

FULMINANT HEPATITIS IN DENGUE INFECTION

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Abstract. Eight cases of liver failure and encephalopathy were observed among twenty cases of grade 3 and grade 4 dengue hemorrhagic fever/dengue shock syndrome admitted to the Department of Pediatrics, University Hospital, Kuala Lumpur from January 1990 to December 1991. All patients with deterioration in mental status showed a marked increase in liver enzymes (aspartate and alanine aminotransaminases) and severe coagulopathy. Six patients needed cerebral protection, including ventilation, intravenous sedation and muscle relaxants. There was one death during the period of study and one case of residual hemiparesis in a boy who had, in addition, intracerebral hemorrhage. All other survivors had complete recovery of liver and neurological function.

INTRODUCTION

Dengue fever with hemorrhagic manifestations was first reported in the Phillipines in 1953 and in Malaysia in 1962 (Rudnick *et al*, 1965). Since then there have been several epidemics reported in Southeast Asia. Over the past three decades there has been a changing pattern in the clinical pattern of dengue cases in this region (George *et al*, 1974, 1984; George, 1987; Nimmannitya *et al*, 1987; Hadinegoro and Nathin, 1990). This change could be due to patients surviving the acute stage of the disease and demonstrating severe manifestations which occur subsequently.

Patients with dengue infection may present with varying degrees of encephalopathy, usually manifest by a change in the sensorium such as lethargy, drowsiness, restlessness and occasionally seizures and coma.

From 1973 to 1982 liver involvement in dengue infection was mild and manifest by raised liver enzymes. Since 1986 there have been cases of fulminant hepatitis with high mortality reported in pediatric cases in Malaysia and Thailand (George 1987; Suvatte *et al*, 1990; Innis *et al*, 1990). This mode of presentation had caused difficulty in the correct diagnosis and management. In view of the emerging trend in dengue infection, we have undertaken a retrospective review of twenty critically ill dengue patients admitted to the Department of Pediatrics, University Hospital, Kuala Lumpur from January 1990 to December 1991.

MATERIALS AND METHODS

Patients

Of the 20 patients, 14 were in grade 3 dengue shock syndrome (DSS) (WHO, 1986) and 6 patients were in grade 4 DSS at the time of presentation or during the hospital admission.

There were 11 boys and 9 girls ranging from 4 months to 11 years of age. All patients had symptoms and signs of dengue infection and all were serologically positive for dengue IgM ELISA. Twelve patients had features of mild encephalopathy (group 1) as follows: headache, photophobia, lethargy, mild-moderate drowsiness. In addition a two year old boy had generalized weakness of the upper motor neurone type after two weeks of unspecified fever.

Eight patients had severe encephalopathic features (group 2) as follows: deteriorating conscious levels, seizures and coma. Four in this group were under 12 months of age, the others were aged 3, 6, 10 and 11 years. Three infants had seizures and the remainder had restlessness and decreased conscious levels. Liver size ranged from 0.5 to 5 cm subcostally but, when accompanied by ascites, the liver size was difficult to ascertain. Two were in grade 4 DSS at presentation, the other 6 were in grade 3 DSS. Due to the overwhelming encephalopathy the provisional diagnosis was Reye's syndrome in 4 patients and acute meningitis/encephalitis in 2 patients. DSS was considered as a differential diagnosis in these 6 patients.

Investigations

Serial measurements of full blood count, hematocrit, glucose, urea, creatinine, electrolytes, arterial blood gases, coagulation profile and liver function were done. Where possible paired serum samples were obtained from patients for serological testing by hemagglutination inhibition (HI) and IgM ELISA (Lam *et al*, 1987). Acute samples were inoculated into mosquito larvae for virus isolation (Lam *et al*, 1986). Serum ammonia was measured in six patients in group 2. Fibrinogen and fibrin degradation products (FDP) were measured in seven patients with severe coagulopathy. Four patients in group 2 underwent brain CT scanning. One patient in group 1 underwent lumbar puncture.

Student's *t*-test and chi-square test were applied in comparing the laboratory characteristics of the patients in these two groups.

RESULTS

The mean hematocrit, sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), partial thromboplastin time (PTT) and prothrombin ratio (PTR) for group 1 and group 2 patients are shown in Table 1. The AST, ALT, PTT, PTR levels were significantly higher in group 2 compared with group 1 ($p < 0.05$). The serum sodium was lower in group 2 compared with group 1 ($p < 0.05$). There was no significant difference in the hematocrit and blood urea levels in both groups. Figs 1 and 2 illustrate the distribution of patients with respect to the levels of liver enzymes and coagulopathy.

Levels of serum ammonia in 6 patients in group 2 were within normal limits or slightly elevated. Two infants had transient hypoglycemia in the early phase of the disease. Hypoglycemia in these patients was readily corrected by increasing the concentration of glucose infusion. In seven patients with severe coagulopathy fibrinogen levels were low and FDP was negative. One patient had uncontrolled gastrointestinal bleeding and normal fibrinogen levels. He was thought to have dysfibrinogenemia.

Three patients had jaundice evident on day 2-7 of admission. Their total bilirubin ranged from 200-864 micromoles/l with equal proportions of

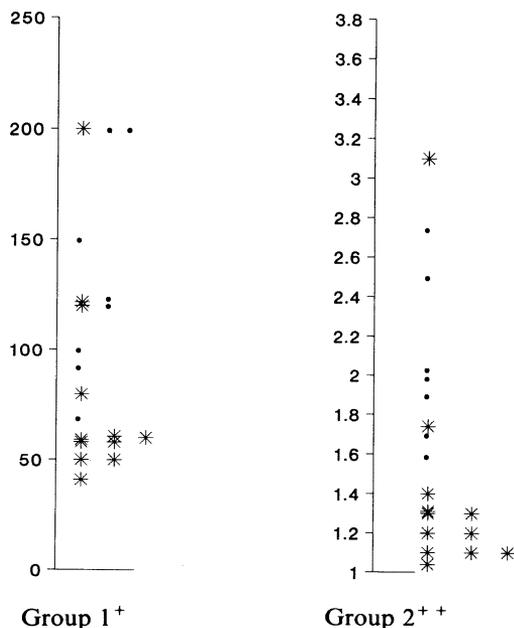
Table 1

Laboratory results at presentation [mean (SD)].

	Group 1 (n=12)	Group 2 (n=8)	p value
PTR	1.40 (0.52)	2.26 (0.62)	<0.05
PTT	79.8 (44.0)	131.8 (45.3)	<0.05
AST	197 (149)	2095 (985)	<0.05
ALT	80 (3.5)	1791 (905)	<0.05
Na ⁺	130.3 (3.5)	122.0 (3.6)	<0.05
PCV	48 (10)	39.7 (7)	>0.10

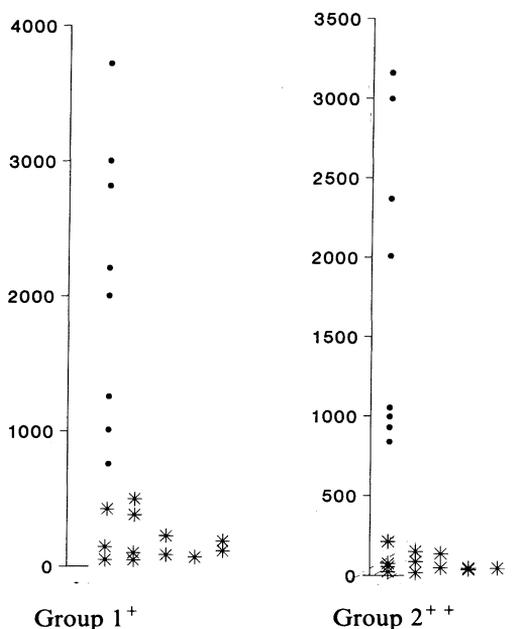
- PTR - Prothrombin time ratio
- PTT - Partial thromboplastin time (sec)
- AST - Aspartate transaminase (IU/l)
- ALT - Alanine transaminase (IU/l)
- Na⁺ - Serum sodium (mmol/l)
- PCV - Packed cell volume

conjugated and unconjugated fractions. Jaundice resolved over 3-8 weeks. One patient underwent liver biopsy on day 28 because of deepening jaundice. Histology showed extensive necrosis with residual viable hepatocytes, marked cholestasis and infiltration of lymphocytes, neutrophils and plasma cells.



+ Fig 1—Distribution of prothrombin time ratio

+ + Fig 2—Distribution of partial thromboplastin time (seconds)



+ Fig 3—Distribution of aspartateaminotransaminase (iu/l)

+ + Fig 4—Distribution of alanine aminotransaminase (iu/l)

Brain CT scan in the four patients showed cerebral edema without intracranial bleed. One of these patients, an 11 year old boy, underwent repeat scanning on day 10. This revealed intracerebral hemorrhage in the right parietal-occipital lobes with cerebral edema. In this patient intracranial pressure (ICP) was monitored with an intraventricular catheter and cerebrospinal fluid was removed when ICP exceeded 30 mm Hg. He was treated with dexamethasone 4 mg/kg/day. The cerebrospinal fluid of one patient in group 1, who had upper motor neurone weakness, was positive for dengue IgM.

Dengue infection was confirmed in all patients by IgM ELISA and HI. Japanese encephalitis (JE) was excluded serologically in those cases presenting with encephalopathy symptoms. In group 2, five patients had primary dengue infection and dengue 3 virus was isolated in one patient. In group 1, all patients had secondary dengue infection. Two strains of dengue virus were isolated.

Six patients in group 2 were ventilated for 7-20 days. Cerebral protection in these patients consisted of controlled mandatory ventilation with intravenous sedation and muscle relaxant.

There were 19 survivors. The liver function and coagulation of these patients returned to normal. One patient in group 2 died on day 14 from uncontrolled gastrointestinal hemorrhage. The patient with intracerebral hemorrhage developed residual hemiparesis and hemianopia. The boy with upper motor neurone weakness showed improvement in neurologic function.

DISCUSSION

From January 1990 to December 1991, 215 pediatric patients with serologically confirmed dengue infection were admitted to this hospital. The patients in this series represent the most critically ill (10%) among pediatric dengue patients admitted. The incidence of liver failure was 3.7%. There was only 1 death in a patient with hepatic and renal failure and uncontrolled gastrointestinal hemorrhage. All patients had evidence of plasma leakage : hemoconcentration, pleural effusion, ascites and hypovolemia. It should be noted that the normal hematocrit range for an infant in this population is 30-35%, ie lower than the corresponding value for adults.

Group 2 patients had severe encephalopathy and severe liver dysfunction. The clinical picture at presentation was difficult to distinguish from Reye's syndrome. The features in common with Reye's were cerebral edema, raised intracranial pressure and liver dysfunction (Reye *et al*, 1963; Crocker and Bagnell, 1981). There were distinguishing features. The serum ammonia was either normal or only slightly elevated, possibly due to gastrointestinal hemorrhage. Jaundice is not a feature in Reye's syndrome. The liver pathology in Reye's syndrome is that of fatty infiltration. This was not the picture seen in the 1 patient who had a liver biopsy, although it was performed only on day 28 of admission. All our patients had thrombocytopenia and features of increased vascular permeability which are not seen in Reye's syndrome.

The role of hypotension and resultant anoxia in the initiation of liver impairment is uncertain in this study. Only 2 of the patients with severe liver impairment were in shock while 4 other patients who presented with shock had mildly elevated liver enzymes. The severe damage to the liver relative to that of other organs, especially the kidneys, may indicate a primary insult to the liver.

Reports of post-mortem liver biopsies have shown extensive necrosis of hepatocytes and the presence of sparse dengue antigen in liver tissues. Dengue virus however, was not isolated in the liver tissues that were cultured (Innis *et al*, 1990). The etiology of liver failure may be resolved by a liver biopsy done early in the course of the disease as soon as the coagulopathy is corrected.

Patients with severe encephalopathy had significantly low serum sodium concentrations. It is unlikely that hyponatremia is the main cause of the encephalopathy because correction of the serum sodium was not accompanied by an improvement in the conscious level. Hyponatremia may aggravate the cerebral edema and the increased intracranial pressure.

Chen *et al* (1991) reported detection of IgM antibodies in the cerebrospinal fluid of dengue patients but their neurological status during and after the illness was not stated. IgM antibodies for dengue and not JE was detected in one of the patients who had residual pyramidal tract signs. His pre-morbid neurologic status was, however, said to be abnormal.

From the serological investigations carried out on these patients, it was interesting to note that severe manifestations resulted from primary as well as secondary infections. Four of the 5 patients with primary infections in group 2 were infants in whom maternal antibodies could cause immune enhancement leading to severe manifestations. Dengue 2 and dengue 3 viruses have been associated with severe dengue infections and it is not surprising that we found this to be so in this study.

Assessment of liver function and serum ammonia in patients with encephalopathy is helpful in the differentiation from Reye's syndrome. A positive IgM for dengue helps in the early confirmation of the disease. The general principles of management are supportive and symptomatic in all patients. Exchange blood transfusion in the management of severe liver failure has been reported by Suvatte *et al* (1990). In our experience this has not been necessary. Those patients with severe liver impairment were critically ill for a longer period of time and they required closer monitoring of the neurologic status. Some of these patients had cerebral protection in the form of restriction of crystalloid infusion, early mandatory ventilation and closer monitoring of the intra-arterial, central venous and intracranial pressure.

The use of steroids was found to be controversial in previous studies (Pongpanich and Humponpant, 1973; Futrakul *et al*, 1981; Sumarmo *et al*, 1982; Sumarmo, 1987) but they were used in one particular patient in high doses because of severe cerebral edema. Whether this played a role in his recovery is debatable.

Fulminant hepatitis with encephalopathy is a serious manifestation of dengue infection. Early recognition, prompt fluid resuscitation with physiologic replacement therapy, close monitoring of the neurologic status and cerebral protection and control of the intracranial pressure are essential in ensuring complete recovery from this devastating illness.

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