CASE REPORT

FATAL DENGUE ENCEPHALITIS

Prasonk Witayathawornwong

Department of Pediatrics, Petchabun Hospital, Petchabun, Thailand

Abstract. Central nervous system involvement is not an uncommon manifestation of dengue virus infection, but encephalitis is a rare entity. We report the case of a 5-year-old girl with fever and convulsions. She developed coma and shock during the high fever stage without abnormal bleeding.Treatment was supportive and symptomatic. The shock was poorly controlled. High fever persisted for 7.5 days then she expired. Cerebrospinal fluid (CSF) and blood dengue-IgM antibody showed dengue infection.

INTRODUCTION

The indirect effects of dengue infection on the central nervous system may be an explanation for encephalopathy. The encephalopathy was thought to be secondary to vasculitis with resultant fluid extravasation, cerebral edema, hypoperfusion, hyponatremia, and hepatic and renal failure (Nimmannitya *et al,* 1987; Jimenez *et al,* 1988; Lum *et al,* 1993). However, cases of dengue encephalitis have been increasingly reported with the presence of IgM antibody to dengue in the CSF and virus isolation from brain tissue and the CSF of patients with neurological symptoms, suggesting direct virus invasion and replication in the CNS (Lum *et al,* 1996; Miagostostovich *et al,* 1997; Hommel *et al,* 1998; Ramos *et al,* 1998; Thisyakorn *et al,* 1999; Kankirawatana *et al,* 2000; Pancharoen *et al,* 2001; Nogueira *et al,* 2002).

CASE REPORT

A 5-year-old girl, who had previously been well, was admitted to Petchabun Hospital on 15 June, 1999, having had fever for 4 days and convulsions for half an hour. On admission, she was stuporous, with no meningeal or other abnormal neurological signs. The temperature was 39ºC, respiratory rate 26/minute, blood pressure 110/70 mmHg, and body weight 18 kg. There was no rash, lymphadenopathy, or hepatosplenomegaly. The results of the rest of the physical examination were normal. A diagnosis of acute encephalitis was made. A complete blood count (CBC) showed hematocrit 34%, WBC 7,600/mm^3, neutrophils 67%, lymphocytes 31% and atypical lymphocytes 2%, platelets 153,000/mm^3. CSF analysis revealed normal pressure, clear and colorless, RBC 10/mm^3, no WBC, protein 744 mg/dl, sugar 120 mg/dl, blood sugar after lumbar puncture was 153 mg/dl, Indian ink negative, and Gram stain negative. Urinalysis was normal. Initial management was supportive and symptomatic; intravenous fluid, anticonvulsants and antibiotics. Five hours after admission she developed coma but still responded to deep pain. The blood pressure was normal. She developed respiratory insufficiency, then mechanical ventilation was introduced. Shock (BP 70/40 mmHg) and deep coma developed on the second day with high fever (39.0ºC), but no abnormal bleeding. Repeat CBC showed a hematocrit of 35%, WBC 5,800/mm^3, neutrophils 54%, lymphocytes 42% and atypical lymphocytes 4%, and platelets 138,000/mm^3. A vasopressor drug was used without improvement. Shock was poorly controlled and high fever persisted (38.5º-39.5ºC) for 3.5 days, then she expired (total fever of 7.5 days). Repeat CBC on the third day showed a hematocrit of 34%, WBC 4,700/mm^3, neu-

Correspondence: Dr Prasonk Witayathawornwong, Department of Pediatrics, Petchabun Hospital, Petchabun Province 67000, Thailand.
Tel: 66 (0) 5672-1751, 01- 8867521; Fax: 66 (0) 5672-2091
E-mail : prasonkw@thaimail.com

Table 1
Serological data.

Serology	Blood	CSF
(HI)		
DEN	<20	-
JE	<20	-
(ELISA)		
JE IgM	0	9
DEN IgM	153	66
DEN IgG	0	35

CSF for Herpes simplex virus (HSV), and mumps virus : IgM=0,0 respectively (test afte JE was not found). Virus isolation was not done.

trophils 38%, lymphocytes 52% and atypical lymphocytes 10%, and platelets 124,000/mm^3. CSF culture for bacteria and hemoculture were negative. A postmortem examination was refused by her parents.

DISCUSSION

The initial diagnosis of the patient was encephalitis. Japanese encephalitis (JE) virus was suspected to be the causative agent because Petchabun Province (the lower part of northern region of Thailand) is endemic for this organism (Chokephaibulkit *et al,* 2001) and there was no history of JE vaccination for this patient. Consciousness deteriorated into deep coma, and shock developed later without signs of bleeding. Uncontrolled shock then death are due to the severity of the disease (Chimelli *et al,* 1990; Janssen *et al,* 1999; Nogueira *et al,* 2002). Blood and CSF showed only dengue IgM, not JE IgM.

IgM can not cross the blood-brain barrier. Detection of dengue IgM in the CSF of a patient with encephalitic symptoms suggests dengue encephalitis (Lum *et al,* 1996). The CSF was tested later for Herpes simplex virus (HSV) and mumps virus but was not found. Serology of the patient showed primary dengue infection. It is possible the patient had dengue hemorrhagic fever but the patient died before the fever defervesced. Dengue encephalitis can arise in primary or secondary dengue infection; in dengue fever or dengue hemorrhagic fever (Lum *et al,* 1996; Ramos *et al,* 1998; Janssen *et al,* 1999).

Although there is evidence that dengue 2 and 3 viruses have neurovirulent properties (Lum *et al,* 1996; Miagostovich *et al,* 1997), dengue encephalitis is still a rare disease. These findings imply that there may be factors associated with dengue viruses entering the brain. Direct dengue invasion may occur by disruption of the blood-brain barrier at hemorrhagic foci (Chatuverdi *et al,* 1991) or by mutation at a specific point in the envelope glycoprotein of the dengue virus allowing it to pass through the blood-brain barrier (Sistayanarain *et al,* 1996). Mutation of other viruses, such as the poliovirus type 3, where a point mutation in the non-coding region is associated with an increase in the neurovirulence of the virus (Evans *et al,* 1985). Infected circulating mononuclear infiltration of the brain, a Trojan horse mechanism (Peluso *et al,* 1985), may allow dengue to indirectly invade the brain. The exact mechanism by which dengue enters the brain should be further elucidated. The outcome of dengue encephalitis may be an uneventful recovery (Lum *et al,* 1996; Kankirawatana *et al,* 2000; Pancharoen *et al,* 2001), neulogical sequele or death (Chimelli *et al,* 1990; Lum *et al,* 1996; Hommel *et al,* 1998; Janssen *et al,* 1999; Thisyakorn *et al,* 1999; Nogueira *et al,* 2002).

ACKNOWLEDGEMENTS

The author thanks Dr Usa Thisyakorn (Department of Pediatrics, Faculty of Medicine, Chulalongkorn University), Dr Anannitya Visudhiphan (Department of Pediatrics, Ramathibodi Hospital, Mahidol University) for worthy consultation about the case presentation and Officials of the Regional Medical Science Center, Phitsanulok Province for dengue serology testing.

REFERENCES

Chatuverdi UC, Dhawan R, Khanna M, Mathur A. Breakdown of the blood-brain barrier during dengue virus infection of mice. *J Gen Virol* 1991; 72: 859-66.

Chimelli L, Dumas HM, Barretto NM, Grandelle R, Dias M, Gray F. Dengue: neuropathological findings in 5 fatal cases from Brazil. *Clin Neuropathol* 1990; 9: 157-62.

Chokephaibulkit K, Kankirawatana P, Apintanapong S, Pongthapisit V, Yoksan S. Viral etiologies of encephalitis in Thai children. *Pediatr Infect Dis J* 2001; 20: 216-8.

Evans DMA, Dunn G, Minor PD, *et al.* Increased neurovirulence associated with a single nucleotide change in a non coding region of the Sabin type 3 poliovaccine genome. *Nature* 1985; 314: 548-50.

Hommel D, Talarmin A, Deubel V, *et al.* Dengue encephalitis in French Guiana. *Res Virol* 1998; 149: 235-8.

Janssen HLA, Bienfait HP, Lansen CL, *et al.* Fatal cerebral oedema associated with primary dengue infection. *J Infect* 1999; 36: 344-6.

Jimenez DR, Santana JL, Ramirez-Ronda CH. Neurological disorders associated to dengue infection. *Bol Assoc Med PR* 1988; 80: 208-11.

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.

Lum LCS, Lam SK, Choy YS, George R, Harun F. Dengue encephalitis: A true entity? *Am J Trop Med Hyg* 1996; 54: 256-9.

Lum LCS, Lam SK, George R, *et al.* Fulminant hepatitis in dengue infection. *SoutheastAsian J Trop Med Public Health* 1993; 24: 467-71.

Miagostovich MP, Ramos RG, Nicol AF, *et al.* Retrospective study on dengue fatal cases. *Clin Neuropathol* 1997; 16: 204-8.

Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue hemorrhagic fever with unusual manifestations. *Southeast Asian J Trop Med Public Health* 1987; 18: 398-406.

Nogueira RMR, Filippis AMB, Coelho JMO, *et al.* Dengue virus infection of the central nervous system (CNS) : a case report from Brazil. *Southeast Asian J Trop Med Public Health* 2002; 33: 68-71.

Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. *Southeast Asian J Trop Med Public Health* 2001; 32: 341-5.

Peluso R, Haase A, Stowring L, Edward M, Ventura P. A Trojan mechanism for the spread of visna virus in monocytes. *Virology* 1985; 147: 231-6.

Ramos C, Sanchez G, Pando RH, *et al.* Dengue virus in the brain of a fatal case of hemorrhagic dengue fever. *J Neurol* 1998; 4: 465-8.

Sistayanarain A, Maneekarn N, Polprasert B, *et al.* Primary sequence of the envelope glycoprotein of a dengue type 2 virus isolated from patient with dengue hemorrhagic fever and encephalopathy. *Southeast Asian J Trop Med Public Health* 1996; 27: 221-7.

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.