Case Report

Acute Disseminated Encephalomyelitis Associated with Dengue Infection in Children: A Case Report and Review Literature

Vitchayaporn Emarach Saengow MD[1], Oragarn Wongfukiat MD[2]

[1] Department of Pediatrics, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand
[2] Department of Radiology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand

Dengue virus, the second most common mosquito-borne disease, can manifest with wide range of neurological complications. These complications can encompass both central and peripheral nervous system. In the present study we report a 5-year-old boy diagnosed with serotype 1 [DEN-1] of dengue fever. At presentation, he had alteration of consciousness and status epilepticus along with liver failure and Reye's syndrome. While the dengue infection and metabolic disturbance were resolved, his consciousness was not improved. Furthermore, the MRI was performed and illustrated a typical demyelinating disease. The patient was then considered as a case with dengue fever and acute disseminated encephalomyelitis [ADEM]. Following the prescription, he underwent five days of therapy with pulse methylprednisolone. The neurological outcome had unexpected slow improvement. This study is in agreement with previously reported cases regarding the cytopathic effects of dengue virus on CNS. Moreover, we suggest that ADEM should be considered in the differential diagnosis in patients with dengue infection presenting encephalopathy.

Keywords: Dengue infection, Acute disseminated encephalomyelitis, ADEM, Neurological complication of dengue infection

J Med Assoc Thai 2018; 101 (3): 423-6
Website: http://www.jmatonline.com

Dengue, an acute viral disease transmitted by Aedes mosquitoes, is highly endemic in many tropical and subtropical areas of the world. Dengue virus [DENV] is a single positive stranded RNA virus of the family Flaviviridae, genus Flavivirus. DENV has four serotypes, DEN1, DEN-2, DEN-3, and DEN-4. DEN-2 and DEN-3 are the common serotypes causing neurological complications[1-3]. Dengue has been classified as a non-neurotropic virus, however, from previous studies, the neurological complications of dengue infection range from 0.5% to 47%[1]. The clinical presentation of dengue infection has a wide spectrum, varying from a simple febrile illness to a life threatening hemorrhagic fever with neurological complications. Although these neurological difficulties can be varied, the most common is found to be dengue encephalopathy, which occurs due to toxic and metabolic disturbance[1-3]. The present case study was diagnosed as dengue and acute disseminated encephalomyelitis [ADEM] complication. There are few reports in literature on dengue patients developing rare ADEM complication.

Correspondence to:

Saengow VE. Department of Pediatrics, Maharat Nakhon Ratchasima Hospital, Chang Peuk Road, Muang, Nakhon Ratchasima 30000, Thailand.
Phone: +66-44-245162, **Fax**: +66-44-235166
Email: giftemarach@gmail.com

Case Report

A feverish 5-year-8-month old Thai boy presented to our institution with temperature over 39°C, vomiting, and with watery diarrhea that lasted for seven days. Later he developed alteration of consciousness and generalized tonic clonic seizure, which led to status epilepticus. Physical examination showed neither evidences of plasma leakage, hypotension, hepatomegaly, nor pleural effusion. Neurological examination showed comatose, the pupils were 3 mm reacting to light along with corneal reflex. Doll's eye sign, and gag reflex were also observed. Other features detected were decorticating posture with spastic tone and hyperreflexia to all extremities' joints. There was no neck stiffness observed. The blood test was done and the result was immunodiagnosed as dengue fever according to positive serum non-structural protein 1 [NS1]. However, he was negative test for both serum IgG and IgM antibodies to DENV. The serum polymerase chain reaction [PCR] for dengue type 1 was positive. The complete blood count showed thrombocytopenia but no hemoconcentration (Hct 36.4%, WBC 12,100/uL, PMN 79%, Lym 17.5%, Mono 2.8%, and Platelet 131,000). There were

How to cite this article: Saengow VE, Wongfukiat O. Acute disseminated encephalomyelitis associated with dengue infection in children: a case report and review literature. J Med Assoc Thai 2018;101:423-6.

highly elevated level of aspartate transaminase [AST] and alanine transaminase [ALT] without evidence of cholestasis jaundice, (D-Bili 0.4 mg/dL, T-Bili 0.8 mg/dL, AST 2,390 U/L, ALT 9,921 U/L, ALP 191 U/L, TP 6.2 g/dL, Alb 3.7 g/dL, Globu 2.5 g/dL). Abnormal coagulogram (PT 29.4 seconds, INR 2.34, PTT 30.3 seconds, TT 23.8 seconds), normal blood sugar (110 mg/dL), and slightly elevated level of ammonia (83.0 umol/L) were observed.

Firstly, the cause of encephalopathy and status epilepticus in the present patient was described as Reye's syndrome and hepatic failure, which occurred as the complication of dengue infection. Although within a week of treatment and supportive care, the fever subsided and the metabolic laboratory tests returned to normal levels, his consciousness and seizure remained. While the patient was considered in comatose stage, the continuous VEEG monitoring showed generalized medium to high amplitude delta and theta activities. No electrographic seizure was observed. Lumbar puncture was performed, OP 20 cmH_2O, CP 18 cmH_2O, WBC 0 cell/HPF, protein 98 mg/dL, sugar 104 mg/dL, blood sugar 120 mg/dL, G/S with no organism seen, C/S with no growth, and cerebrospinal fluid [CSF] PCR for dengue was negative. Moreover, the magnetic resonance imaging [MRI] of the brain showed patchy confluent hyperintensities on T2-weighted and T2/FLAIR images in the bilateral periventricular frontal, parietal, and temporal lobes, and deep and subcortical white matter of bilateral frontal and parietal lobes. Rather symmetrical involvement of the thalami, midbrain, pons and cerebellar hemispheres were also observed (Figure 1). The diffusion weighted imaging analysis [DWI] illustrated limited discussion of lesions. Susceptibility weighted image [SWI] showed small area of hemorrhage involving both thalami (Figure 2).

Based on the clinical characteristic of encephalopathy and MRI, he was later diagnosed as ADEM. He received five days of pulse methylprednisolone. His seizure and consciousness were improved one week after treatment and he was subsequently discharged two months post admission due to contracted nosocomial complications as he developed pneumonia and urinary tract infection. The neurological examination prior to discharge showed drowsiness and spastic quadriparesis. After 6 month-follow-up, his consciousness was normal but the quadriparesis and spastic tone persisted.

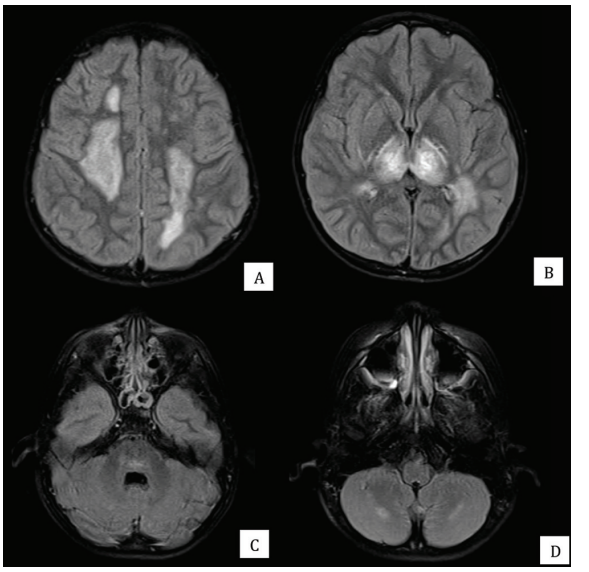

Figure 1. Axial T2/FLAIR images showing patchy confluent hyperintensities with involvement of the bilateral frontal and parietal lobes (A). Relatively symmetrical involvement of the thalami, midbrain, pons and cerebellar hemispheres were observed (B-D).

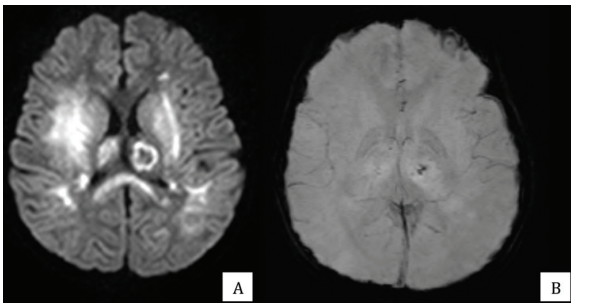

Figure 2. Axial DWI showed restricted diffusion of the thalami and white matter lesions (A), with presence of the hemorrhage in thalami on SWI (B).

Discussion

Previously, DENV was believed to have no neurotropic effect. Later studies have identified the neurological complications of DENV infection and categorized them in three following groups, 1) dengue encephalopathy that leads to the leakage of plasma, hemorrhage, shock, and metabolic derangement (the most common neurological complication), 2) dengue encephalitis that is associated to direct neurotropic effect of DENV, and 3) post-infection disorders, ADEM[1-4].

ADEM is an immune-mediated inflammatory demyelinating condition that mainly affects the white matter of the brain and spinal cord. ADEM in children is simply distinguishable with alternative diagnosis such as clinical features of encephalopathy and multifocal MRI brain lesion. As ADEM is para-

infection or post-infection demyelinating disorder of the central nervous system. It usually happens three to six weeks after the main infection occurred. The common viral infections that can cause ADEM are measles, chickenpox, rubella, mumps, influenza, Epstein-Barr virus, and in rare cases, DENV[4].

In the present study, we report a case of a pediatric patient diagnosed as dengue fever with ADEM. The dengue infection was detected by positive serum NS1 and plasma PCR for dengue type 1. The neurological manifestation in this patient was encephalopathy and convulsive status epilepticus. The laboratory results showed metabolic disturbance and liver failure occurred. At first, the possibility of Reye's syndrome was considered but later, with the treatment and correction of metabolic derangement, the clinical features of encephalopathy did not improve. After further investigations, lumbar puncture and MRI were carried out. The CSF analysis showed mild elevation of CSF protein, no CSF pleocytosis was detected, the CSF PCR for DENV was negative, and the brain MRI was typical of ADEM. In previous studies, all of the cases were 26 to 58 years of age, while our patient was a 5-year-old boy[5-8]; therefore, our study is considered as the first report of a pediatric patient with dengue infection and ADEM. In previous reports, most patients presented with encephalopathy developed conditions like our patient, except in two cases from Japan[7] and Brazil[9], which presented with paraparesis and hemiparesis. The current study along with the previous study in India (Gera et al)[10] indicated that seizure was the main neurological symptom in patients with dengue and ADEM complication. Most previous studies had negative laboratory result for dengue infection or did not discriminate the serotype[6]. There was only one study from Brazil that identified type 3 of dengue virus (DEN-3), widely known as a cause of neurological manifestation, from their cases[9]; however, in our case, type 1 dengue infection was detected, which was unlikely to lead to severe neurological manifestation that our patient had displayed.

Our finding agrees with other studies of ADEM complicated dengue infected cases that showed the onset of neurological symptoms earlier than the other viruses causing ADEM, which the onset range 5 to 7 days after the fever onset[5-8]. It is noteworthy that the brain MRI findings indicated diagnosis of ADEM and the observations were similar to almost all other case reports such as in cases that involved bilateral thalami or bilateral subcortical white matter. There was only one case from Japan (Yamamoto et al)[7] that showed normal MRI of the brain but abnormal MRI of spine, which was correlated to the clinical features of paraparesis without encephalopathy.

The neurological outcome after treatment in previous studies showed varied results from complete recovery, to partial recovery, to death. The neurological outcome in the case from Brazil was not evaluated. Based on literature review, the only case that resulted in mortality was reported from India by Sundaram et al[11]. The cause of death in the mentioned case was multiorgan failure. Compared with other patients who had partial recovery, our case had the worst neurological outcome, which could be explained by the younger age group and the history of Reye's syndrome.

The summery of clinical and radiologic findings from previous case reports are shown in Table 1.

ADEM, caused by dengue infection, is known to be a scarce complication. It should be carefully considered along with special attention to dengue patients admitted with clinical encephalopathy or neurological deficit that cannot be explained by other metabolic causes. The present study indicated that clinical course of dengue infection with ADEM in children requires further study.

Conclusion

The present report suggests that ADEM should be considered as the differential diagnosis of neurological complication on dengue infection. DENV type 1 can cause severe neurological complication and this should be considered in patient with dengue infection with clinical encephalopathy.

What is already known on this topic?

DENV has neurological complication. The most common neurological complication is metabolic disturbance that cause encephalopathy. While, there are previous reports of rare complication of DENV such as ADEM, there are few reports in children.

What this study adds?

This case report identified the association between DENV and the rare neurological complication of ADEM. We reported pediatric case and reviewed the literature to determine the difference between each case reports. This case report mentioned that ADEM should be in the differential diagnosis in pediatric patients who have Dengue infection with clinical of encephalopathy.

Acknowledgement

The author would like to cordially thank Mr.

Table 1. Clinical manifestation and radiologic findings from case reports of acute disseminated encephalomyelitis with dengue infection

Study Country Year	Age (year) Sex	Days of onset	Neurological manifestation	Dengue PCR	MRI findings	Outcome
Yamamoto et al.[7] Japan 2002	58 Male	7 days	Paraparesis Visual impairement Bladder disturbance	Negative	Lesion from T7 to T11, normal MRI brain	Partial recovery
Brito et al.[9] Brazil 2007	37 Female	5 days	Left hemiparesis Speech disturbance	DEN-3 Serum	Callosal-septum interface, right centrum semiovale, corona radiate, bilateral thalami	N/A
Gera et al.[10] India 2010	27 Male	5 days	GTC seizure Encephalopathy	N/A	Periventricular, white matter of bilateral fronto-parietal, bilateral thalami, midbrain, pons, cerebellar	Complete recovery at 8 months
Sundaram et al.[11] India 2010	27 Male	5 days	Encephalopathy Stiffness of neck	N/A	Bilateral hippocampi, thalami, cerebellar, pons	Dies Multiorgan failure
Gupta et al.[6] India 2013	26 Female	6 days	Alteration of consciousness	N/A	Bilateral periventricular white matter of frontal and parietal lobe, corpus callosum, temporal neocortex, cerebellar	Complete recovery
The present study	5 Male	7 days	Alteration of consciousness Statsu epilepiticus	DEN-1 Serum Negative CSF	Bilateral thalami and bilateral subcortical white matter	Partial recovery

PCR = polymerase chain reaction; GTC = generalized tonic-clonic; CSF = cerebrospinal fluid; N/A = not applicable for Dengue PCR but have evidence positive of non-structural protein 1 [NS1] antigen and/or dengue immunoglobulin M (by MAC-ELISA test)

Jiraruj Chomcheoy, MD for his cooperation during the patient hospitalization. Special thanks also go to the Pediatric pulmonologist, group of pediatric Maharat Nakhon Ratchasima Hospital.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol 2013;12:906-19.
2. Verma R, Sahu R, Holla V. Neurological manifestations of dengue infection: a review. J Neurol Sci 2014;346:26-34.
3. Singh P, Aneja S. Neurological manifestations of dengue. Pediatr Infect Dis 2012;4:160-4.
4. Eyre M, Absoud M, Wassmer E. Childhood CNS inflammatory demyelinating diseases. Paediatr Child Health 2014;24:439-46.
5. Kankirawatana P, Chokephaibulkit K, Puthavathana P, Yoksan S, Apintanapong S, Pongthapisit V. Dengue infection presenting with central nervous system manifestation. J Child Neurol 2000;15:544-7.
6. Gupta M, Nayak R, Khwaja GA, Chowdhury D. Acute disseminated encephalomyelitis associated with dengue infection: a case report with literature review. J Neurol Sci 2013;335:216-8.
7. Yamamoto Y, Takasaki T, Yamada K, Kimura M, Washizaki K, Yoshikawa K, et al. Acute disseminated encephalomyelitis following dengue fever. J Infect Chemother 2002;8:175-7.
8. Misra UK, Kalita J, Syam UK, Dhole TN. Neurological manifestations of dengue virus infection. J Neurol Sci 2006;244:117-22.
9. Brito CA, Sobreira S, Cordeiro MT, Lucena-Silva N. Acute disseminated encephalomyelitis in classic dengue. Rev Soc Bras Med Trop 2007;40:236-8.
10. Gera C, George U. Acute disseminating encephalomyelitis with hemorrhage following dengue. Neurol India 2010;58:595-6.
11. Sundaram C, Shantveer G, Uppin SG, Dakshinamurthy KV, Borgahain R. Acute disseminated encephalomyelitis following dengue hemorrhagic fever. Neurol India 2010;58:599-601.