

ORIGINAL ARTICLE

THE CLINICAL PROFILE AND OUTCOME OF CHILDREN WITH DENGUE ENCEPHALITIS AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER: A RETROSPECTIVE STUDY FROM JANUARY 2011-JUNE 2017

ABSTRACT

BACKGROUND: Dengue, a mosquito-borne flavivirus, is hyperendemic in the Philippines. One of its rare complication is dengue encephalitis, characterized by altered sensorium, elevated liver enzymes, and high dengue-specific antibody titers. Previously known as non-neurotropic, dengue presents with an increasing incidence of neurologic manifestations.

OBJECTIVE: To describe the clinico-demographic profile and outcome of laboratory-confirmed dengue encephalitis patients.

METHODS: This is a retrospective study that used purposive sampling to describe laboratory-confirmed dengue encephalitis cases aged 0-18 years. The clinico-demographic profiles and outcomes were collected using chart review, and variables were analyzed using descriptive statistics.

RESULTS: 14 laboratory-confirmed cases were reviewed. Most (57%) were males aged 3 days-15 years. Fever lasted 3-11 days. Following nonspecific signs and symptoms, neurological manifestations developed within 1-5 days, the most common being seizures (71%). Majority (57%) had anemia. All, except one, exhibited leukopenia and thrombocytopenia. Elevated liver enzymes, bleeding parameter derangements, electrolyte, and glucose imbalances were noted. All were seropositive for dengue IgM, and 5 dengue IgM in the CSF. Most common EEG findings showed generalized slowing. Neuroimaging reports were normal in some or showed cerebral edema in the others. Half of the patients recovered fully, 3 showing partial recovery from neurologic changes, and 3 others had neurologic sequelae. One infant expired.

CONCLUSIONS AND RECOMMENDATIONS: Dengue encephalitis should be considered in patients living in an endemic country, presenting with fever with neurologic changes or elevated liver enzymes, with a risk for developing neurologic sequelae or death.

KEYWORDS: *Dengue Encephalitis, Neurotropic virus, Severe Dengue*

Kristine Alvarado-Dela Cruz, MD¹

Madelyn P. Pascual, MD²

Maria Eva Luna-Dizon, MD¹

¹Section of Infectious Diseases, Philippine Children's Medical Center

²Section of Child Neurology, Philippine Children's Medical Center

Correspondence:

Dr. Kristine Alvarado-Dela Cruz

Email: kgalvaradomd@gmail.com

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INTRODUCTION

Dengue is a major health problem in most tropical and subtropical areas¹ and is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50-million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries.² The number of dengue cases reported annually to WHO has increased from 0.4 to 1.3 million in the decade 1996–2005, reaching 2.2 million in 2010 and 3.2 million in 2015.^{6,7} In 2013 dengue was estimated to be responsible for approximately 3.2 million severe cases and 9000 deaths.³ Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.³ Dengue encephalitis is an extremely rare manifestation of severe dengue disease.¹²

In the Philippines, in which dengue is hyperendemic; the incidence of dengue cases shows an increasing trend in recent years. In January 1 to December 31, 2018, the suspected dengue cases reported nationwide is 42% higher compared to the same time period in 2017, with case fatality rates increasing from 30% in 2015 to 55% in 2018.³⁷ The clinical spectrum of dengue fever ranges from asymptomatic infection to severe dengue and dengue shock syndrome. In 2009, WHO adjustments in the classification of the disease resulted in the recognition of two main presentations of dengue. These are referred to as dengue fever and severe dengue. Neurological dengue is classified as a form of severe dengue.^{38,39}

Although dengue virus is classically considered non-neurotropic, in recent years, neurological manifestations of dengue have been documented.¹² Murthy has classified the spectrum of neurological manifestations seen in dengue into 3 categories: 1) those related to neurotropic effect of the virus, like: encephalitis, meningitis, myositis and myelitis; 2) those due to the systemic

complications of infection, like: encephalopathy, stroke and hypokalemic paralysis, and 3) finally, post-infectious complications, like: encephalomyelitis, optic neuritis and Guillain Barré syndrome.¹¹ A prospective case-controlled study conducted by Cam et al. on 5,400 cases of dengue hemorrhagic fever (DHF) in Vietnam, has shown dengue infection causing encephalitis results to significant morbidity in terms of neurologic sequelae. Dengue-associated encephalopathy accounted for 0.5% of all cases. The mortality rate among children with dengue-associated encephalopathy was 22%.¹⁴ Dengue encephalitis patients usually present with altered sensorium, elevated liver enzymes and high antibody titers at the time of admission.¹⁰ Acute encephalitis, defined by the presence of an inflammatory process of the brain in association with clinical evidence of neurologic dysfunction, is a serious and potentially debilitating condition, which may lead to adverse outcomes of prolonged neurologic sequelae or death.

The incidence of dengue has grown dramatically around the world in recent decades. Neurologic involvement occurs in 4%-5% of confirmed dengue.⁴⁰ Dengue infection in patients with suspected central nervous system (CNS) infection is noted to range from 4.2% in southern Vietnam²⁸ to 13.5% in Jamaica³³ whereas, the incidence of dengue among patients with clinical manifestations of encephalitis-like illness ranges from 18%⁴¹ to 22%.³³ Among confirmed neurological dengue cases studies have documented encephalitis to be the presenting clinical manifestation in 52%³³ to 56%.²⁸

The annual incidence of dengue encephalitis is most likely underestimated, especially in developing countries because of problems with pathogen detection. In the Philippines, the Epidemiology Bureau of the Department of Health established the Philippine Integrated Disease Surveillance and Response (PIDSR) system in 2007, under which the surveillance on Acute Encephalitis Syndrome (AES) and Bacterial Meningitis (BM) falls.

An integrated surveillance for Acute Meningitis-Encephalitis Syndrome (AMES) was established in 2014 as a combination of both AES and BM, that collates data on both conditions. Presently, there are no local studies describing the clinico-demographic profiles and outcomes of dengue encephalitis cases in the Philippines.

This study aimed to provide clinico-demographic profiles and outcomes of pediatric cases of dengue encephalitis; to provide epidemiological data of such in the Philippines for better case detection, prognostication, prevention, counseling of patients and family members, public health interventions, work-up, and subsequent monitoring. Furthermore, the results of the study may be used as a baseline for further studies on dengue infection.

This study described the clinico-demographic profiles and outcomes of children with dengue encephalitis in a tertiary hospital in the Philippines from January 2011 to June 2017. Specifically, this determined the clinico-demographic features of children with dengue encephalitis in terms of the following: age, gender, geographic location, nutritional status, presenting features, clinical signs, history of previous dengue infection and subsequent outcome, receipt of dengue vaccine, presence of co-morbidities, laboratory examinations, and/or imaging techniques (complete blood count, ALT, AST, glucose, serum electrolytes, BUN, Creatinine, PT and PTT, Dengue NS1, Dengue IgG, IgM, CSF IgM-capture ELISA, EEG, Chest X-ray, Cranial ultrasound, Cranial CT scan and/or MRI).

Another objective was to determine the outcome of patients with dengue encephalitis in terms of: (a) Full Recovery (with complete resolution of neurologic signs and symptoms), (b) Partial Recovery (with partial resolution of neurologic signs and symptoms), (c) Presence of neurologic sequelae, or (d) Death.

METHODOLOGY

This is a retrospective observational study, that used purposive sampling to retrieve and review hospital charts of laboratory-confirmed dengue encephalitis cases aged 0-18 years.

Inclusion Criteria

All of the following criteria were fulfilled prior to study enrolment: (1) Children aged 0-18 years, (2) admitted at a tertiary hospital in the Philippines from January 2011 to June 2017, and (3) patients who fulfill the clinical case definition in AMES surveillance, and are laboratory confirmed cases of acute dengue encephalitis.

Exclusion Criteria

Patients with the following were excluded in the study: (1) bacterial, tuberculous, fungal, parasitic, other viral or immune etiology; (2) patients with encephalomyelitis (eg. Acute Disseminated Encephalomyelitis), or (3) patients without samples submitted for routine CSF and serum analyses.

The Child Neurology census from January 2011- June 2017 was reviewed, revealing 3,124 probable cases of Central Nervous System (CNS) infection, 209 cases of which having a final discharge diagnosis of encephalitis/ encephalopathy, records of which were retrieved for review. Of these, 18 cases were eventually discharged as dengue encephalitis/ encephalopathy.

The Acute Meningoencephalitis Syndrome (AMES) Surveillance reports from January 2011- June 2017 were retrieved from the National Reference Laboratory, to search for laboratory-confirmed cases of dengue encephalitis. Of the 18 cases discharged as dengue encephalitis/encephalopathy, 16 had dengue-specific IgM antibody in the CSF or serum sample detected by Dengue NS1 or IgM-capture ELISA. Also, four patients who were initially treated as cases of dengue encephalitis were excluded due to the presence of Japanese encephalitis-specific IgM (3 cases) and Chikungunya virus IgM (1 patient) in the CSF. A total of 14 cases were included in the study.

Definition of terms

An *Acute Meningoencephalitis Syndrome (AMES) Surveillance case* - is a person with sudden onset of fever and at least one of the following: change in mental status (including altered consciousness, confusion or inability to talk), new onset of seizures (excluding simple febrile seizures), neck stiffness and other meningeal signs.

Dengue encephalitis cases – are suspected dengue patients that meet the clinical case definition defined by AMES surveillance, and a laboratory confirmed dengue infection (as defined by the presence of dengue specific-IgM antibody in serum or CSF detected by dengue NS1 or IgM-capture ELISA, in the absence of co-infection with other etiologic agents).

Approval was obtained from the hospital's Institutional Review Board (IRB). Hospital charts of patients who fulfilled all of the inclusion, and none of the exclusion criteria were retrieved and reviewed.

The following clinico-demographic data were noted in the study-defined patient data sheet: age, gender, geographic location, nutritional status, clinical history, receipt of dengue vaccine, presenting features, clinical signs, duration of hospital stay, co-morbidities, management, as well as laboratory and imaging examinations done. Clinical outcomes were categorized as follows: full recovery, partial recovery from neurologic changes, presence of neurologic sequelae; or death. An attempt to retrieve and review the outpatient follow-up charts was done, of which none can be located. Neuroimaging and encephalogram results done post-hospital discharge were located, and were subsequently reviewed.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. All valid data were included in the

analysis. Missing variables was neither replaced nor estimated. STATA 12.0 was used for data analysis.

RESULTS

During the period covered by the study, 14 cases of laboratory-confirmed dengue encephalitis were recorded. All patients were referred to the intensive care unit. Of the 14 patients enrolled, 9 patients were managed as severe dengue, 4 as neonatal sepsis with CNS infection and 1 as Viral Encephalitis, unspecified. Eleven patients with one or a combination of the following concomitant illnesses: Pneumonia (7), Clinical sepsis (4), Generalized epilepsy with global developmental delay (1), Necrotizing fasciitis, chest (1), Patent Ductus Arteriosus (1) were identified, and were all subsequently managed during the hospital stay.

Table 1. Demographic and clinical profile of patients with dengue encephalitis (n=14)

	Frequency (%); Median (Range)
Age at onset (years)	2.5 years (3 days to 15 years)
Gender	
Male	8 (57.14)
Female	6 (42.86)
Region of Location/Residence	
NCR	10 (71.4)
III	2 (14.3)
IV - A	2 (14.3)
Weight (kg)	12.3 (2.1 to 65)
Height (cm) (n = 3)	61 (51 to 156.6)
BMI (kg/m ²) (n=3)	15.59 (15.38 to 21.23)
Nutritional assessment*	
Obese	2 (14.3)
Overweight	0
Normal	10 (71.4)
Wasted / underweight	1 (7.14)
Severely wasted	1 (7.14)
Day of illness upon admission	3 (1 to 6)
Duration of febrile phase (days)	6 (3 to 11)
Hospital stay (days)	13.5 (6 to 41)
Time of onset of fever to development of neurologic changes (days)	2 (1 to 5)
Presence of comorbidities/ concomitant illnesses	8 (57.14)
Previous hospitalization	1 (7.14)
Previous dengue infection	0
Intervention given**	
Intravenous fluid support	14 (100)
Antibiotics	10 (71.4)
Pressors	3 (21.43)
Rehabilitation	1 (7.14)
Received dengue vaccine	0

*Nutritional assessment is based on weight for age (z-score)²⁰,

**Multiple response

Clinical characteristics

All patients were admitted during the first week of illness, ranging from the 1st to the 6th day (median, 3rd day), presenting with fever, coupled

with nonspecific signs and symptoms (Table 2). There was gastrointestinal bleeding in two children, with hematemesis in one and coffee ground material in the orogastric tube in another. Three patients (21%) became jaundiced, with no evidence of hepatomegaly. Enlargement of the liver was noted in 2 patients (14%). (Table 2). The time that elapsed from the onset of the febrile period until the onset of the neurological changes ranged from 1 to 5 days (median of 2 days).

Table 2. Presenting symptoms and clinical signs of patients with dengue encephalitis (n=14)

Presenting symptoms	Frequency (%)
Fever	14 (100)
Decreased appetite/poor suck	11 (78.57)
Cough/colds	9 (64.3)
Vomiting	6 (42.9)
Irritability	5 (35.7)
Loose stools	4 (28.6)
Headache	3 (21.4)
Abdominal pain	2 (14.3)
Clinical Signs	
Rash	5 (35.7)
Flushed skin	4 (28.6)
Pallor	3 (21.4)
Jaundice	3 (21.4)
Bleeding	2 (14.3)
Abdominal enlargement	2 (14.3)
Hepatomegaly	2 (14.3)

Table 3 Neurologic findings in patients with dengue encephalitis (n=14)

Neurologic changes	Frequency (%)
Seizures	10 (71.4)
Generalized	7 (70)
Focal	1 (10)
Both	2 (20)
Decreased sensorium/ Increased sleeping time	8 (57.14)
Behavioral changes	4 (28.6)
Disorientation	3 (21.4)
Incoherent words	2 (14.3)
Aphasia	1 (7.1)
Neurologic examination findings	
Nuchal rigidity	3 (21.4)
Bulging anterior fontanel	2 (14.3)
Spasticity	1 (7.1)
Development of Babinski reflex	1 (7.1)
Hyporeflexia (DTR +1)	1 (7.1)

More than half (57%) of children developed decrease in sensorium. The youngest patient exhibited spasticity, nuchal rigidity, and a bulging anterior fontanel. Babinski reflex and hyporeflexia were noted in one 10-year-old patient. Seizures, mostly generalized (n=7), were recorded in 71% of patients, and were the most common reason for hospital admission. (Table 3)

Upon admission, more than half (57%) of children had depressed hemoglobin for age (Table 4), 5 (83%) of which were within normal range for weight based on nutritional assessment at the time of confinement. Only one (7.1%) patient, aged 6 years, developed hemoconcentration, an evidence of plasma leakage due to increased vascular permeability¹⁹.

Among those tested, majority had elevated ALT (8 of 10) and AST (5 of 6). One patient with consistently normal BUN registered high creatinine levels (maximum of 114.92 $\mu\text{mol/L}$). Hypokalemia was noted in half the children whom serum electrolytes were measured, other results were mostly normal. Three had high glucose, while one had hypoglycemia. Partial prothrombin time was prolonged in 40% of 10 children, and PT INR in 50% of these. Half of the patients showed radiologic evidence of pneumonia, 3 (21%) showed pleural effusion.

Table 4. Laboratory results of patients with dengue encephalitis (n=14)

	Median \pm SD (Range)	Frequency (%)		
		Normal	Decreased	
Hemoglobin (g/dL)	125.48 \pm 17.45	6 (42.9)	8 (57.1)	
		Normal	Decreased	Hemo-concentrated
Hematocrit (%)	37.85 \pm 5.48	6 (42.9)	7 (50)	1 (7.1)
		With leukopenia	No leukopenia	
WBC (1000 cells/mm ³)	9.23 \pm 3.85 (1.7 to 28.4)	13 (92.9)	1 (7.1)	
		With thrombocytopenia	No thrombocytopenia	
Platelet count (cells/mm ³)	133.0 \pm 77.0 (4 to 400)	13 (92.9)	1 (7.1)	
		Normal	Elevated	
ALT (u/L) (n=10)	76.5 (13 to 3165)	2 (20)	8 (80)	
AST (u/L) (n=6)	190.5 (27 to 650)	1 (16.7)	5 (83.3)	
BUN (mmol/L) (n=4)	4.4 (1.05 to 5.1)	4 (100)	0	
Creatinine (umol/L) (n=5)	74 (27 to 91.46)	4 (80)	1 (20)	
		Normal	Decreased	
Serum sodium (mmol/L) (n=10)	140.57 \pm 7.9	7 (70)	3 (30)	
Serum potassium (mmol/L) (n=10)	3.86 \pm 0.4	7 (70)	3 (30)	
Serum calcium (mmol/L) (n=10)	2.22 \pm 0.3	6 (60)	4 (40)	
		Normal	Elevated	
PT (INR) (n=10)	1.15 \pm 0.2	5 (50)	5 (50)	
		Normal	Prolonged	
PTT (seconds) (n=10)	44.99 \pm 10.5	5 (50)	5 (50)	
		Normal	Elevated	Decreased
Glucose (mg/dl)	88.31 \pm 23.5	11 (78.6)	3 (21.4)	1 (7.2)
		Normal	With Pneumonia	Pneumonia With Effusion
Chest Xray		7 (50)	7 (50)	3 (21.4)

All patients had CSF analysis done, 8 were collected during the first week of illness. Pleocytosis for age was seen in only one patient. CSF white blood cells (WBC) ranges from 0-8 cells x 10⁶/L (median 2.14 cells x 10⁶/L), all with 100% lymphocytic predominance. Other findings included slight hypoglycorrhachia (14.3%), and a mild increase in the protein level (14.3%) in 2 patients (43 and 45% respectively). Majority of the patients (71.4%) had normal CSF analysis.

Table 5. CSF findings of patients with dengue encephalitis (n=14)

	Mean \pm SD; Median (Range)	Frequency (%)	
		Colorless/ Clear	Xanthochromic/ Hazy
Gross exam		11 (78.6)	3 (21.4)
		Normal	With Pleocytosis
WBC (cells x 10 ⁶ /L)	2.14 \pm 2.6	13 (92.9)	1 (7.1)
		Normal	Elevated
Protein (g/L)	0.33 (0.2 to 1.07)	12 (85.7)	2 (14.3)
		Normal	With Hypoglycorrhachia
CSF: SERUM glucose	65.86 \pm 17.8	12 (85.7)	2 (14.3)

Table 6. Dengue-specific test results of patients with dengue encephalitis (n=14)

	Frequency (%)	
	Positive	Negative
Dengue IgM (+) in CSF	5 (35.7)	9 (64.3)
Dengue IgM (+) in serum	14 (100)	0
Dengue IgG (+) in serum (n=6)	4 (66.7)	2 (33.3)
Dengue NS1 (+) in serum (n=2)	2 (100)	0

Concomitant blood and CSF bacterial cultures were done on all patients, all of which were negative for any bacterial pathogen.

Table 7. Neuroimaging (Cranial CT scan/ultrasound) of patients with dengue encephalitis (n=9)

	Frequency (%)				
	Abnormal				
Normal	6 (66.7)				
3 (33.3)	Cerebral edema		Meningeal enhancement	Thick, wavy echogenic sulci	Hyperechoic subdural and subarachnoid spaces
	5 (55.6)		2 (33.3)	1 (16.7)	1 (16.7)
	Diffuse	Temporo-parietal lobe	Capsulo-thalamic region		
	3 (60.0)	1 (20.0)	1 (20.0)		

Neuroimaging (Table 7) revealed intracranial changes in 67% of patients, with findings such as cerebral edema (55.6%), and meningeal enhancement (33.3%).

Abnormality in waveforms was seen in 7 (87.5%) of 8 children who underwent EEG. Findings included continuous slowing of the background activity (86%), focal slowing (71%) and epileptiform

discharges (29%). Follow up EEG done in three patients, 3 weeks to a month after hospital discharge showed normal results in 2 patients, and significant improvement in the generalized background slowing in one patient. The most commonly used medication for seizure control was phenobarbital (92.9%).

Table 8. Outcome of patients with dengue encephalitis

Outcome	Frequency (%)
Fully recovered from neurologic changes	7 (50)
Partially recovered from neurologic changes	3 (21.43)
Neurologic sequelae present	3 (21.43)
Death	1 (7.14)

DISCUSSION

Dengue virus belongs to the *Flaviviridae* family, which includes a number of neurotropic viruses such as Japanese encephalitis virus, St. Louis encephalitis virus, and tick-borne encephalitis virus.¹⁴ The signs and symptoms, as well as the characteristic laboratory markers for severe dengue were not seen in the majority of our patients with dengue encephalitis. A study done by Mufazzar in 2006 supports this finding, as he found that not all patients with dengue encephalitis develop complications of severe dengue.²⁸

Antenatal and post-partum dengue infection secondary to vertical transmission has been documented to occur in neonates in several earlier reports^{23,24}. Interestingly, this study found four neonates who had dengue specific IgM via serology, three of which also had dengue IgM in the CSF. None of these neonates were suspected to have an acute dengue infection during the hospital admission and were instead treated as cases of neonatal sepsis. Review of the patients' clinical course revealed that all four neonates fulfilled the minimum criteria for probable dengue. CSF analysis was done due to the consideration of concomitant CNS infection, and samples were sent to AMES surveillance for analysis. Results of the AMES surveillance was not known

during the hospital stay of the patients, and all four neonates were discharged. Three neonates fully recovered, while one still showed signs of fair suck, with improved activity upon discharge. Three out of four neonates demonstrated dengue IgM in the CSF, the exception also showing full recovery upon discharge. Two of the four neonates' mothers had an unremarkable maternal history. One mother was febrile upon delivery due to urinary tract infection, the mother of the neonate with partial recovery expired 5 days after delivery due to preeclampsia, and an unknown febrile illness. During the patients' hospital stay, there was no mention whether the mother was worked-up for the possibility of having acute dengue. It is yet to be established what the poor prognostic factors are for neonates presenting with dengue encephalitis, as there are limited studies regarding this.

Neurologic manifestations due to dengue have been well reported, and has previously been thought to result from the multisystem derangement that occurs in severe dengue infection, with liver failure, shock and coagulopathy causing cerebral insult as opposed to encephalitis defined by a localized invasion of the CNS. Recent studies, however^{10,11,13,14,21}, describe a possible direct neurotropic effect of dengue virus. The incidence of dengue with neurologic complications is unclear, with calculations ranging from 0.5%¹⁴ to 6.2%²⁶ of DHF cases. Kankirawatana et al. states that 18% of children with suspected encephalitis in a Thai hospital were found to have dengue infection.²⁷ In the absence of a definitive histological examination of the brain, dengue encephalitis is exemplified by the identification of dengue specific antibodies or dengue antigen in the CSF. Detection of IgM in CSF is indicative of viral replication in CNS, but the titer is generally lower and short-lived when compared with serum, making it an unreliable marker. It is because of this that in previous studies, patients were considered as cases of dengue encephalitis when there is serologic evidence of dengue infection, coupled with focal neurologic manifestations or neuroimaging abnormalities. This

consideration has also been employed in this study. In previous studies, mechanism of CNS infiltration has been observed via (1) virus-induced, cytokine-mediated breakdown of the blood-brain barrier, (2) via infiltration of virus-infected macrophages, or (3) by direct invasion of the virus itself. In accordance with these recent reports, we found 5 (35.7%) of 14 patients had dengue-specific IgM in the CSF, indicating a localized infection of the CNS. These patients consisted of 3 neonates, and 2 children. Of the 3 neonates, 2 recovered completely prior to discharge, with hospital stay of 8 and 41 days respectively. One neonate with IgM positive CSF exhibited fair activity prior to discharge. Two other children with IgM positive CSF both stayed at the hospital for 27 days, one was discharged with minimal verbal output and occasional disorientation, and one exhibiting focal deficit and whom hypoxic-ischemic encephalopathy was also considered.

The clinical manifestations and findings in this study were consistent with those reported in the literature and reviews of dengue encephalitis. Fever was present in all cases. Following non-specific signs and symptoms, decreased sensorium and new onset seizures were the most common neurologic manifestations, the latter being the most common reason for consult and subsequent hospital admission. Elevation in liver enzymes, dengue-related nephropathy, glucose and electrolyte derangements, elevated prothrombin time, prolonged activated thromboplastin time, and signs of plasma leakage were seen in some of our patients. It has been well recognized that cerebral dysfunction may result from these findings, and may account for some neurologic manifestations seen. Interestingly, hemoconcentration was not observed in the cases seen in this study. The paucity of subjects limits the investigator in concluding a correlation exists between this observation and severe dengue in general. CSF analysis of the patients showed the following, a minority with slight hypoglycorrhachia and pleocytosis, all with absolute (100%) lymphocytosis, the findings of which were

consistent with viral encephalitis in general. The most common EEG and neuroimaging findings were likewise consistent with dengue encephalitis.^{10,11,13,14,21,27,35} Most patients manifested with generalized or focal background slowing via EEG, and neuroimaging findings ranged from being normal, to having evidence of cerebral edema, some with changes consistent with acute meningoencephalitis. Testing for correlation between established factors for poor prognosis, which were noted in some of the patients, such as extremes of age, under or over nutrition, presence of co-morbidities, signs of plasma leakage, hepatic involvement, and patient outcome could not be done due to the very limited subjects.

Among the *Flaviviridae*, antigenic cross-reactivity appears to involve a group-reactive antigen shared by all members. In patients with previous Japanese encephalitis, these circulating low-titer antibodies may show cross-reactivity with dengue virus. This was evident in the cases seen in this study as four patients who were initially treated as cases of dengue encephalitis, were excluded in this study due to the presence of Japanese encephalitis-specific IgM (3 cases) and Chikungunya virus IgM (1 patient) in the CSF.

On the basis of previous reports^{10,11,13,14,21} and of the findings of this study, dengue infection encompasses an expanding clinical spectrum that rarely involves encephalitis due to a direct viral neurotropism.

Mortality due to dengue encephalitis varies from 5%²² to 22%¹⁴ in previous studies. The reported morbidity and mortality due to dengue encephalitis itself is low with most survivors recovering fully.^{10,34,35} Documented sequelae from encephalitis included weakness, spasticity³⁵ and focal spasms.³⁶ Encephalitis accompanied by post-infectious neurological manifestations however may have a prolonged recovery. Our study limited our investigation to laboratory-confirmed dengue encephalitis in the absence of co-infection with other viruses in the CNS, and only a single mortality was observed. The single mortality observed in this

study is a 1-year-old male with dengue IgM antibody detected in the serum, who's immediate cause of death was dengue shock, presenting as generalized seizures and hypotension. Neurologic manifestations were observed in 6 (42.9%) of patients upon discharge, ranging from mild to severe. The presence of long-term or permanent neurologic sequelae cannot be inferred since the only follow-up data available were the follow-up EEG of two patients, which showed improvement in the generalized background slowing in one, and a normal EEG in another patient taken 3 weeks from discharge. It would be interesting to know the long-term outcome of each patient using an established outcome scoring system on subsequent patient follow-up consults, so as to determine whether neurologic changes that have been present on discharge would lead to eventual recovery or deterioration. This exercise, however, is beyond the scope of this study.

According to the World Health Organization (WHO), the real burden of dengue encephalitis is underreported. Although CSF analysis for dengue is locally available, and is government subsidized in sentinel hospitals under the national surveillance program, the relative contraindication of performing an invasive procedure in the context of a clinically unstable patient with thrombocytopenia, and the cost of the test in private institutions restricts definitive laboratory confirmation of dengue encephalitis. Clinical dengue infection in the presence of focal neurologic findings is suggestive of the disease, however, laboratory confirmation via CSF analysis is necessary to determine whether the encephalitis is due to dengue neurotropism, or a systemic consequence of severe disease itself.

Due to the potential risk for significant morbidity and mortality, it is recommended that dengue encephalitis be highly considered in patients with severe dengue so that prompt case detection and appropriate management ensue. The small sample size, heterogeneity of clinical profile, and patient response are probably responsible for outcome variations.

CONCLUSION AND RECOMMENDATIONS

In conclusion, dengue encephalitis is emerging as an important, albeit rare entity that should be entertained as a differential diagnosis in dengue patients with neurologic manifestations in all age groups. Likewise, it should be included in the differential diagnosis of any CNS infection in an endemic country, as evidenced by the 4 neonates managed as neonatal sepsis but turned out to be positive for dengue IgM.

It is recommended that prospective studies be done on this subject as we recognize the limitations of a retrospective study. Likewise, long-term follow-up on patients should be performed for prognostication.

REFERENCES

1. Liu JW, Khor BS, Lee CH, Lee IK, Chen RF, Yang KD. Dengue hemorrhagic fever in Taiwan. World Health Organization Dengue Bulletin. 2003; 27:3-24. 2.
2. Global Strategy for dengue prevention and control, 2012–2020. World Health Organization, Geneva, Switzerland, 2012. Accessed 10 Apr 2017 at http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf
3. Dengue and severe dengue (Fact sheet N°117). World Health Organization, Geneva, Switzerland, 2016 [cited 24 June 2016]. Available from: <http://www.who.int/me-diacentre/factsheets/fs117/en/>
4. Republic of the Philippines Department of Health website. Accessed 15 Apr 2017. https://www.doh.gov.ph/sites/default/files/statistics/2016_Dengue_W47_1.pdf.
5. Tunkel AR, Glaser CA, Bloch KA, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan S, Scheld WM, Whitley RJ. The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. CID Jun 2008;47.
6. World Health Organization (WHO) Regional Office for South-East Asia. Dengue: guidelines for diagnosis, treatment, prevention, and control. Special Programme for Research and Training in Tropical Diseases. 2009. Available from: 147. <https://doi.org/WHO/HTM/NTD/DEN/2009.1>
7. Global Strategy for dengue prevention and control, 2012–2020. World Health Organization, Geneva, Switzerland, 2012. Available from:

8. Cherry JD, Harrison GJ, Kaplan SL, Steinbach, MD, Hotez PJ. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed. 2014. Elsevier Saunders, USA. Ch. 45.
9. M. States, W. Advi, T. Grade, et al. Dengue vaccine: WHO position paper – July 2016. 29 JULY 2016, 91th YEAR. World Health Organization weekly epidemiological record; p.350
10. Rao SM, Pradeep M, Dnyaneshwar M and Alai T. Dengue encephalitis – clinical spectrum and outcome. Intern Med Inside. 2013; 1:8. <http://dx.doi.org/10.7243/2052-6954-1-8>
11. Murthy JM. Neurological complications of dengue infection. Neurol India 2010; 58: 581-584
12. Rao S, Kumar M, Ghosh S, Gadpayle AK. A rare case of dengue encephalitis. BMJ Case Rep 2013; doi:10.1136/bcr-2012-008229. [4]
13. Deepak Madi et. al. Dengue Encephalitis – A Rare Manifestation of Dengue Fever. Asian Pacific Journal of Tropical Biomedicine 4, no. Suppl 1 (2014): S70-2 doi:10.12980/APJTB.4.2014C1006.
14. Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, Heegaard ED. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg 2001; 65(6):848-51. <https://www.ncbi.nlm.nih.gov/pubmed/11791985> (accessed 19 April 2017).
15. Peacock JL, Peacock PJ. Research design. (ed). Oxford handbook of Medical Statistics. United States: Oxford University Press; 2011. pp. 60-61.
16. Department of Health National Epidemiology Center Public Health Surveillance and Information Division. Field Health Services Information System (2013) Manila, Philippines. Annual Report.
17. Philippine Integrated Disease Surveillance and Response Report. (2014) Department of Health. Manila, Philippines. Annual Report.
18. Committee on Immunization. ^[1] ^[2] Pediatric Infectious Disease Society of the Philippines. (May 20, 2016). Statement on the use of dengue vaccine. Manila, Philippines.
19. Technical working group. Philippine Pediatrics Society. (October 18, 2010) 2010 Interim guidelines on fluid management of dengue fever and dengue hemorrhagic fever. Manila, Philippines.
20. Philippine Pediatric Society. Preventive Pediatric Health Care Handbook, eighth ed., 2016.
21. Samanta M, Kundu, CK, Guha G, Chatterjee S. Unique Neurologic manifestations of Dengue Virus in Pediatric Population: A Case Series. Journal of Tropical Pediatrics. 2012, Vol 58, No. 5.
22. Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health 2001; 32:341-5.
23. Chin PS, Khoo PC, Hani, AW, Chem YK, Norizah I, Chua KB. Acute dengue in a neonate secondary to perinatal transmission. Med J Malaysia. 2008 Aug;63(3):265-6.
24. Chye JK, Lim CT, Ng KB, Lim JM, George R, Lam SK. Vertical transmission of dengue. Clin Infectious Diseases. 1997
25. Porta M. A Dictionary of Epidemiology, 5th ed. NY. 2001. Oxford University Press; 5:p. 53.
26. Hendarto SK, Hadinegoro SR. Dengue encephalopathy. Acta Paediatr Jpn 1992;34:350-7.
27. Kankirawatana P, Choekhaibulkit K, Puthavathana P, Yoksan S, Somchai A, Pongthapisit V. Dengue infection presenting with central nervous system manifestation. J Child Neurol 2000;15:544-7.
28. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, et al. Neurological manifestations of dengue infection. Lancet 2000;355:1053-9.
29. Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health 2007;12:1087-95.
30. Muzaffar J, Krishnan V, Gupta N, Kar P. Dengue encephalitis: why we need to identify this entity in a dengue-prone region. Sing Med J. Nov 2006. Vol.47: pp.975-7.
31. Administrative Order 2012-0006. Revised Dengue Clinical Case Management Guidelines 2011. Department of health of the Republic of the Philippines. 2012: 66-7.
32. Kliegman RM, Stanton BF, Geme GW III, Schor NF, De Maso DR, Denison MR, et al, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier, Inc. 2016..
33. Jackson ST, Hann Chu JJ, Chia P, Morgan OS, Ng LC. Dengue encephalitis. Intech. 2011: 11-12. Available from: <http://www.intechopen.com/books/flavivirus-encephalitis/dengue-encephalitis>
34. Angibaud G, Luaute J, Laille M, Gaultier C. Brain involvement in dengue fever. J of clin neuroscience. Jan 2001, 8:63-5.
35. Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J of Trop Med and Pub Health. Jun 2001, 32:341-5.
36. Soares C, Fairia L, Peralta LC, De Freitas MR, Pucchioni-Sohler M. Dengue infection: neurological manifestations and cerebrospinal fluid analysis. J of Neurol sciences. Nov 2006, 249: 19-24.
37. Department of Health National Epidemiology Bureau, Public Health Surveillance and Information Division. Field Health Services Information System (2013-2018) Manila, Philippines. Annual Reports

38. WHO (1997) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed., Geneva: World Health Organization, 1997.
39. WHO (2009b) Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organisation and Special Programme for Research and Training in Tropical Diseases, 2009.
40. Puccioni-Sohler, M., Soares, C. N., Papaiz-Alvarenga, R., Castro, M. J., Faria, L. C. & Peralta, J. M. (2009) Neurologic dengue manifestations associated with intrathecal specific immune response. *Neurology* 2009 Vol 27,(October 2009) pp.1413-7
41. Kankirawatana P, Chokephaibulkit K, Puthavathana P, Yoksan S, Apintanapong S, Pongthapisit V. (2000) Dengue infection presenting with central nervous system a manifestation. *Journal of Child Neurology*, Vol.15,(August 2000), pp.544-7