NEUROLOGICAL MANIFESTATIONS IN DENGUE PATIENTS

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Abstract. To determine the frequency and the natural history of neurological manifestations of dengue infection in Thai children, 1,493 children diagnosed with dengue infection by serology and admitted to the Department of Pediatrics, Chulalongkorn Hospital, Bangkok, Thailand from 1987 to 1998 were reviewed from prospectively recorded medical charts. There were 80 children identified with neurological manifestations, an incidence of 5.4% of all dengue patients. Of these, there were 41 males and 39 females, with ages ranging from 3 months to 14 years. They were categorized into 20 cases of dengue fever, 26 cases of dengue hemorrhagic fever and 34 cases of dengue shock syndrome. All cases experienced the neurological manifestations during the febrile stage of the illness. The patients were classified into an encephalitic group (called "dengue encephalopathy") (42), a seizure group (35) and a miscellaneous group (3). Encephalitic patients presented with alteration of consciousness (83.3%), seizure (45.2%), mental confusion (23.8%), nuchal rigidity (21.4%), spasticity of limbs (9.5%), positive clonus (4.8%), hemiplegia (2.4%) and positive kernig (2.4%), and were older than those in the other groups. Patients in the seizure group presented with seizure (100%) and positive clonus (2.9%). Abnormal laboratory findings included hyponatremia, abnormal liver enzymes and CSF pleocytosis. Dengue IgM and dengue PCR were not demonstrated in 16 CSF specimens. An autopsy finding of a child in the encephalitic group showed histologic evidence of encephalitis, the only case of confirmed dengue encephalitis in this study. One patient with encephalitic symptoms suffered from long-term neurological sequelae. The overall mortality rate was 5%. In conclusion, neurological manifestations including seizure and encephalopathy in children with dengue are not uncommon whereas dengue encephalitis is a rare entity.

INTRODUCTION

The association of dengue infection with unusual neurological manifestations was first reported by Sanguansermsri *et al* in 1976. Since that time, there have been reports from several Southeast Asian countries, including Thailand (Sumarmo *et al*, 1978; Kho *et al*, 1981; Nimmannitaya *et al*, 1987; George *et al*, 1988; Thisyakorn and Thisyakorn, 1994; Thisyakorn *et al*, 1999; Solomon *et al*, 2000). This 12-year study was conducted to determine the incidence and the natural history of neurological manifestations in Thai dengue patients and search for evidence of direct viral involvement in brain inflammation, or "dengue encephalitis", in this group of patients.

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MATERIALS AND METHODS

One thousand four hundred and ninety-three children aged 0-15 years who were clinically and serologically (using either enzyme-linked immunosorbent assay or hemagglutination-inhibition tests) diagnosed with dengue infection and who were admitted to the Department of Pediatrics, Chulalongkorn Hospital, Bangkok, Thailand from 1987 to 1998, were reviewed from prospectively recorded medical charts.

Those with neurological manifestations were identified and classified into 3 groups: encephalitic, seizure and miscellaneous. Those who had only minor alteration of conscious-

ness and those who developed symptoms and signs only during the hypotensive stage of the illness were excluded. Encephalitic patients were defined as those who had alteration of consciousness to the level of stupor, semi-coma or coma, and/or mental confusion. Patients in the seizure group were defined as those who developed seizures without definite encephalitic symptoms and signs, except for the brief postictal period of depressed sensorium.

Data collection from the study patients included age and sex, neurological manifestations and stage of disease at the onset of manifestation, disease classification (World Health Organization criteria), laboratory findings and outcome.

Statistical analysis included percentage, mean and range for demographic data, and Student's *t* and chi-square tests for comparing non-categorized and categorized variables respectively.

RESULTS

There were 80 children with neurological manifestations giving an incidence of 5.4% of all serologically-proven dengue infections. The patients' age ranged from 3 months to 14 years. There were 42 males and 38 females. The diseases of patients were categorized into 20 cases of dengue fever (DF), 26 cases of dengue hemorrhagic fever (DHF) and 34 cases of dengue shock syndrome (DSS). All patients showed neurological manifestations during the febrile stage of the disease. The patients were classified into encephalitic (42), seizure (35) and miscellaneous (3) groups. Children in the first group were significantly older than those in the other two, and most of them were experiencing secondary dengue infection. One encephalitic patient suffered from long term neurological sequelae (spasticity and muscle weakness). Three patients in the encephalitic group and one in the seizure group died, with the overall mortality rate of 5% (Table 1).

Leading neurological manifestations of encephalitic patients included 35 cases of conscious change (83.3%), 19 cases of seizure (45.2%), 10 cases of mental confusion (23.8%) and 9 cases of nuchal rigidity (21.4%). All patients in the seizure group presented with convulsion and one patient had other concomittant manifestations (Table 2). Three cases in the miscellaneous group presented with nuchal rigidity (2), positive Brudzinski reflex (1) and bulging anterior fontanelle (1).

Serum sodium was examined in 36 children from the encephalitic group, and 21 from the seizure group. Of these, serum sodium was

Table 1
General data of study patients in encephalitic, seizure and miscellaneous groups.

General data		Encephalitic group (n = 42)	Seizure group (n = 35)	Miscellaneous group (n = 3)
Age	- range (yr)	0.3 - 14	0.3 - 13	0.5-11
	- mean (yr)	7.08	2.65	4.13
Incidence		1:48	1:57	1:666
Sex (M:F)		22:20	18:17	2:1
Primary: secondary infection		11:31	19:16	2:1
DF:DHF:DSS		11:11:20	9:12:14	0:1:2
Outcome- longterm sequelae		1 (2.4%)	0 (0%)	0 (0%)
	- mortality	3 (1.7%)	1 (2.9%)	0 (0%)

Note: yr = years, M= male, F = female, DF = dengue fever, DHF = dengue hemorrhagic fever, DSS = dengue shock syndrome

Table 2
Neurological manifestations of study patients in encephalitic and seizure groups.

Neurologic manifestations	Encephalitic group (n = 42)	Seizure group (n = 35)
Alteration of consciousness	35 (83.3%)	0 (0%)
Seizure	19 (45.2%)	35 (100%)
Mental confusion	10 (23.8%)	0 (0%)
Nuchal rigidity	9 (21.4%)	0 (0%)
Spasticity	4 (9.5%)	0 (0%)
Positive clonus	2 (4.8%)	1 (2.9%)
Positive kernig	1 (2.4%)	0 (0%)
Hemiplegia	1 (2.4%)	0 (0%)

Table 3
Laboratory findings of study patients in encephalitic and seizure groups.

Laboratory findings	Encephalitic group	Seizure group
Na - number tested	36	21
- range (mEq/l)	120-146	124-154
- mean (mEq/l)	133.4	135.1
- < 135 mEq/l	20 (55.6%)	10 (27.8%)
- < 130 mEq/l	10 (27.8%)	4 (11.1%)
AST - number tested	14	7
- range (IU/l)	35-6,550	175-2,905
- mean (IU/l)	1,503.9	1,257.9
- > 50 IU/l	12 (85.7%)	7 (100%)
ALT - number tested	14	7
- range (IU/l)	14-3,270	50-1,445
- mean (IU/l)	597.1	806.3
- > 50 IU/l	11 (78.6%)	6 (85.7%)

Note: Na = serum sodium, mEq/l = milliequivalents per liter, < = less than, AST = aspartate aminotransferase, IU/l = international units per liter, ALT = alanine aminotransferase

< 135 and < 130 mEq/l in 55.6% and 27.8% of the encephalitic group respectively, compared to 47.6% and 19.0% of the seizure group respectively. Serum transaminases were examined in 14 children from the encephalitic group, and 7 from the seizure group. Of these, serum AST and ALT were > 50 IU/l in 85.7% and 71.4% of the encephalitic group respectively, compared to 100% and 85.7% of the seizure group respectively (Table 3). Lumbar puncture was done in 20 children from the encephalitic group and 11 children from the seizure group, and showed CSF pleocytosis in 20% of the encephalitic group, compared to 27.3% of the seizure group. However, dengue IgM and PCR for dengue virus performed in CSF of 16 children were all negative (Table 4). At autopsy, the brain tissue of one patient from the encephalitic group showed a histologic evidence of encephalitis, indicating the only case of dengue encephalitis in this study.

Table 4
CSF findings of study patients in encephalitic and seizure groups.

CSF findings	Encephalitic group	Seizure group
wbc in CSF		
- number tested	20	11
- range (cell/mm^3)	0 - 40	0 - 20
- mean (cell/mm^3)	4.0	4.7
- > 5 cells/mm^3	4 (20.0%)	3 (27.3%)
CSF dengue IgM		
- number tested	16	0
- positive	0 (0%)	
CSF dengue PCR		
- number tested	16	0
- positive	0 (0%)	

Note: wbc = white blood cell, CSF = cerebrospinal fluid, mm^3 = cubic millimeter, IgM = immunoglobulin M, PCR = polymerase chain reaction

DISCUSSION

Our hospital-based data showed that Thai children with dengue infection and neurological manifestations were not uncommon. This has been observed since the large outbreaks of dengue infection in Thailand in 1987 (Nimmannitaya *et al*, 1987). It is believed that dengue virus type 3, possibly the most neurovirulent type of dengue virus, was dramatically more common during these outbreaks and may account for these new manifestations (Pancharoen and Thisyakorn, 1998a).

This hypothesis is supported by several reports of this neurological association with dengue infection from other Southeast Asian countries where dengue virus type 3 infection was epidemic (Kho *et al*, 1981; George *et al*, 1988). However, before concluding an atypical presentation is an unusual neurological manifestation in dengue patients, one should rule out possible co-infections (Pancharoen and Thisyakorn, 1998b).

Encephalitic children from our study, especially older children, presented with fever and alteration of consciousness, without recognition of dengue infection at the onset of neurological manifestations. The majority of them had symptoms of a depressed sensorium to the level of stupor and some had mental confusion. These manifestations mimicked viral encephalitis but mostly resolved within 24-48 hours. This study showed that long-term neurological sequelae were rare. A previous study of Thai children examining the first clinical impression of viral encephalitis, indicated that dengue virus was one of the most common causative agents (Thisyakorn and Thisyakorn, 1999). Thus one should consider dengue infection in the differential diagnosis of older children presenting with acute onset of high grade fever and altered level of consciousness or confusion. Close follow-up of these children and/or performing a dengue rapid test will help support the diagnosis of dengue infection.

Seizures are not uncommon in dengue infants (Pancharoen and Thisyakorn, 2001) and were believed to be due to febrile seizures. However, a study on causes of fever in 82 children presenting with first febrile convulsion showed that there was no single serologically proven case of dengue infection (Pancharoen *et al*, 2000). Several children from our study did not present with the typical features of febrile seizures. Age > 6 years, seizures after 2 days of fever and the existence of signs of meningeal irritation, indicated that the convulsions might have had a specific primary cause. However, some children had possible confounding factors such as hyponatremia, co-infection, liver failure, history of previous febrile seizure and drug ingestion. It is difficult to determine exactly whether the seizures in dengue patients were caused by the neurovirulence of dengue virus itself, provoked by other factors or represented simple febrile seizures. Further investigation is necessary in order to prove this association.

The first six cases of "dengue encephalitis" were reported, demonstrating dengue virus in CSF, using techniques of viral isolation, PCR and the presence of dengue IgM (Lum *et al*, 1996). One year later, a study demonstrated dengue virus antigen by an immunoperoxidase technique in three fatal cases of dengue infection with encephalitic presentation (Miagostovich *et al*, 1997). The only case of dengue encephalitis from our study was confirmed by histology. However, the techniques to demonstrate dengue virus were not available in 1986 when the patient died. We suggest that CSF and brain histology are important specimens to prove the direct involvement of the brain by the virus. However, lumbar puncture must be cautiously performed and may not be done if the findings are not expected to change the treatment. CSF should be examined for dengue IgM, PCR for dengue virus and virus isolation, especially in specimens with pleocytosis. Histology and techniques to demonstrate the virus should be performed in all brain specimens from fatal cases.

In conclusion, neurological manifestations including encephalic presentations and seizures are not uncommon with dengue infection in children. Children with encephalitic presentation are usually older than those who present with a seizure alone. The overall prognosis of this neurological manifestation is excellent. Dengue encephalitis is a rare entity.

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