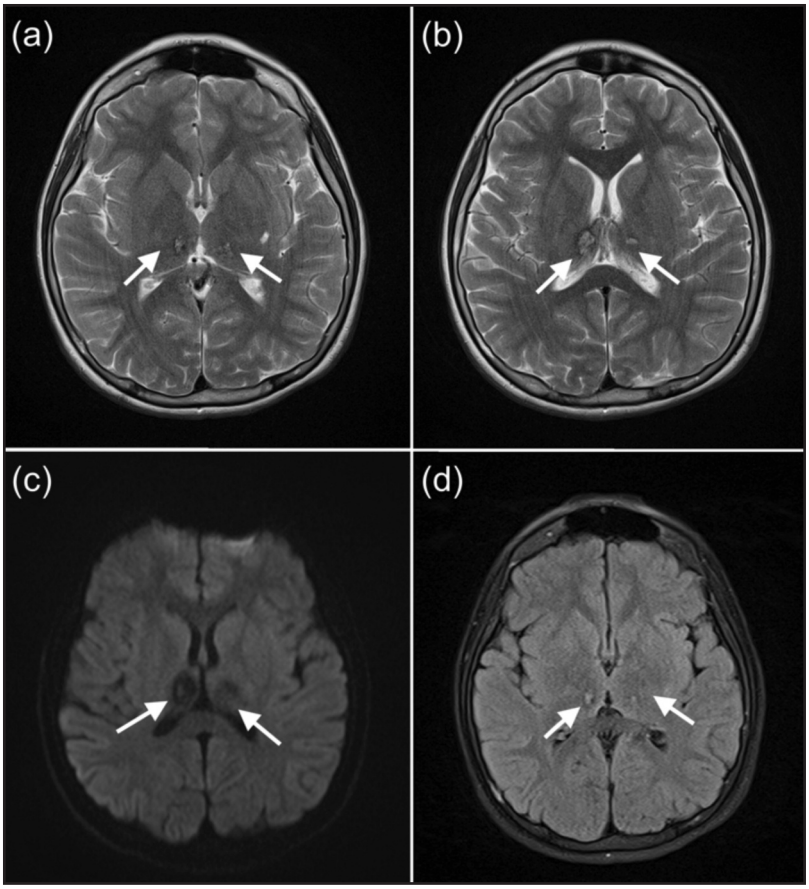

Fig. 2: Brain MRI images of the patient that were acquired at 3 months after treatment. (a&b)

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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REFERENCES

1. World Health Organization. Dengue and severe dengue: Fact sheet, Updated 13 September 2018. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.
2. Sudhir U, Anil Kumar T, Gupta B, Punith K. Dengue Meningoencephalitis. J Indian Acad Clin Med 2010; 11(2): 141-3.
3. Madhavi C, Kejriwal GS, Giridhar GG. Role of Neuro-Imaging in Dengue Encephalitis. Int J Med Health Res 2010; 11(2): 141-3.
4. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997; 19(2): 81-92.
5. Yadav S, Das CJ, Kumar V, Lodha R. Acute Necrotizing Encephalopathy. Indian J Pediatr 2010; 77: 307-9.
6. Fong CY, Saw MT, Li L, Lim WK, Ong LC, Gan CS. Malaysian outcome of acute necrotising encephalopathy of childhood. Brain Dev 2021; 43(4): 538-47.
7. Abbas Q, Jafri SK, Ishaque S, Jamil MT. Acute necrotizing encephalopathy of childhood secondary to dengue infection: A case report from Pakistan. J Pediatr Neurosci 2017; 12: 165-7.