A Case of Dengue Virus and Enterovirus Co-Infection

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**Summary**
A 8 month old boy with diagnosis of dengue fever was hospitalised due to fever, lethargy and vomit. Clinical examination showed: lethargy, rate in the lungs. dehydration, low blood pressure, tachycardia, diarrhoea, no rashes and blisters on the skin. Investigation showed: 7.69 g/l protein in CSF, Cerebral Oedema in the skull CT scanners. 12 hours after admission, he had convulsion and apnoea; one hour latter he developed the sign of shock. The management was as dengue shock syndrome protocol, but the child deteriorated and died. The latter investigation indicated a positive test with enterovirus.

**Conclusion:** The case had co infection of two viruses which were dengue and EV71, so fluid therapy should be considered. Especially, it should be considered other viral co-infection when managing unresponsive dengue shock.

**Introduction**
Dengue fevers are common in Viet Nam as well as in other tropical countries. They usually present in four types including non specific mild fever illness, dengue fever, dengue hemorrhagic fever and dengue shock syndrome [1]. However, there are evidence of encephalitis due to dengue virus, but the illnesses are mild.

Enterovirus infections are common in summer and spring, due to a RNA virus. Most of the cases are mild and benign, but some may have encephalitis or myocarditis. Encephalitis and meningitis caused by EV71 are neither rare nor severe [2]. Co-infection of two different viruses may challenge the diagnosis, have poor prognosis and difficult management.

**Case Study**
A boy, 8 months old, was admitted to the hospital due to fever, vomit and lethargy. He had a history of high fever with over 39°C, continuously and poorly response to acetaminophen. He did not have upper airway infection or gastrointestinal problems such as runny nose, cough, poor feeding and diarrhea. Due to getting tired and less active, his parent brought him to a private clinic where he was diagnosed dengue fever. The investigation in the second day of illness showed a positive test with NS1, hematocrit of 35%, normal thrombocytes of 335,000, CRP under 6, normal liver enzymes of GOT 80.9 and GPT 51.9. He was treated at home with acetaminophen and fluids.

In the next two days, the fever seemed to decrease. However, he vomited aggressively with more than 10 times a day before he refused to eat and was getting to lethargy than he was hospitalized.

**History**
He was the second boy, with a history of normal delivery, full term and 2.7 kg at birth, normal mental and physical development with up to date vaccination.

**Examination on Arrival**
He could breathe spontaneously with 45 times per minutes; no retraction and SpO2 were 99%. The air entry equally in both lungs. The heart rate was 150 beats per minutes without murmurs. The pulses were strong in all extremities. The blood pressure was 80/60 mmHg, and refill was 2 second. He was sleepy (V/AVPU). Neurological exams revealed a stiff neck, bulging fontanel, but no convulsions or paralysis. He was pale, but no rash or blemishes were found. Ha had moderate dehydration with sunken eyes and poor urine output. Intestinal exams showed: distention, clear gastric fluids, no hepatop-spleeno-megaly and still aggregated vomits, diarrhea twice a day. Body weight was 8 kg.

The cerebral spinal fluids suggested encephalitis in a patient with dengue fever.

**Investigators on arrival**
Hb were 101 mg/dl, Hct were 37.6; Thrombocytes were 335 000; CRP were 0.24; GOT were 80; GPT were 51.9, Protein were 49.3 and Albumin were 30; PT were 130; APTT were 31s, Fih: 1.8. Blood gas: pH 7.35, pCO2: 44, PO2: 56, HCO3: 18. Dengue NS1A test was positive, Dengue IgM was positive, Dengue IgG was negative. Blood lead level was 4.3 mcg/dl. Blood culture and CSF culture were negative.

The CT scanner of the brain showed the edema in both hemispheres.

**5 hours after arrival**
He had epileptic status, three times in 3 hours, and poor response management (midazolam, barbiturates). He went to coma later (P/AVPU).

**CSF analysis**: yellowish, one cell, protein: 7.69 g/l, Glucose: 3.3 mmol/l, Clo: 110. PCR TB, HI-B, Streptococcus (-); PCR Enterovirus (+).

He was treated with anti-brain edema (mannitol), sedation (barbiturates), antibiotics (vancomycin and ceftriaxon).12 hours after arrival, he was intubated due to prolong convulsion. At that time, the investigation were WBC 10.8; Hb: 104; Hct: 31.5; Thrombocytes: 114 000; CRP=0.31; GOT: 225; GPT: 594; Protein: 32.2; Albumin: 18.8; PT: 49; APTT: 44; Fibrinogen: 1.7.13 hours after admission, he went to shock: pulses of 200 bpm, absent femoral pulses, cold extremities, blood pressure 72/30, refill 3 second; poor urine output (0.5 ml/kg/h). A bolus of Natriclorua 0.9% 10 ml/kg was given twice, vasopressors.
was used (dopamin 10 mcg/kg/h and noradrenalin), mechanical ventilation and sedation by ketamine. 14 hours after arrival, he had acute pulmonary edema, unresponsive shock (heart rate 190 bpm, refill 3 second, CVP+3 cm H2O), poor urine output, and liver 3 cm under costal margin, high fever, coma (P/A/VPU). Then, he was given Albumin, and the max dosage of Dopamine and Noradrenalin), electrolytes and acid–base correction.

**Cardio ultrasound at hour 12:** EF 43%

After 24 hours of treatment, he was still in deep coma with Glasgow score of 3 points, dilated pupils, unresponsive shock and died.

**Discussion**

As a ARN virus of the Flaviviridae, dengue can cause encephalitis as a complication of dengue fever. According to Solomon [3], encephalitis due to dengue was of 47% except for normal cerebral spinal fluid; only 2/9 patients with encephalitis had virus and antibody found in the CSF.

The present of virus in the CSF could be explained by the escape of virus through the damaged vascular system. The pathiology of dengue encephalitis was not clear so that dengue encephalitis was confirmed after differentiating other causes.

This patients had neurological signs and symptoms on admission (vomit, lethargy, bulging fontanel, stiff neck), but he did not in shock. All investigations about coagulation, blood gas, liver and renal functions were normal. However, only 12 hours after admission, he got worse with severe neurological manifestations: epileptic status, coma and apnea. Shock developed 30 minutes after that, and poorly responded to fluids and inotrope. The cause of shock was consideration. It could be septic shock or cardiogenic shock. That suggested a co-infection. The CT scanner of the brain saw the bilateral cerebral edema, no hemorrhage or tumor. Besides the signs and symptoms of viral illness and neurological disorders, the baby did not have rashes or blemishes (Figure 1).

The management based on the protocol of dengue fever in day 4. In spite of the management, the child got worse that can not be expected by dengue encephalitis. Ceftriaxone and Vancomycin were indicated in case of bacterial meningitis. That’s was due to the significant increase of protein in the CSF of 7.69 g/l, but non cell and normal glucose and clo which suggested TB, meningitis or poisoning.

13 hours after arrival, shock appeared and poorly response to fluids and inotrope, acute pulmonary edema developed after two boluses of 10 ml/kg normal saline which suggested another infection such as enterovirus. The management of dengue hemorrhagic fever was supportively and mainly dehydration, but management of enteroviral infection might limit fluids.

Encephalitis due to EV 71 was confirmed when virus presenting in the CSF through blood stream, but the possibility to identify EV71 in the CSF of patients with neurological problems was low at less than 10%; that mortality of encephalitis caused by EV71 was high of 86.7% [4,5]. Cerebral edema develops on CT because of damage to the blood–brain barrier that increases albumin permeability

A study in North Korea [6] recommended that immunoglobulin and milrinone should be in the treatment of EV71 infection with neurological complications [2,4]. Immunoglobulin injected into patients could help prevent the synchronize of cytokine. Milrinone can increase the vasodilation, contraction and muscle relaxation. The treatment of milrinone (0.5 μg/kg/minute) and immunoglobulin had lower mortality rate comparing to the treatment with dopamine or dobutamine and Immunoglobulin (18.2% vs 57.9%) [6].

**Conclusion**

The case had co infection of two viruses which were dengue and EV71, so fluid therapy should be considered. Especially, it should be considered other viral co-infection when managing unresponsive dengue shock.

Needing fast viral laboratory system with high sensitivity and specificity, especially in the area with high density of viral diseases.

**References**