Pediatric Dengue Encephalopathy: A Review

Ilham Setiorizaldi¹, Amandianti Arimbi Tedjaningrum¹, Cindy Grace Panggabean¹, Enjelina Nangin¹, Jeffrey Christian Mahardhika², Chandni P. Daryanani²*

Abstract
Dengue encephalopathy is a very common neurological complication of dengue fever. Dengue encephalopathy or dengue hemorrhagic fever (DHF) with Central Nervous System (CNS) involvement used to be considered a relatively rare condition. However, the number of cases reported in human studies was increasing every year. Many factors caused the encephalopathy dengue. Possible mechanisms are hepatic failure (hepatic encephalopathy), cerebral hypoperfusion (shock), cerebral edema (vascular leakage) electrolyte disturbances, and intracranial hemorrhage due to thrombocytopenia or coagulopathy, which are secondary mechanisms of hepatic failure. Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of brain can be done to make certain of the diagnosis. The results can suggest the presence of extensive involvement of the bilateral cerebellar region, brain stem, and thalamus along with peculiar rim enhancement. Treatment in Intensive Care Unit (ICU) with a multidisciplinary team is required due to the patients' decreased level of consciousness, underlying problems of airway, breathing, and circulation, comorbidities, and considerations of specific etiology.

Keywords: Dengue fever, encephalopathy, pediatric

Background
Dengue encephalopathy is a very common neurological complication of dengue fever. Dengue encephalopathy or dengue hemorrhagic fever (DHF) with central nervous system (CNS) involvement used to be considered a relatively rare condition. However, the number of cases reported in human studies has been increasing every year.¹ Rampengan, et al. stated that from 2006-2010, 2.8% of dengue patient developed encephalopathy.² While Karyanti showed that encephalopathy developed in 3.1% of cases in Jakarta from 2007-2009.³ Diagnosis of dengue encephalopathy is based on clinically diagnosed DHF according to the World Health Organization (WHO) criteria, with CNS manifestations including abrupt onset of hyperpyrexia, non-transient alteration of consciousness, headache, vomiting with or without seizures and normal cerebrospinal fluid (CSF).¹ Dengue encephalopathy is usually secondary complications that happen because of multisystem derangement like shock, hepatitis, coagulopathy, and concurrent bacterial infection. While have the same CNS symptoms, dengue encephalitis is a different entity, which occurs due to direct neuronal infiltration by the dengue virus.⁴

Classification and Clinical Manifestations
The new classification of the World Health Organization classifies dengue infections into three categories, which is: (1) Dengue Fever Without Warning Signs, (2) Dengue Fever with warning signs, (3) Severe dengue. CNS involvement is one of several criteria of severe dengue fever.⁵ Neurological complications of dengue virus infection are classified into three categories based on pathogenesis, namely: (1) Metabolic disorders, eg encephalopathy; (2) Viral invasion, including encephalitis, meningitis, myositis, and myelitis; (3) Autoimmune reactions, including acute disseminated encephalomyelitis, optic neuromyelitis, optic neuritis, myelitis, encephalopathy, and Guillain-Barré syndrome.⁶,⁷

Dengue encephalitis main symptoms and signs were considered acute signs of cerebral involvement. From CSF parameters, we could find normal cell count or pleocytosis, and normal or high level of protein. CT/MRI brain would prevail normal or signal changes in involved regions. The main differences between encephalitis and encephalopathy are in CT/MRI results.
In encephalopathy, there were suggestive of extensive involvement of the bilateral cerebellar region, brainstem, and thalamus along with peculiar rim enhancement, better be found in MRI. While CSF parameters and symptoms might be the same as encephalitis. Encephalopathy caused by dengue fever can manifest as reduced sensitivity, cognitive impairment, convulsions, and personality and behavior disorders, such as acute mania, depression, emotional lability, anxiety, psychosis, and agoraphobia. Brain edema, anoxia, hemorrhage, intense hyponatremia, liver or kidney failure, release of toxic substances, metabolic acidosis, and direct organ invasion are commonly reported precursors of encephalopathy in patients with severe dengue.

Acute disseminated encephalomyelitis is acute inflammatory demyelinating disorder of the central nervous system. It has monophasic course and multifocal white matter involvement that occur during or after dengue virus infection. CSF parameters could be normal or indicating inflammation. CT/MRI could present an extensive involvement of the white matter of the frontal, parietal, or temporal lobes and lesions of basal ganglia, brainstem, cerebellum, corpus callosum, and periventricular regions.

**Treatment**

Most cases of encephalopathy are found in DHF during or after the critical phase, but may occur in the febrile phase. Few cases are found among DF patients. Currently there is no specific treatment of dengue encephalopathy due to its unclear and complex pathogenesis. Treatment is based on emergency conditions presented in patients. Treatment in Intensive Care Unit (ICU) with a multidisciplinary team is required given the decreased level of consciousness, complication of airway, breathing, circulation (ABC) problems, the presence of comorbidities, and considerations of specific etiology.

First and foremost, clinicians must maintain adequate airway and oxygenation with oxygen therapy. Intubation may be needed in patients with respiratory failure or semi-coma/coma. Secondly, intracranial pressure (ICP) increase should be prevented by following measures: (1) Give minimal IV fluid to maintain adequate intravascular volume, ideally the total IV fluid should not exceed 80% maintenance; (2) Switch to colloidal solution earlier if hematocrit continues to rise or a large volume of IV is needed in cases with severe plasma leakage; (3) Administer diuretic if indicated in cases with signs and symptoms of fluid overload; and (4) Consider the use of steroids to reduce ICP. Dexamethasone 0.5 mg/kg/day intravenously every 6-8 hours is recommended.

Due to involvement of hepatic failure in dengue encephalopathy, clinicians should decrease ammonia production with the use of lactulose 5-10 ml every 6 hours for induction of osmotic diarrhea. Local or systemic antibiotics should be administered to eliminate bowel flora. Avoid unnecessary drugs because most drugs have to be metabolized by the liver.

Laboratory parameters should be kept in normal ranges. Blood sugar should be maintained. If hypoglycemia occurs, glucose infusion should be given at infusion rate between 4-6 mg/kg/hour. The presence of acid-base and electrolyte imbalance such as hypo/hypernatremia, hypo/hyperkalemia, hypocalcemia and acidosis could be found as one of the causes of encephalopathy. Thus, must be corrected promptly.

Since intracranial hemorrhage could be the cause of encephalopathy in severe dengue, as reported by de Souza, et al., intravenous Vitamin K1 could be given as prophylaxis. The dosage is 3 mg for <1 years old, 5 mg for <5 years old and 10 mg for >5 years old and adults. Platelets and fresh frozen plasma are quite routinely used as prophylaxis. However, numerous studies showed that there was no significant decrease of bleeding incidence between dengue patients who were given platelets or fresh frozen plasma and those who were not. Moreover, transfusion of blood products increases the risk of fluid overload and increased ICP in dengue patients. Therefore, transfuse blood only in hemorrhagic conditions and with caution, preferably packed red cells.

Other treatments such as anticonvulsants for control of seizures, H2-blockers or proton pump inhibitors may be given as indicated. Clinicians should consider plasmapheresis or hemodialysis or renal replacement therapy in cases of clinical deterioration. The use of renal replacement such as continuous veno-venous hemodialysis is important in managing fluid states in the recovery phase of dengue hemorrhagic fever in those with renal impairment.

**Prognosis**

Prognosis of dengue encephalopathy is similar to prognosis of severe dengue. Several prognostic factors were reported to be correlated with the outcome of severe dengue, such as platelet count less than 100,000 cells/mm³, serum albumin <35 g/L, Aspartate Aminotransferase (AST) > 400 U/L, Alanine aminotransferase (ALT) > 400 U/L, and total bilirubin >17 µmol/L.
In Indonesian children, prognostic factors of severe dengue were reported as such: overweight/obesity, vomiting, hepatomegaly, and prolonged activated partial thromboplastin time (APTT).\textsuperscript{13} Study in India showed that mortality was observed in 10\% cases of neurological complications due to dengue fever in pediatric patients.\textsuperscript{14}

**Conclusions**

Dengue encephalopathy common neurological complication of dengue fever. Possible mechanisms are hepatic failure (hepatic encephalopathy), cerebral hypoperfusion (shock), cerebral edema (vascular leakage) electrolyte disturbances, and intracranial hemorrhage due to thrombocytopenia or coagulopathy, which are secondary mechanisms of hepatic failure. Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of brain can be done to make certain of the diagnosis. The results can suggest the presence of extensive involvement of the bilateral cerebellar region, brain stem, and thalamus along with peculiar rim enhancement. Treatment in Intensive Care Unit (ICU) with a multidisciplinary team is required due to the patients’ decreased level of consciousness, underlying problems of airway, breathing, and circulation, comorbidities, and considerations of specific etiology. A number of prognostic factors should be considered in managing patients of dengue encephalopathy and severe dengue in general such as low platelet counts, hypo-bilirubinemia, high AST and ALT levels, overweight/obesity, vomiting, hepatomegaly, and prolonged APTT.

**List of abbreviations**

- DHF: Dengue Hemorrhagic Fever
- CNS: Central Nervous System
- CT: Computed Tomography
- MRI: Magnetic Resonance Imaging
- ICU: Intensive Care Unit
- WHO: World Health Organization
- CSF: Cerebrospinal Fluid
- ABC: Airway Breathing Circulation
- ICP: Intracranial Pressure
- IV: Intraavenous
- AST: Aspartate Aminotransferase
- ALT: Alanine Aminotransferase
- APTT: Activated Partial Thromboplastin Time

**Declarations**

**Ethics approval and consent to participate**

All procedures performed in this study involving human participants were in accordance with the ethical standards of Unggul Karsa Medika Hospital ethical board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Consent for publication**

Not applicable

**Availability of data and materials**

Not Applicable

**Competing interests**

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