

DENGUE WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

Usa Thisyakorn and Chule Thisyakorn

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University,
Bangkok, Thailand

Abstract. Dengue has spread to new geographic areas affecting both children and adults, and it has become a global threat. Dengue with central nervous system involvement includes febrile seizures, encephalopathy, encephalitis, aseptic meningitis, intracranial hemorrhages, intracranial thrombosis, subdural effusions, mononeuropathies, polyneuropathies, Guillain-Barré syndrome, and transverse myelitis. These manifestations may be associated with co-infections, co-morbidities, or complications of prolonged shock. It is important to consider dengue as a cause for the above neurological presentations, particularly in endemic territories for dengue disease.

Keywords: dengue, nervous system

INTRODUCTION

Dengue, a mosquito-borne viral disease, is currently an expanding global problem. Dengue virus includes all four dengue serotypes DEN-1, DEN-2, DEN-3, and DEN-4, which belong to the genus *Flavivirus* in the family *Flaviviridae*. Dengue virus disease ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) (Thisyakorn and Thisyakorn, 2015). Dengue with organopathy has been reported as unusual or atypical manifestations including the involvement of the following systems, sites, and manifestations: neurological,

gastrointestinal, hepatic, renal, cardiac, respiratory, musculoskeletal, lymphoreticular, bone marrow, eye, post-infectious fatigue syndrome, depression, hallucination, psychosis, and alopecia (Thisyakorn and Thisyakorn, 1994a; Gulati and Maheshwari, 2007). These may be explained as complications of severe profound shock or associations with the hosts' underlying conditions/diseases or coinfections (Hemungkorn *et al*, 2007). The mentioned organopathies may be underreported, underrecognized, or not related to dengue. However, it is essential that proper clinical assessment is carried out for appropriate management, and causal studies should be done (Thisyakorn and Thisyakorn, 1994a, b).

Correspondence: Professor Usa Thisyakorn, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.

Tel: 66 (0) 2354 7584

E-mail: fmeduty@mail.md.chula.ac.th

CENTRAL NERVOUS SYSTEM INVOLVEMENT IN DENGUE PATIENTS

There have been reports of dengue infection with central nervous system involve-

ment from Southeast Asian countries since 1976. Sanguanserm Sri *et al* (1976) from Chiang Mai University, Thailand reported a DHF patient with encephalopathy, Wuler *et al* (1972) from Indonesia reported a girl with DHF and obvious signs and symptoms compatible with Reye's syndrome, (*ie*, high level of serum transaminases, ammonia, and characteristic histopathologic changes in the liver). Tin *et al* (1976) from Myanmar (formerly Burma) reported severe forms of DHF with encephalitic symptoms associated with loss of consciousness lasting from 2-to-5 days in nine children varying in ages from 8 months-to-9 years. Cerebrospinal fluid examinations in all cases were normal. DEN-2 was isolated from the acute sera of two cases while DEN-3 was isolated from the liver of another case. Sumarmo *et al* (1978) from Indonesia reported four virologically proven cases of encephalopathy in DHF and DSS patients with DEN-2 and DEN-3 viruses isolated from the sera. In 1981, Kho *et al* from Indonesia reported 41 cases of virologically proven DHF with neurological signs compatible with acute encephalopathy; all patients were seen in Jakarta from 1975 to 1977. Two of these children showed typical signs and symptoms of Reye's syndrome as confirmed by histopathology of their livers. Nimmannitya *et al* (1978) reported 18 cases of DHF with neurological manifestations seen at the former Children's Hospital, Thailand between 1972 and 1981; gross hemorrhage in the brain was noted in 6 of the 10 fatal cases while cerebral edema was noted in three cases. In 1988, George *et al* from Malaysia reported four cases of DF with cerebral and hepatic symptoms. Renal impairment was detected in two patients .

In 1987, Thisyakorn and Thisyakorn

from Chulalongkorn University, Thailand conducted a prospective study in 505 serologically and/or virologically confirmed dengue patients. Fourteen patients had unusual manifestations, mainly involving central nervous system. All of their demographic data, unusual manifestations, and outcomes are shown in Tables 1 and 2. Lumbar puncture was done in six patients; all showed negative findings. None of the six patients had specific dengue IgM in their cerebrospinal fluid. Autopsies performed in two patients revealed massive centrolobular liver necrosis in both. Pathological examination of the brain revealed intracerebral hemorrhage at fronto-temporal area in one patient and viral encephalitis in the other. Comparison of all the data between dengue patients with usual and unusual manifestations is shown in Table 3, which shows that patients who had unusual manifestations tended to be in the younger age group, and those with unusual manifestations had higher mortality (Thisyakorn and Thisyakorn, 1994b).

Thisyakorn *et al* (1999) conducted a prospective study over a seven-year period from 1987 to 1994 to determine the clinical and laboratory findings of dengue patients with central nervous system manifestations in two provinces, namely Bangkok, the capital city of Thailand and Songkhla, a province in the southern region of Thailand. Thirty serologically confirmed dengue patients with central nervous system manifestations were seen during the period of study. Their ages ranged between 3 months and 14 years with a mean age of 6.2 years. Seventeen were boys, and 13 were girls. The central nervous system manifestations included alteration of consciousness (76.7%), seizures (63.3%), pyramidal tract

Table 1
Clinical data of 14 patients with dengue infections and unusual manifestations.

No	Age (yr)	Sex	Severity of diseases	Prior medications	Nutritional status
1	7	Female	DSS	Yes	Normal
2	8/12	Female	DHF grade III	Yes	1 st degree malnutrition
3	5	Male	DSS	Yes	Normal
4	12	Female	DF	No	Normal
5	7	Female	DHF grade III	Yes	Normal
6	4	Female	DHF grade III	Yes	Normal
7	14	Male	DF	Yes	Normal
8	5	Female	DSS	Yes	Normal
9	1 ⁶ /12	Female	DHF grade II	Yes	1 st degree malnutrition
10	3 ⁸ /12	Female	DHF grade III	Yes	Normal
11	2 ⁴ /12	Male	DSS	Yes	Normal
12	7	Female	DHF grade II	Yes	Normal
13	1	Female	DSS	Yes	Normal
14	6	Male	DHF grade III	Yes	Normal

DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.

Table 2
Clinical manifestations and outcomes of 14 patients with dengue infection and unusual manifestations.

No	Unusual manifestations	Outcome
1	Alteration of consciousness, jaundice	Expired
2	Alteration of consciousness, convulsion, jaundice	Expired
3	Alteration of consciousness, convulsion, jaundice	Survived
4	Alteration of consciousness	Survived
5	Alteration of consciousness	Survived
6	Alteration of consciousness, convulsion, adult respiratory distress syndrome	Survived
7	Alteration of consciousness, convulsion	Survived
8	Reye-like syndrome	Expired
9	Reye-like syndrome	Survived
10	Jaundice	Survived
11	Alteration of consciousness, convulsion, jaundice	Expired
12	Alteration of consciousness, convulsion	Survived
13	Alteration of consciousness, jaundice	Survived
14	Adult respiratory distress syndrome	Survived

signs (36.7%), meningeal signs (30%), and headache (26.7%). Eleven patients had primary while 19 had secondary dengue infection. Cerebrospinal fluid examination showed lymphocytic pleocytosis in 6 out of

28 patients while presence of anti-dengue IgM antibodies was detected in 2 out of 19 specimens of cerebrospinal fluid tested. Two patients died; autopsy was done on one patient and the result of the brain

Table 3
Clinical data of patients with dengue infections at Chulalongkorn Hospital, 1987.

Clinical data	Usual manifestations	Unusual manifestations
Cases, <i>n</i>	491	14
Age, <i>n</i> (5)		
< 5 yrs	126 (25.7)	8 (57.1)
5-10 yrs	241 (49.1)	4 (28.6)
>10 yrs	124 (25.3)	2 (14.3)
Girls, <i>n</i> (%)	252 (51.3)	10 (71.4)
DSS, <i>n</i> (%)	255 (51.9)	10 (71.4)
With prior medications, <i>n</i> (%)	389 (79.2)	13 (92.9)
With malnutrition, <i>n</i> (%)	60 (12.2)	2 (14.3)
Death, <i>n</i> (%)	1 (0.2)	4 (28.6)

DSS, dengue shock syndrome.

examination was compatible with viral encephalitis (Thisyakorn *et al*, 1999).

With the geographical expansion of dengue illness, there have been increasing reports of dengue patients with neurological manifestations. A diverse range of central nervous system manifestations in dengue patients include febrile seizures, encephalopathy, encephalitis, aseptic meningitis, intracranial hemorrhages, intracranial thrombosis, subdural effusions, mononeuropathies, polyneuropathies, Guillain-Barré syndrome, and transverse myelitis. Exhaustive investigations should be done in these cases to exclude concurrent infections. It is essential that proper clinical assessment is carried out for appropriate management, and causal studies should be done. Unlike encephalitis caused by other viruses, most dengue patients with encephalopathy and encephalitis had uneventful recoveries. Long-term neurological sequelae in these patients were rare (Thisyakorn and Thisyakorn, 1994a, b; Thisyakorn *et al*, 1999; Gulati and Maheshwari, 2007).

CONCLUSION

Neurological manifestations in dengue patients are diverse, including febrile seizures, encephalopathy, encephalitis, aseptic meningitis, intracranial hemorrhages, intracranial thrombosis, subdural effusions, mononeuropathies, polyneuropathies, Guillain-Barré syndrome, and transverse myelitis. Exhaustive investigations should be done in these cases to exclude concurrent infections. It is essential that proper clinical assessment is carried out for appropriate management.

REFERENCES

- George R, Liam CK, Chua CT, *et al*. Unusual clinical manifestations of dengue virus infection. *Southeast Asian J Trop Med Public Health* 1988; 19: 5855-90.
- Gulati S, Maheshwari A. Atypical manifestations of dengue. *Trop Med Int Health* 2007; 12: 1087-95.
- Hemungkorn M, Thisyakorn U, Thisyakorn C. Dengue infection: a growing global health threat. *BioSci Trends* 2007; 1: 90-6.
- Kho LK, Sumarmo, Wulur H, Jahja EC, Gubler

- DJ. Dengue hemorrhagic fever accompanied by encephalopathy in Jakarta. *Southeast Asian J Trop Med Public Health* 1981; 12: 83-6.
- Nimmannitya S, Thisyakorn U, Hemshrichart V. Dengue hemorrhagic fever with unusual manifestations. *Southeast Asian J Trop Med Public Health* 1978; 18: 398-406.
- Sanguansermsri T, Poneprasert B, Phornphutkul C, *et al.* Acute encephalopathy associated with dengue infection. Bangkok: SEAMEO TROP MED Network 1976: 10-1.
- Sumarmo, Wulur H, Jahja E, Guber DJ, Sutomenggolo TS, Saroso JS. Encephalopathy associated with dengue infection. *Lancet* 1978; 1: 449-50.
- Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever: unusual manifestation and problems in management. *JAMA SEA* 1994a; 10: 102-3.
- Thisyakorn U, Thisyakorn C. Dengue infection with unusual manifestations. *J Med Assoc Thai* 1994b; 77: 410-3.
- Thisyakorn U, Thisyakorn C, Limpitikul W, Nisalak A. Dengue infection with central nervous system manifestations. *Southeast Asian J Trop Med Public Health* 1999; 30: 504-6.
- Thisyakorn U, Thisyakorn C. Dengue: a global threat. *J Med Assoc Thai* 2015; 98 (suppl 1): S118-22.
- Tin U, Myo A, Than NS, *et al.* Dengue hemorrhagic fever with encephalitis symptoms. Conference on dengue hemorrhagic fever: current knowledge. Bangkok: SEAMEO-TROP MED Network, 1976: 1.
- Wuler H, Djoharman S, Rumalean L, *et al.* Reye's syndrome associated with dengue virus infection. Seoul: Fourth Asian Congress of Pediatrics, 1972.